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14918
(1072)

FINAL REPORT

ABOUT SERVICES RELATING TO THE

TRANSFER OF TECHNOLOGY

PHARMACEUTICAL CHEMICALS MULTI-PURPOSE PILOT PLANT

IN

IRAN

UNIDO CONTRACT NO. 85/39

PROJECT NO.DP/IRA/83/014

ACTIVITY CODE:DP/02/32.1

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INTRODUCTION

The present final report about services relating to the transfer of technology, pharmaceutical chemicals multi-purpose pilot plant in Iran consists of 3 parts:

Part 1: Main Rep ,rt
Part 2: 2nd Report, Suggestions for Changes in Equipment
Part 3: Appendices

Part 1 and part 2 have already been submitted to UNIDO as draft reports to supply technical information for the meeting at UNIDO headquarters taking place from June 24th, to June 28th, 1985.

Part 1 was finished shortly before the meeting took place, part 2 was prepared in the process of the meeting following a wish of the members of the meeting. Part 3 is the appendix to the main report.

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1. GENERAL BACKGROUND INFORMATION

The immediate objectives of the Project DP/IRA/83/014 titled "Transfer of Technology through the Establishment of a Pharmaceutical Chemicals Multi-Purpose Pilot Plant" are in brief:

Transfer of technology for production of essential drugs from intermediates and raw materials through chemical synthesis.

developing capability leading to research and development activities and its application in the pharmaceutical industry.

Establishment of facilities for process development, adaption and integration of technology through a multi-purpose pilot plant. This will enable the base to be established prior to the installation and operation of full industrial-scale plants.

The aim of the project is to establish and put into operation a multi-purpose plant for the production of pharmaceutical chemicals at the site of TEMAD, a unit of Daru Paksh, located in Karaj, 28 kms from Teheran.

To achieve this aim terms of reference for contractor services were prepared by UNIDO and companies were invited to take part in a tender. As a result of this tender 5 companies submitted offers, which were evaluated by UNIDO. On May 8th, and 9th, 1985 discussions were held on the project at the UNIDO headquarters with representatives of Iran Government, UNDP and UNIDO taking

part. The main results of the discussion were:

None of the 5 offers meets the terms of reference fully and as such no offer can be considered suitable in the present form.

Out of the 5 offers the representatives of DARU PAKSH would like to limit consideration to the following companies

Chemokomplex
Cipla
Reinikainen
Sarabhai

Among others also several decisions concerning technical questions were met which have direct impact on the present report:

First of all changes in the list of drugs to be produced were proposed as follows and the importance of quality of services and independence of equipment and raw materials was emphasized. Out of the list of drugs included in the UNIDO terms of reference priority should be given to the following:

Chlordiazepoxide
Clofibrate
Clotrimazole
Diazepam
Ethambutol
Indomethacin
Mebendazole
Nalidixid Acid
Nicotinamide
Oxyphenbutazone

Paracetamol
Procaine Hydrochloride
Propranolol

In addition to above, the following drugs can be considered for production in a multi-purpose plant:

Metronidazole
Sulfamethoxazole
Trimethoprim

It was decided to ask the companies for the following further clarifications:

Type and level of technology, raw materials and intermediates required and sources and coefficients of consumption.

Equipment list and specifications and independent sources particularly from Western Europe from which equipment are available.

To guarantee that equipment with technology transferred and design will give required quality and quantity.

20 - 30 % Reserve capacity should be provided in the project and maximum possible unit processes.

Environmental aspects.

Handling and storage of hazardous chemicals.

Effluent treatment.

Air pollution.

Contractor should be willing to assist DARU PAKSH after the establishment of guarantee runs in research and development, training, improving technology for a period of two years and if so what are the terms.

Other clarifications proposed by UNIDO especially concerning patents.

The possibility of using prefabricated structures for the plant should be examined and offers be invited.

Finally it was decided to appoint a short term consultant for 2 months. He was to

"check all the criteria of different offers, examine the possibility of integrating into some of the offers also the technology of Chemie Linz where feasible and make rec mendations of an integrated offer for consideration before June 20th, 1985. The project should have optimum design, flexibility, unit processes and reasonable level of technology."

As a result of the meeting the writer of the report was appointed as a short term consultant.

2. WORK PLAN

2.1. GENERAL CONSIDERATIONS

From the beginning it was clear that it would be extremely difficult to analyse the project and give the recommendations required before June 20th, because the technical data which were required for the evaluation were not or only partially given in the different offers.

Therefore in the first stage a questionnaire containing the questions for all data needed for a technical comparison of the offers was worked out by the UNIDO officer in charge Mr. Chari and the writer and was sent to all the companies.

Since the answers to the questionnaire could be expected only shortly before the date of submission of this report it was decided by the author to work out a strategy to allow quick analysis of all data coming in. According to this strategy a framework was set up in which based on the processes offered as well as the standard production processes for all products an "optimum" choice of technology was made based on technological and economical aspects mainly.

Corresponding to the "optimum" technology an "optimum" list of equipment including estimate of cost was set up indicating the requirements to assure for all the products the proposed production capacity. Because of the relatively high costs for equipment this "optimum" version is mainly of theoretical value but as the intended framework it has been a great help in quick evaluation of offers.

2.2. SOURCES OF INFORMATION USED IN THIS REPORT

2.2.1. OFFERS

The main source of information were of course the submitted offers of the companies. None of the offers contained enough information to carry out conclusive analysis.

Reinikainen offer does not contain any technical information except the statement that only technologies for 12 out of 18 drugs are offered. There are no indications about processes or starting materials.

Sarabhai's offer is also very short. The readiness to offer technologies for production of 14 drugs is indicated. Since the starting materials are mentioned a basis for evaluation of production processes was given.

Cipla indicated in its offer that technology for 9 drugs is in the house, for 7 drugs available in India and for 2 abroad. From a scheme of plant utilisation in the offer starting materials and some other technical data could be taken and used for analysis. Cipla suggested production of metronidazole, sulfamethoxazole and trimethoprim. As far as equipment is concerned the offer refers to the equipment indicated in the terms of reference.

Vegyterv/Chemokomplex submitted the most detailed offer. Process description for 18 drugs was given, in two cases (chlordiaz-epoxide and mebendazole) technology of equivalent products was proposed. As far as equipment is concerned 2 alternatives

were proposed, one according to the terms of reference and one which is favoured in the offer and for which a production programme is given.

2.2.2. SARABHAI-CUBA PROJECT

At present a similar project is on the way in Cuba carried out by Sarabhai. Since some of the technologies used there correspond to those in the Sarabhai offer some data necessary for evaluation were taken from the process description of the Cuba project with permission of Unido. In the report reference to this source is made by indicating Sarabhai/Cuba (S_C).

2.2.3. QUESTIONNAIRE - MEETINGS

The questionnaire which also contained technical questions was sent out by Telex.

Reinikainen did not give specific details in its answers.

Sarabhai sent a telex which was received on June 21st, indicating that the company is in a position to provide technology for metronidazole, sulfamethoxazole and trimethoprim, but that in contrast to the Cuba project technologies for chlordiazepoxide diazepam, indometacin and nalidixic acid cannot be offered. Also some of the educts for synthesis were confirmed.

As far as Cipla is concerned a meeting was held with Dr.Behl

of the subcontractor Vishwakarma Process Technik (India) at UNIDO an June 18th, in which the change of the hitherto subcontractor Vishwakarma to main contractor was confirmed. The new main contractor stated that he is ready only to act as a main contractor. Any answers concerning technical questions were not given and cannot be expected before mid August. A written statement of Dr.Behl was received on June 21st.

As far as Vegyterv/Chemokomplex is concerned meetings were held at Budapest and Vienna. A written official answer to the questionnaire was obtained on June 21st.

2.2.4. MEETING WITH CHEMIE LINZ

According to the wish of the Iranian delegation at the May meeting to integrate technology offered by Chemie Linz where feasible, a meeting was arranged at UNIDO Headquarters on Mai 21st with representatives of Chemie Linz, Dr.O.K.Burger, Chairman and Dipl.Ing. E.Schneider, License Manager, which resulted in an offer of Chemie Linz for two technologies.

2.2.5. MARKET SITUATION - RAW MATERIALS - INTERMEDIATES - PRODUCTS

Information about market prices of raw materials, intermediates and products, which were needed for the evaluation of the offers were in most cases obtained through direct request from suppliers.

2.2.6. MARKET SITUATION EQUIPMENT

As far as equipment is concerned according to the wish of the representatives of Iran in the May meeting, special attention was laid on Western European sources of equipment. After analysis of the types of equipment to be considered in the project market prices were obtained directly from equipment manufacturers.

By chance Achema, the International Meeting of Chemical Engineering, which is one of the greatest exhibitions of chemical equipment, took place in the week from June 9th to 16th, 1985. Two visits were made to Achema to obtain information about the latest developments in equipment required for the project.

2.2.7. STANDARD TECHNOLOGIES - REFERENCE WORKS

Since all the drugs of the project are for a long time introduced into the market, standard reference works exist as well for their production as for their analysis. Several of these reference books were used in the assessment of the technologies.

The Organic Chemistry of Drug Synthesis

D. Lednicer, 1929 - today, John Wiley & Sons, Inc., ISBN 0-471-52141-8.

Pharmazeutische Wirkstoffe: Synthesen, Patente, Anwendungen

A.Kleemann and J.Engel, Georg Thieme Verlag 1982, ISBN 3-13-558402-x.

Arzneimittel: Entwicklung, Wirkung, Darstellung

G.Ehrhart und H.Ruschig, Verlag Chemie GmbH, 1968

Pharmaceutical Manufacturing Encyclopedia

M.Sittig, Noyes Data Corporation, USA 1979.

A list of reference literature concerning the standard processes was also set up, from which validity of patents can be seen. A detailed analysis of this literature and the patents was not required within this report.

2.2.8. PATENTS

Since transfer of technology is closely related to research and development, also the international situation concerning patents is of great importance. Therefore a computer based search of literature was carried out at ETH Zürich, followed by an analysis of the patents obtained through this search.

2.2.9. NOBEL-SWEDEN

On June 21st, 1985 the writer of the report was informed that an offer of the company Nobel-Sweden had arrived including technologies for the production of Niacin, Niacinamide, Procain hydrochloride, Paracetamol and Trimethoprim. Since the time was too short to include this completely new offer into the report, which was already partly written, an additional appendix concerning this offer was envisaged first. Since the offer referred only to a few drugs ard since the offer seemed rather high in price, it was later decided not to consider this offer in the present report.

2.3. TIME SCHEDULE

The work related to this report started on May 13th. In the first phase all information required was to be investigated. it was at first scheduled that this phase should be finished not later than June 17th. Unfortunately as seen from 2.2. some answers to the questionnaire arrived on June 21st only, so that a strict time schedule could not be maintained. Analysis of the results was taken up on June 4th, and had to be maintained according to the information coming in until June 23rd. Writing of the report started on June 10th and could also not be finished before June 23rd.

3. TECHNOLOGIES

3.1. GROUPING OF THE TECHNOLOGIES

According to the results of the May meeting at UNIDO headquarters the products were divided into 3 groups:

A: Products of terms of reference with maintained priority

B: Products of terms of reference with second priority

C: Newly proposed products

The code given to the products in the following list is maintained throughout the report:

Chlordiazepoxide	A1
Clofibrate	A2
Clotrimazole	A3
Diazepam	A4
Ethambutol	A5
Indometacin	A6
Mebendazole	A7
Nalidixic Acid	A8
Nicotinamide	A9
Oxyphenbutazone	A10
Paracetamol	A11
Procaine HCl	A12
Propranolol	A13
Diphenylhydantoin	B1
Isoniazid	B2
Lidocaine HCl	B3

Niazin	B4
Nikethamide	B5
Metronidazole	C1
Sulfamethoxazole	C2
Trimethoprim	C3

3.2. STANDARD PREPARATION PROCEDURES

Since it was the task of the present report to compare the technologies offered and not to make a free choice of production processes, it was first of all tried to relate the offered process technologies to known standard processes. In most cases this correlation succeded in principle, in many cases however the starting material was a late intermediate. To establish an "optimum" choice of technology these processes were reduced to more basic materials wherever it was feasible with respect to equipment and economy of production. In the few cases in which the technology proposed in the offer was not clear, did not seem satisfactory or was not given at all, a known standard process which seemed to be most appropriate to the project was chosen for the "optimum" technology. In the following reaction schemes all the processes considered are given for each product with the following codes indicating the offering firm:

C	Cipla
CL	Chemie Linz
I	Iprochim
O	"optimum" choice
S	Sarabhai
S_C	Sarabhai-Cuba
V	Vegyterv/Chemokomplex

3.3. ANALYSIS OF PATENTS

To check research and development activities concerning the different products a computer search for patents was made in Chemical Abstracts for the time from 1967 - 1985. (For reason of lack of time a search profile had to be chosen which does not guarantee in each case that all patents are cited !) For all compounds patents were found. As far as from a first analysis of the patent abstracts can be seen, there is no development which renders the standard technologies of the offers obsolete. In the following list the number of patents for synthesis is given for each compound, indicating international research activity in the specific field.

To assess research activities done by companies in countries from which offers have arrived, the collected patents for preparation were also analysed with this respect.

		Number of Patents	Country
Chlordiazepoxide	A1	12	S,R
Clofibrate	A2	4	R
Clotrimazole	A3	36	H
Diazepam	A4	78	S
Ethambutol	A5	11	
Indometacin	A6	76	H
Mebendazole	A7	6	H
Nalidixic Acid	A8	27	H,R
Nicotinamide	A9	15	
Oxyphenbutazone	A10	1	H
Paracetamol	A11	16	R
Procaine HCl	A12	4	H
Propranolol	A13	10	

Diphenylhydantoin	B1	1	
Isoniazid	B2	2	
Lidocain HCl	B3	1	
Niazin	B4	42	R,S
Niketh amide	B5	8	H,S
Metronidazole	C1	9	H,R
Sulfamethoxazole	C2	2	
Trimethoprim	C3	58	I,H,S

With patents referring to 9 of the 21 products Hungarian research activities in this field are impressive, also Romania with patents referring to 6 compounds and Switzerland with 5 are well represented, in contrast to India with 1 citation and Austria with no citation.

However it must be kept in mind that the existence of a corresponding patent in a country does not at all mean that these most up to date technologies will be proposed in offers coming from that country. Especially with respect to the significant research and development activities in Hungary in the field of essential drugs, it might be interesting to discuss this point in detail to assess the conditions of transfer of most up to date know-how.

Code of Countries:
H: Hungary
R: Romania
S: Switzerland
I: India

3.4. COMPARISON OF TECHNOLOGIES FROM THE VIEW OF PROCESS

3.4.1. GENERAL REMARKS

Although it was possible to evaluate the different technologies offered in the case of most of the products, a final decision could not be made for 3 products:

Isoniazid	from 4-Cyanopyridine or Isonicotinic acid or Isonicotinic acid, ethyl ester
Niazin	from 3-Cyanopyridine or 5-Ethyl-6-methylpyridine or ß-Picolin or recrystallisation of feed grade
Nicotinamide	from 3-Cyanopyridine or Nicotinic acid

All the technologies described for these products are standard technologies of similar value as far as transfer of know how is concerned. The choice of process will be determined mainly by economic points of view. Since most of the products are bulk chemicals a detailed comparison of prices for all inputs has to be made for which sufficient details have not yet been obtained.

3.4.2. COMPARATIVE SURVEY OF STARTING MATERIALS USED

		C=CIPLA	NC=NOBEL CL=CHEMIE LINZ	I=IPROCHIM	S=SARABHAI	SC=SARABHAI CUBA	V=VEGYTERV	STANDARD METHOD
CHLORDIAZEPOXIDE	A1	SUB	0	ACB-OXIME	0	ACB	0-ALTERNATIVE	ACB/CCB
CLOFIBRATE	A2	p-CHLORO-PHENOL	0	p-CHLOROPHENOL	p-CHLOROPHENOL	p-CHLOROPHENOL	CLOFIBRINIC ACID	p-CHLOROPHENOL
CLOTRIMAZOLE	A3	ABROAD	0	o-CHLOROBENZO-PHENONE	o-CHLOROBENZOIC ACID	0	o-CHLOROTRITYL-CHLORIDE	o-CHLOROBENZO-TRICHLORID
DIAZEPAM	A4	SUB	MCB=CL	ACB	0	MCB	MCB	MCB/CMCB
DIPHENYLHYDAN-TOIN	B1	BENZAL-DEHYD	0	BENZALDEHYD	BENZIL	BENZIL	BENZIL	BENZALDEHYD
ETHAMBUTOL	A5	D-2-AMINO-BUTANOL	0	D-2-AMINO-BUTANOL	D-2-AMINOBUTANOL	0	D-2-AMINOBUTANOL	D-2-AMINO-BUTANOL
INDOMETACIN	A6	ABROAD	0	p-ANISIDIN	0	p-ANISIDIN	N-p-CHLOROBENOYL-N-p METHOXYPHENYLHYDRAZIN	p-ANISIDIN
ISONIAZID	B2	4-CYANO-PYRIDINE	0	ISONICOTINIC ACID	ISONICOTINIC ACID	0	ISONICOTINIC ACID-ETHYLESTER	?
LIDOCAINE HCl	B3	SUB	0	2,6-XYLIDINE	2,6-XYLIDINE	2,6-XYLIDINE	2,6-XYLIDINE	2,6-XYLIDINE
MEBENDAZOLE	A7	3,4-DIAMINO BENZOPHENONE	0	0	p-CHLOROBENZOIC ACID	0	0-ALTERNATIVE	3,4-DIAMINO BENZOPHENONE
NALIDIXIC ACID	A8	SUB	0	0	0	2-AMINO-6-METHYL PYRIDINE	RECRYSTALLISATION FROM NALIDIXIC ACID	2-AMINO-6-METHYLPYRIDINE
NIACIN	B4	3-CYANO-PYRIDINE	MEP=NC	RECRYSTALLISATION FROM FEED GRADE	3-CYANOPYRIDINE	0	B-PICOLIN	?
NIKETHAMIDE	B5	NICOTINIC ACID	0	0	NICOTINIC ACID	NICOTINIC ACID	NICOTINIC ACID	NICOTINIC ACID
NICOTINAMIDE	A9	3-CYANO-PYRIDINE	0	NICOTINIC ACID	3-CYANOPYRIDINE	3-CYANOPYRIDINE	NICOTINIC ACID	?
OXYPHENBUTAZONE	A10	SUB	0	0	PHENOL	(PHENYLBUTAZONE HYDRAZOBENZOL)	4-HYDROXY-HYDRAZO BENZOL	PROTECTED p-AMINO PHENOL
PARACETAMOL	A11	SUB	PHENOL=NC	p-AMINO PHENOL	p-AMINOPHENOL	p-AMINOPHENOL	p-AMINOPHENOL	p-AMINOPHENOL
PROCAINE HCl	A12	SUB	BENZOCAIN=NC	0	BENZOCAINE	BENZOCAINE	BENZOCAINE	BENZOCAINE
PROPRANOLOL	A13	∝-NAPHTOL	∝-NAPHTOL=CL	∝-NAPHTOL	∝-NAPHTOL	0	1-CHLORO-1-NAPHOXY-2-PROPANOL	∝-NAPHTOL.
METRONIDAZOLE	C1	SUB	0	0	+	2-METHYL-5-NITRO-IMIDAZOLE	0	2-METHYLIMIDAZOLE
SULFAMETHOXAZOLE	C2	+	0	0	+	0	0	3-AMINO-5-METHYL ISOXAZOLE
TRIMETHOPRIM	C3	+	ACRYLIC NITRILE=NC	0	+	0	0	3,4,5-TRIMETHOXY-BENZALDEHYD

3.4.2.1. CHLORDIAZEPOXIDE (A1)

Processes offered:

C	:	subcontracting, no further details
CL	:	0
I	:	from ACB-Oxime (2)
S	:	0 (S_C offered from ACB (1))
V	:	0

A detailed process description was not given by any company.

Standard Synthesis: From ACB (1) or 1 step earlier

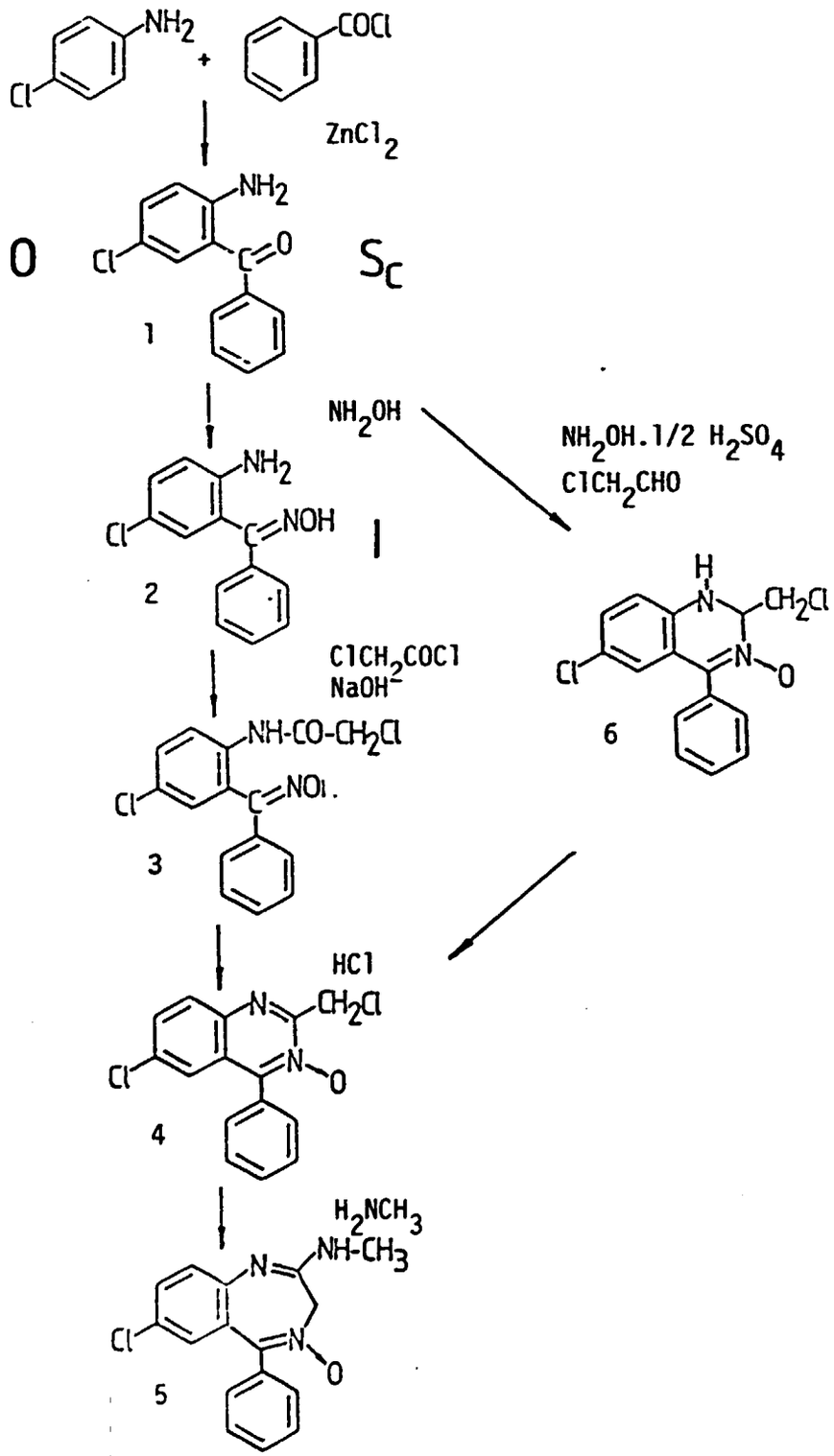
Proposed Starting Material: ACB (1) good availability

Evaluation: Iprochim only company offering defined synthesis
Reaction from 1 to 2 will not be complicated.
Therefore to be considered.

The technological value is very high because synthetic route also leads to other benzodiazepines such as oxazepam, temazepam, nitrazepam and others.

A1

CHLORDIAZEPOXIDE



3.4.2.2. CLOFIBRATE (A2)

Processes offered:

C	:	from p-chlorophenol (no process descr.)
CL	:	0
I	:	from p-chlorophenol (1)
S	:	from p-chlorophenol (1)
V	:	from clofibric acid (2)

Standard synthesis: According to reaction scheme from 1.

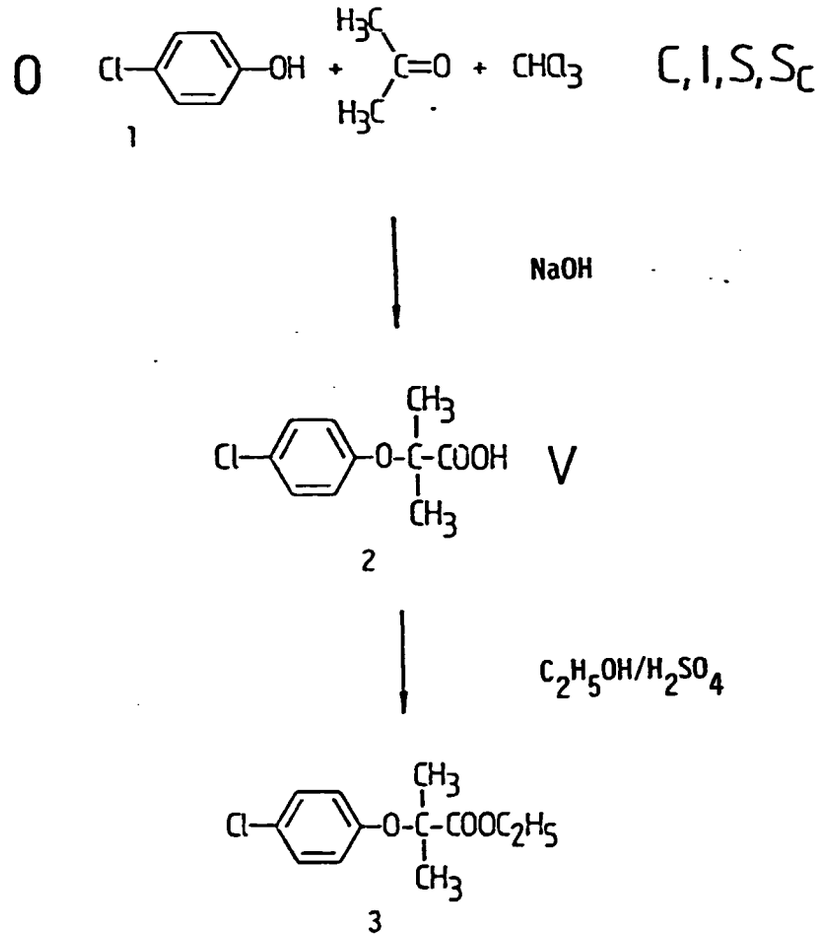
Proposed starting material: p-chlorophenol (1)

Evaluation: The reaction from 1 to 2 is not complicated and should therefore be considered.
All companies offer about the same process according to standard synthesis, only Vegyterv starts from a later intermediate.

Technological value: Step 1 is rather simple
Step 2 contains a vacuum distillation purification, which requires good equipment.

A2

CLOFIBRATE



3.4.2.3. CLOTRIMAZOLE (A3)

Process offered:

C	:	subcontracting from outside India
CL	:	0
I	:	from o-chlorotritylchloride (3) *
S	:	from o-chlorobenzoic acid (?)
V	:	from o-chlorotritylchloride (3)

The Sarabhai synthesis may lead to 1 or to o-chlorobenzophenone

Standard synthesis: According to the reaction scheme from o-chlorobenzotrichloride (2)

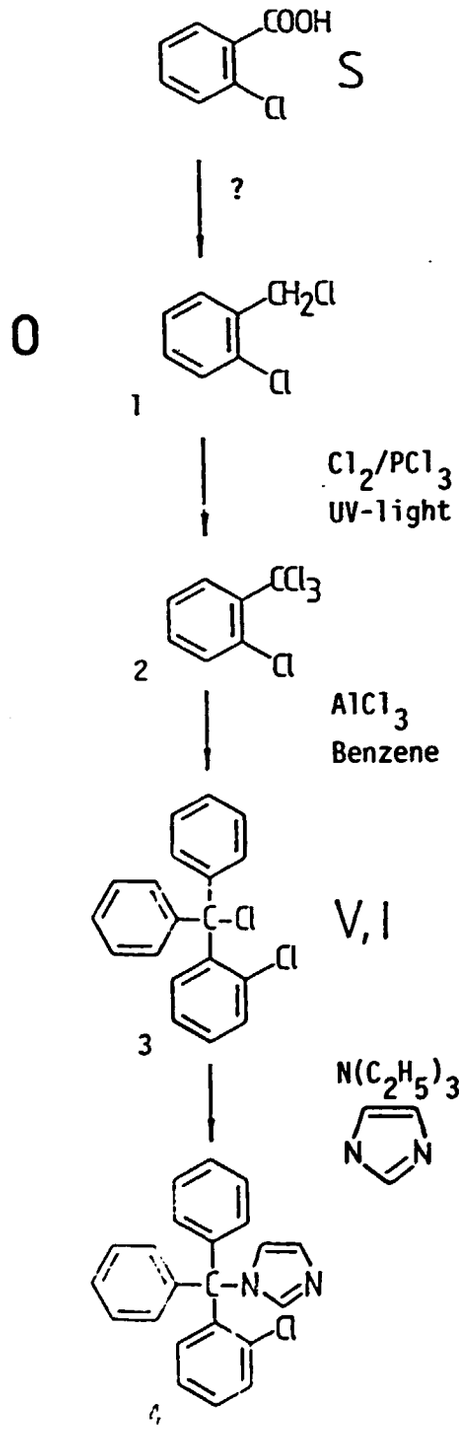
Evaluation: Iprochim* and Vegyterv offer only last step. Different routes are possible, standard technology was chosen

Technological value: Synthesis opens access to Friedel-Crafts reaction, a group of technologically interesting reactions.

* was chanced later to o-Chlorobenzophenone

A3

CLOTRIMAZOL



3.4.2.4. DIAZEPAM (A4)

Process offered:

C	:	subcontracting from India
CL	:	from MCB (5)
I	:	from ACB (1)
S	:	0 (S_C offered from MCB (5))
V	:	from MCB (5)

Standard Synthesis: Reaction of 5 with chloroacetylchloride leads to 6 which is cyclized with hexamethylentetramine to 7

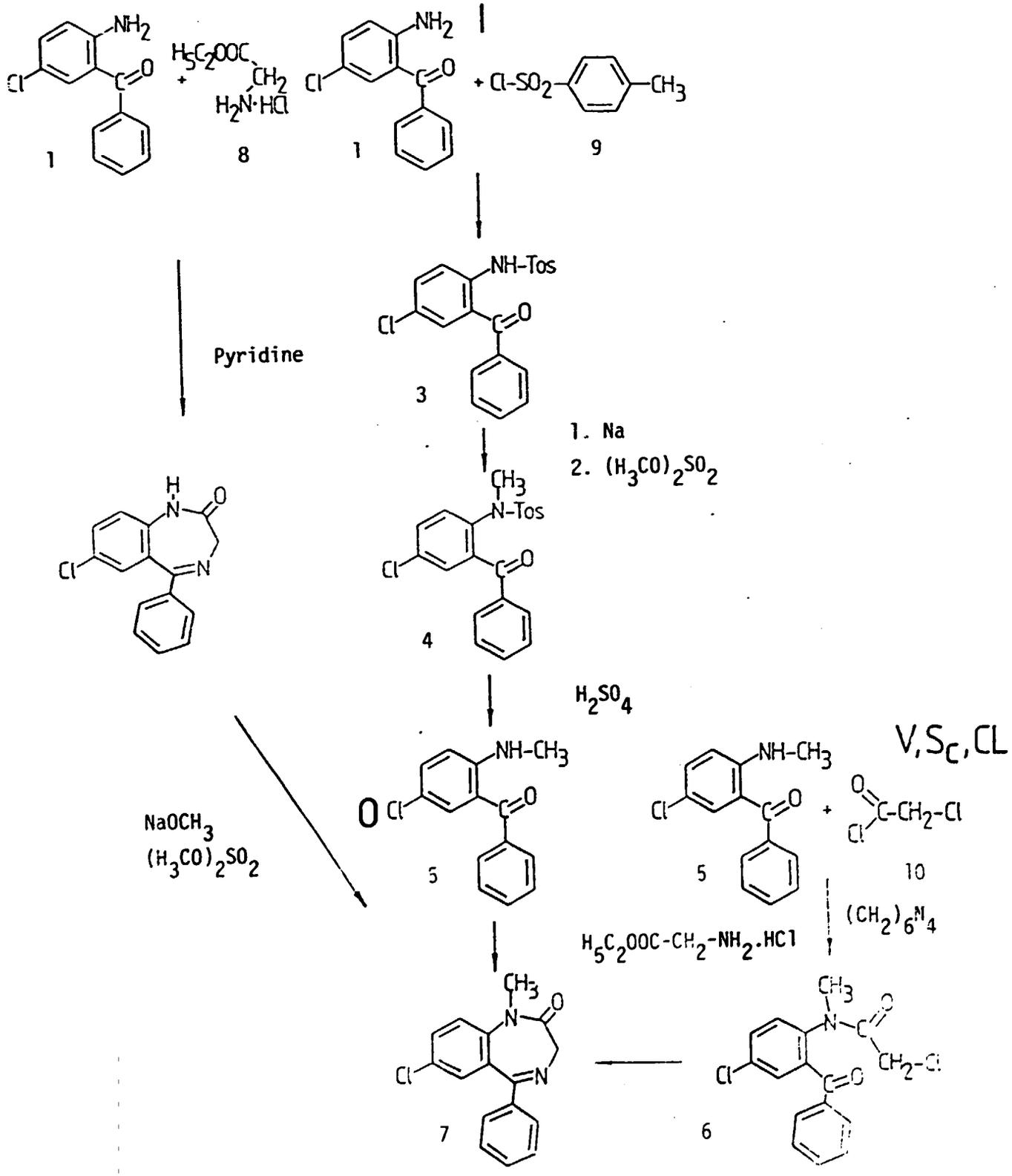
Proposed Starting Material : MCB (5) CMCB (6) is also available.

Evaluation: CL and V offers according to standard process.
I: in the process description only benzodiazepinone with methylbenzenesulfonate given.

Technological value: see chlordiazepoxide

A4

DIAZEPAM


NH2
Cl
O
H5C2OOC
CH2
H2N·HCl
Cl-SO2
CH3
1
8
1
9
NH-Tos
3
Pyridine
1. Na
2. (H3CO)2SO2
CH3
N-Tos
4
H2SO4
NH-CH3
5
NaOCH3
(H3CO)2SO2
V, Sc, CL
C-CH2-Cl
10
(CH2)6N4
H5C2OOC-CH2-NH2.HCl
7
6
CH2-Cl

3.4.2.5. ETHAMBUTOL (A5)

Process offered:

C	:	D-2-aminobutanol (no process descr.)
CL	:	0
I	:	D-2-aminobutanol (1)
S	:	D-2-aminobutanol (1)
V	:	D-2-aminobutanol (1)

Standard Synthesis: According to the reaction scheme

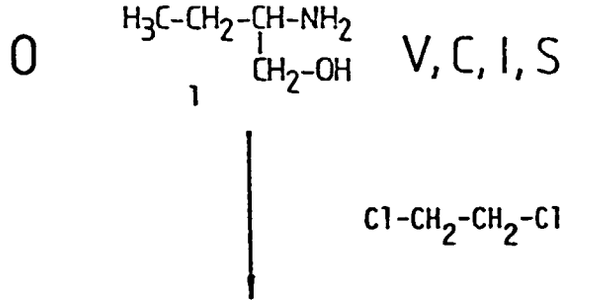
Proposed Starting Material: D-2-aminobutanol

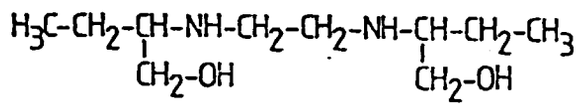
Evaluation: All offers are according to the standard synthesis

Technological value: very important is the purity of the end product. This is achieved by a high vacuum distillation.

A5

ETHAMBUTOL





3

3.4.2.6. INDOMETACIN (A6)

Process offered:

C	:	subcontracting from outside India (no comments on the starting material and process)
CL	:	0
I	:	N-methoxyphenyl-2-formylhydrazin (7) *
S	:	0 (S_C offered from p-Anisidin (1))
V	:	N-p-chlorbenzoyl-N-p-methoxyphenyl-hydrazin (4)

All offers with poor process description

Standard Synthesis: according to the reaction scheme - methode A or B

Proposed Starting Material: p-anisidin (1) because of better availibility.

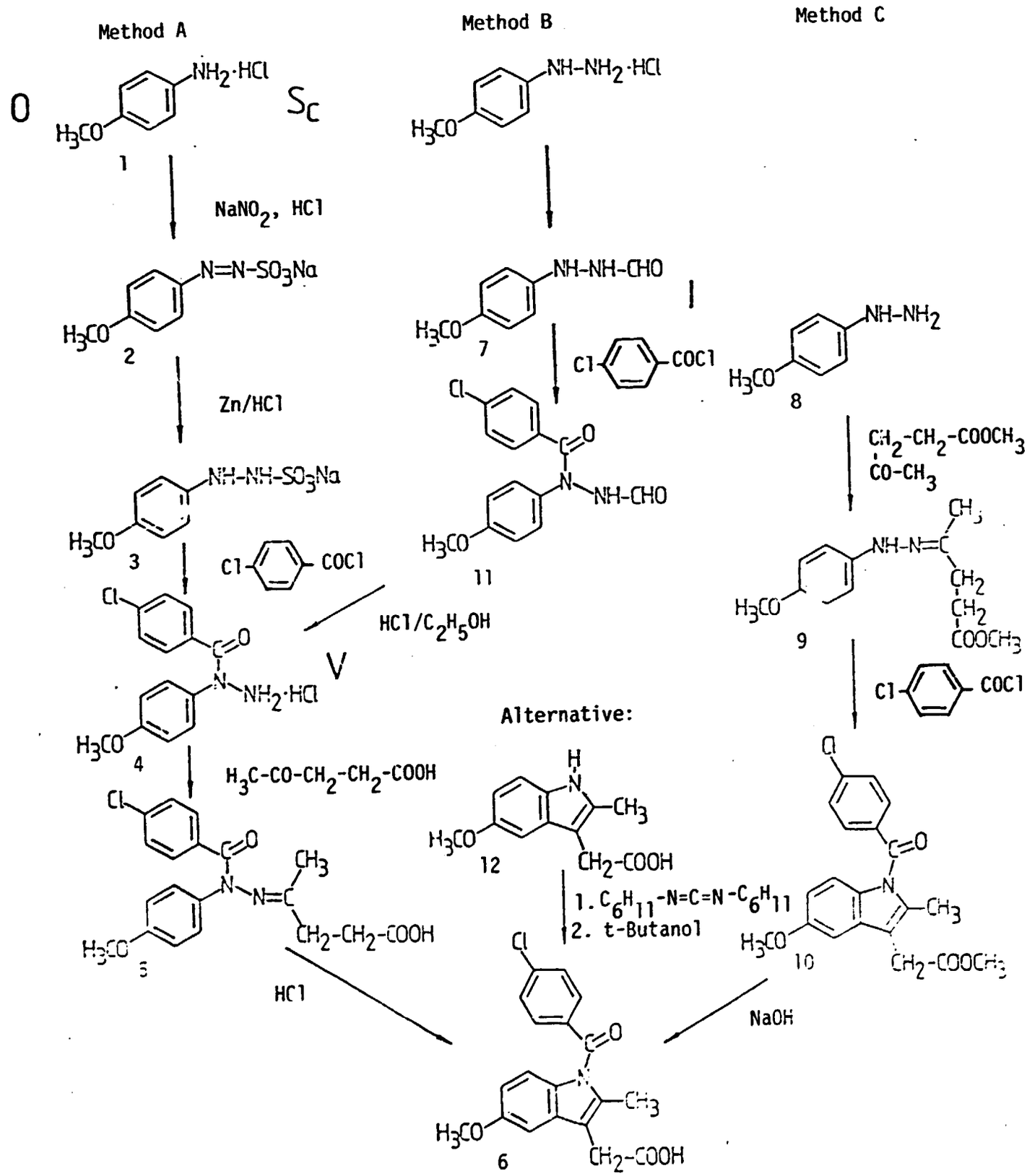
Evaluation: both offers start from late intermediates leading on the same way to Indometacin (6). The most interesting synthesis method C was not chosen by anyone (Sumitomo process) starting via (8).

Technological value: all synthesis are of high technological value with the background of Fischer's indole condensation.

* was later changed to p-Anisidin (1)

A6

INDOMETACIN



3.4.2.7. MEBENDAZOLE (A7)

Process offered:

C	:	3,4-Diaminobenzophenone (5)
CL	:	0
I	:	0
S	:	p-Chlorbenzoic Acid (1)
V	:	0

No offer with process description.

Standard Synthesis: according to the reaction scheme from 3,4-Diaminobenzophenone (5) and S-Methylisothioureasulfat (6) and Methylchloroformate (7).

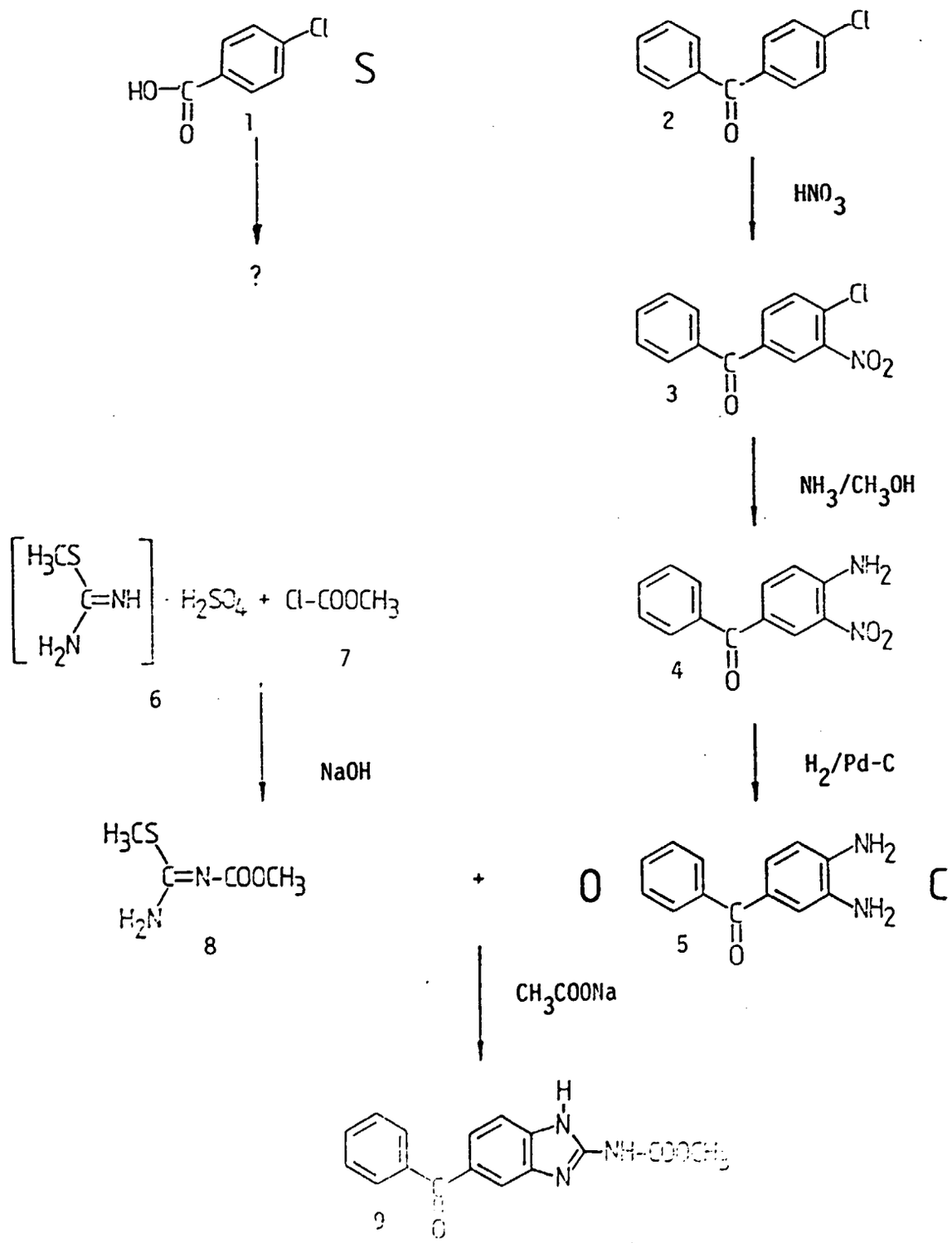
Proposed Starting Material: according to the standard synthesis.

Evaluation: impossibale because of no informations from [illegible]rs. SARABHAI: very early intermediate (way of [illegible]is not indicated).

Technological value: a lot of similar substances may be obtained by this basic scheme of benzylimidazol synthesis such as Lobendazol, Albendazol, Oxibendazol etc..

A7

MEBENDAZOLE



3.4.2.8. NALIDIXIC ACID (A8)

Process offered:

C	:	subcontracting from India (no comments on starting material)
CL	:	0
I	:	0
S	:	0 (S_C from 2-Amino-6-methylpyridine (1))
V	:	recrystallisation from Nalidixic Acid

the only offer from VEGYTERV contains the recrystallisation from Nalidixic Acid.

Standard Synthesis: according to the reaction scheme from 2-Amino-6-methylpyridin (1).

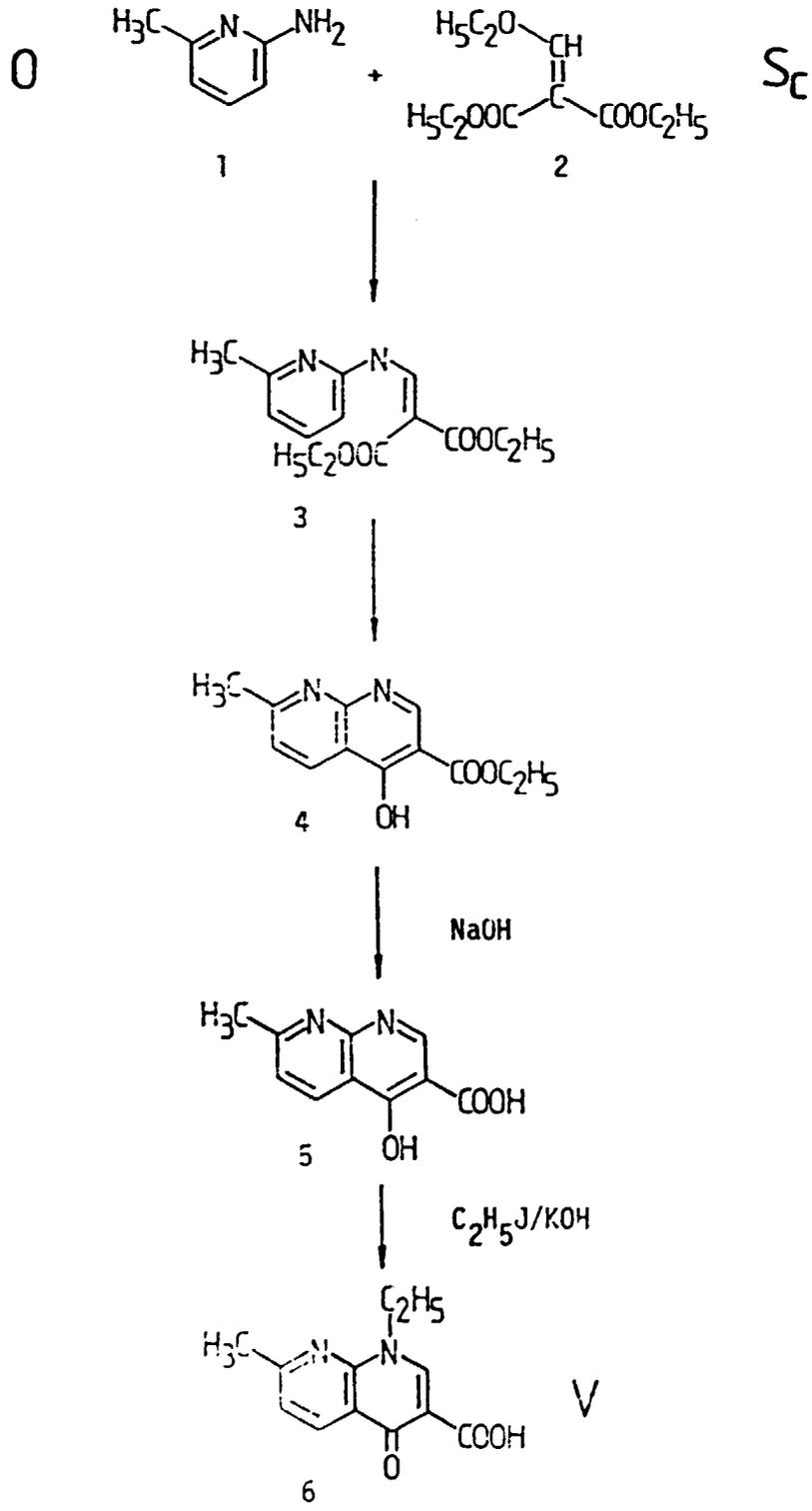
Proposed Starting Material: 2-Amino-6-methylpyridin (1).

Evaluation: no offer for standard synthesis.
SARABHAI offered this synthesis in the Cuba plant.
VEGYTERV indicates that production requires the use of aspecial manufacturing equipment.

Technological value: cyclisation at high temperature (250° C) and ,acuumdistillation.

AS

NALIDIXIC ACID



3.4.2.9. NICOTINAMIDE (A9)

Process offered:

C	:	3-Cyanopyridine (2) (no processdescription)
Cl	:	0
I	:	Nicotinic Acid (1)
S	:	3-Cyanopyridine (2) (no processdescription)
V	:	Nicotinic Acid (1)

All offers with poor or no processdescription.

Standard Synthesis: according to the reaction scheme from Nicotinic Acid (1) (method A) or 3-Cyanopyridine (2) (method B).

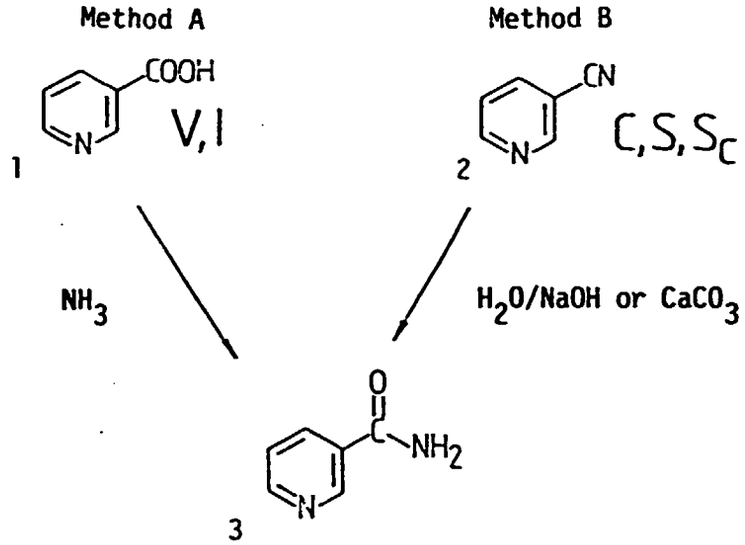
No proposal of the starting material.

Evaluation: all offers for starting material Nicotinic Acid (1) according to standard method A (200° C, feeding of liquid ammonia). SARABHAI offered for Cuba a quite interesting method B by hydrolysis using ion-exchange resins. Economic evaluation (yields, availability and price) will be the main criteria. Alternatively: recrystallisation of feed grade product.

Technological value: basic methods of unit processes

A9

NICOTINAMIDE



3.4.2.10. OXYPHENBUTAZONE (A10)

Process offered:

C	:	subcontracted from India (no starting material indicated, no process description)
CL	:	0
I	:	0
S	:	Phenol (4) (no process description)
V	:	4-Hydroxy-hydrazobenzene (1)

Poor process description from VEGYTERV.

Standard Synthesis: according to the reaction scheme from protected Aminophenol (5).

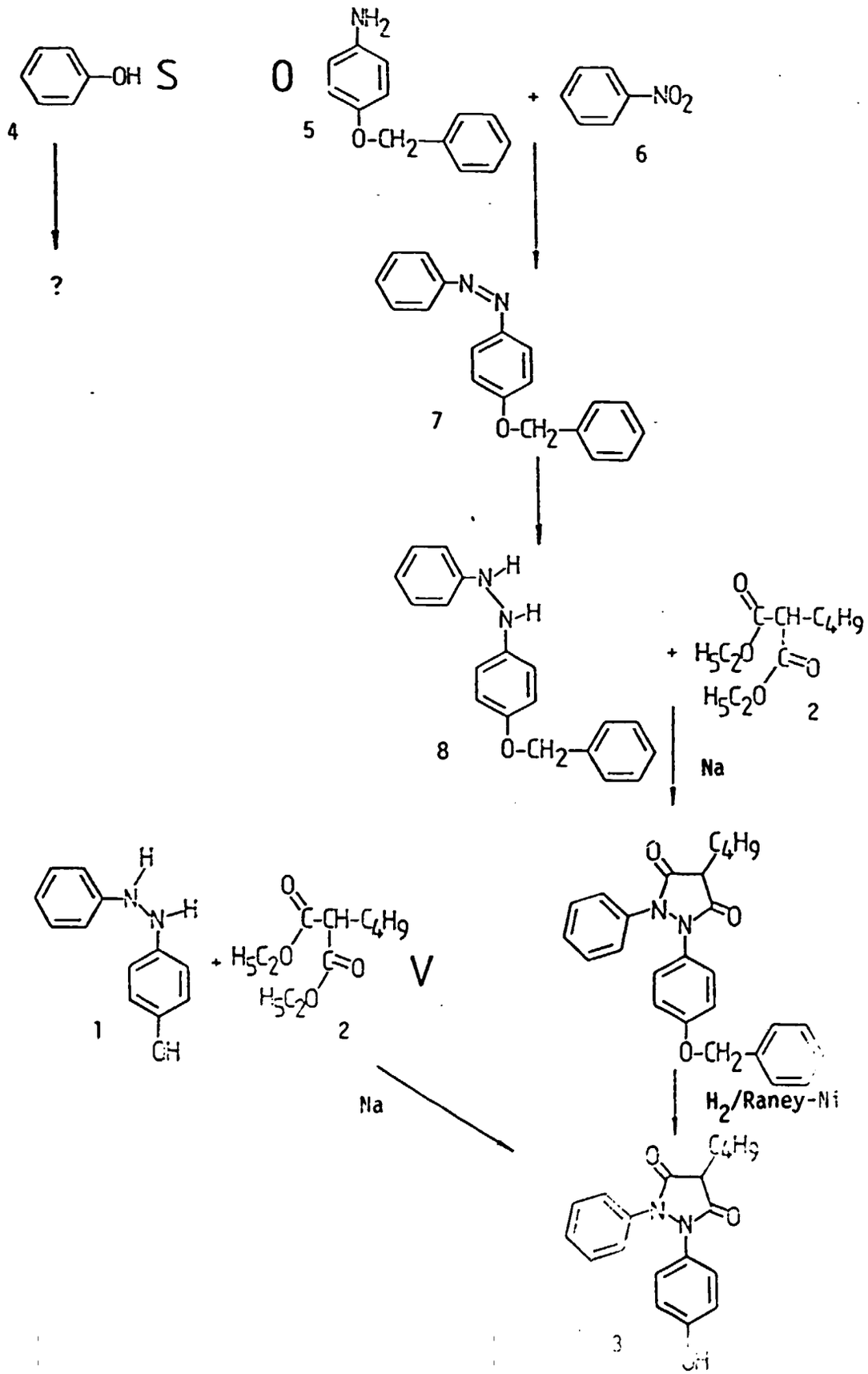
Proposed Starting Material: Benzyloxy or Acetyloxy-aminophenol.

Evaluation: no comment on the process starting from Phenol (4) Starting material 4-Hydroxy-hydrazobenzene (1) seems to be not the optimum synthesis because of the highly sensitive hydroxy groups that usually have to be protected (benzyloxy groups have to be removed be Raney/H_2).

Technological value: a variety of basic synthetic methods very useful also for synthesis of other substances such as Phenylbutazone and Ketophenylbutazone

A10

OXYPHENBUTAZONE



3.4.2.11. PARACETAMOL (A11)

Process offered:

C	:	subcontracting from India (no starting material indecated, no process description).
CL	:	0
I	:	p-Aminophenol (2)
S	:	p-Aminophenol (2)
V	:	p-Aminophenol (2)

All offers with poor or no process description.

Standard Synthesis: according to the reaction scheme from p-Aminophenol (2).

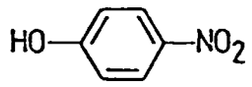
Proposed Starting Material: p-Aminophenol (2).

Evaluation: all offers are according to the standard method.

Technological value: standard easy one step unit process

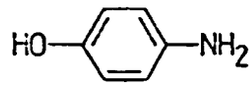
All

PARACETAMOL



1

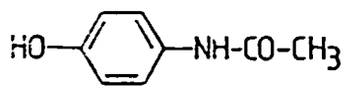
H_2/Raney-Ni

0 

V,I,S,S_C

2

$(H_3C\text{-}CO)_2O$



3

3.4.2.12. PROCAINE HYDROCHLORIDE (A12)

Process offered:

C	:	subcontracting from India (no starting material indicated)
CL	:	0
I	:	0
S	:	Benzocaine (1)
V	:	Benzocaine (1)

All offers with poor or no process description.

Standard Synthesis: according to the reaction scheme methode A from Benzocaine (1).

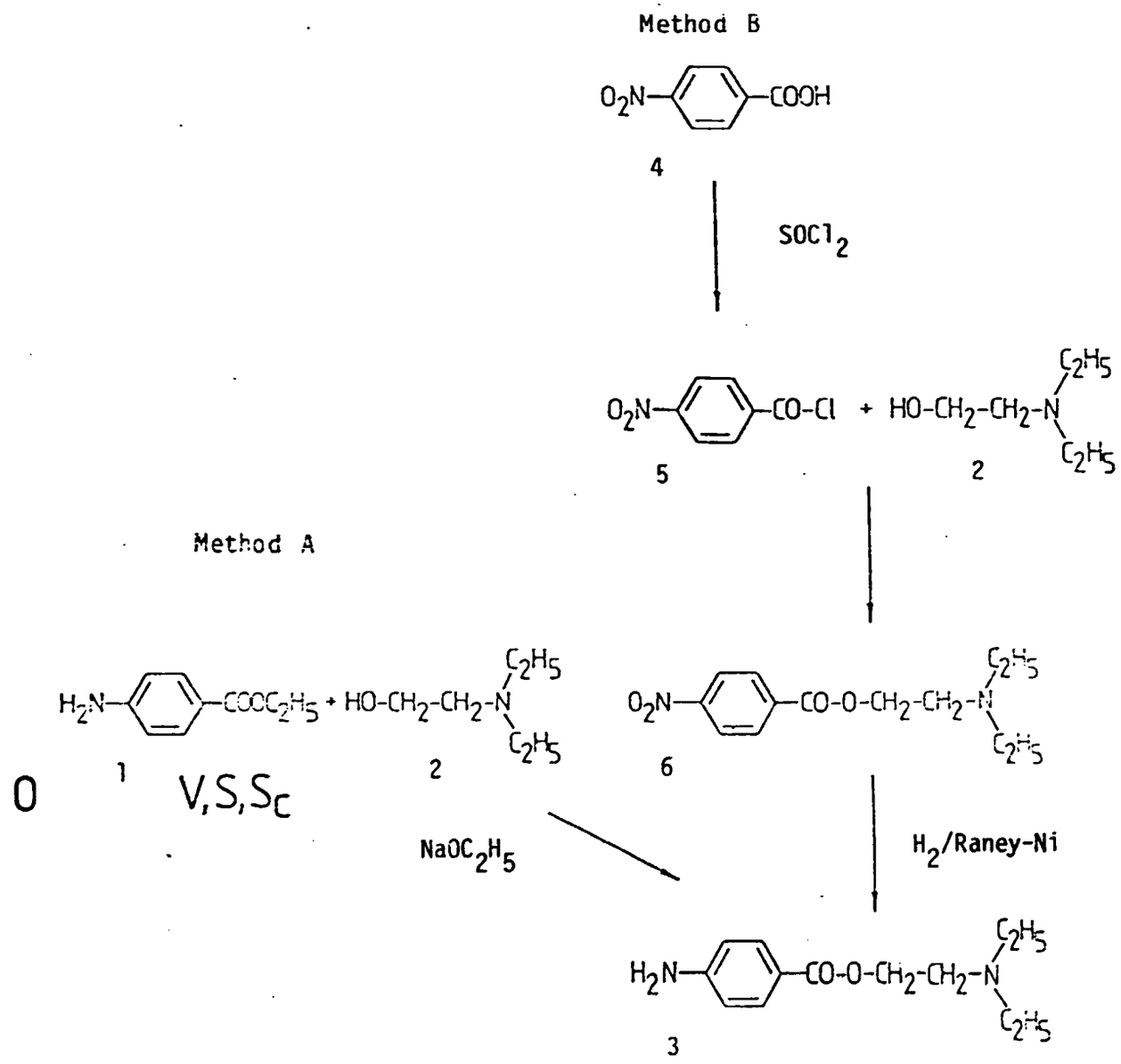
Proposed Starting material: Benzocaine (1).

Evaluation: all offers according to the standard synthesis. The alternative method B requires a Raney-Ni/ H_2 reduction and should be considered although starting from more basic raw materials.

Technological value: a commonly used preparation method for transesterification.

A12

PROCAINE HCl



3.4.2.13. PROPRANOLOL (A13)

Process offered:

C	:	1-Naphtol (1)
CL	:	1-Naphtol (1)
I	:	1-Naphtol (1)
S	:	1-Naphtol (1)
V	:	1-Chlor-1-naphtoxy-2-propanol (3)

All offers with poor or no process description.

Standard Synthesis: according to the reaction scheme from 1-Naphtol (1).

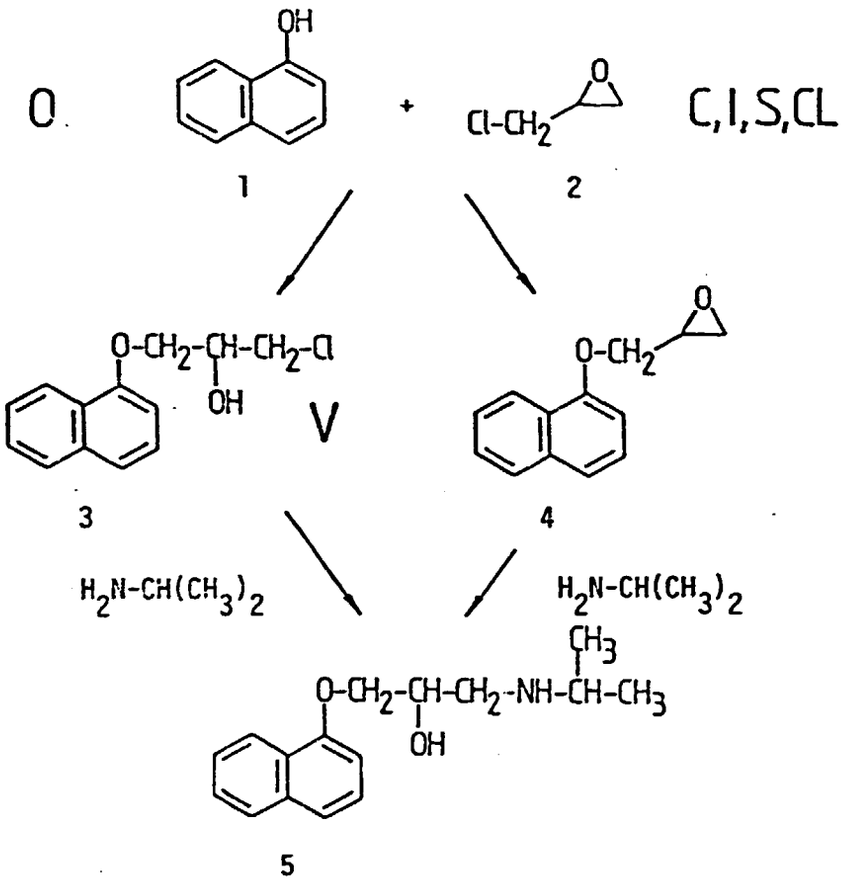
Proposed Starting material: 1-Naphtol (1)

Evaluation: VEGYTERV starts with a rather late intermediate (3). All other offers are according to the standard synthesis.

Technological value: two very commonly used unit processes (Amination, Ether formation)

A13

PROPRANOLOL



3.4.2.14. DIPHENYLHYDANTOIN (B1)

Process offered:

C	:	Benzaldehyd (1) (without process description)
CL	:	0
I	:	Benzoin (2) *)
S	:	Benzil (3)
V	:	Benzil (3)

All offers with poor process description.

Standard synthesis : according to the reaction scheme from Benzaldehyd (1) method A.

Proposed Starting Material : Benzaldehyd (1).

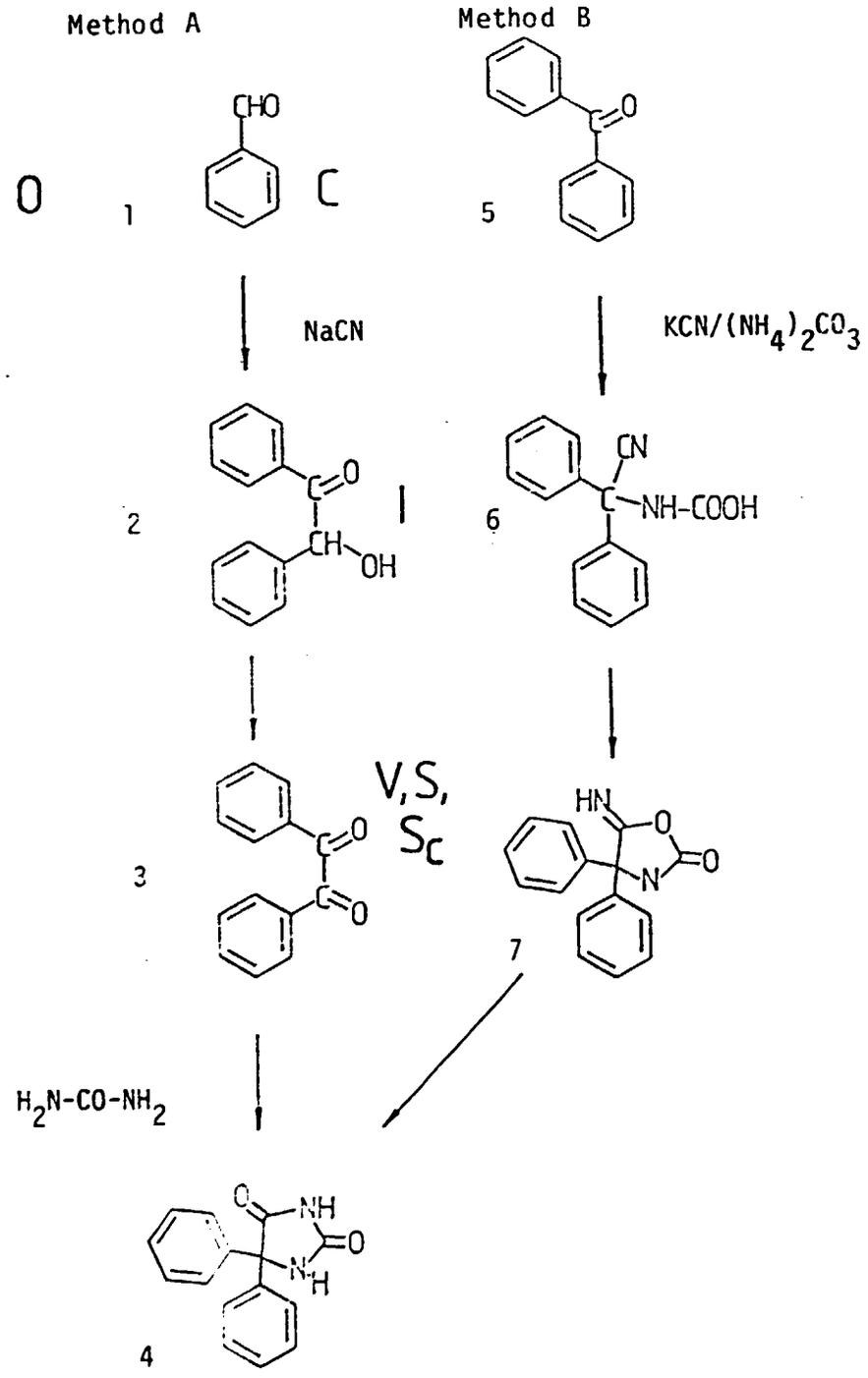
Evaluation : all offers are according to the standard synthesis method A. Just starting from three different intermediates.

Technological value: all processes ara standard reactions without any difficult unit processes.
Interesting unit processes can be seen from Method B from (5).

*) (offer was changed later
-starting from Benzaldehyde)

B1

DIPHENYLHYDANTOIN



3.4.2.15. ISONIAZID (B2)

Process offered:

C	:	4-cyanopyridine (2) (without process description)
CL	:	0
I	:	Isonicotinic Acid (1)
S	:	Isonicotinic Acid (1)
V	:	Isonicotinic Acid-ethyl ester (3)

All offers with poor process description

Standard Synthesis: according to the reaction scheme, starting from (1), (2) or (3).

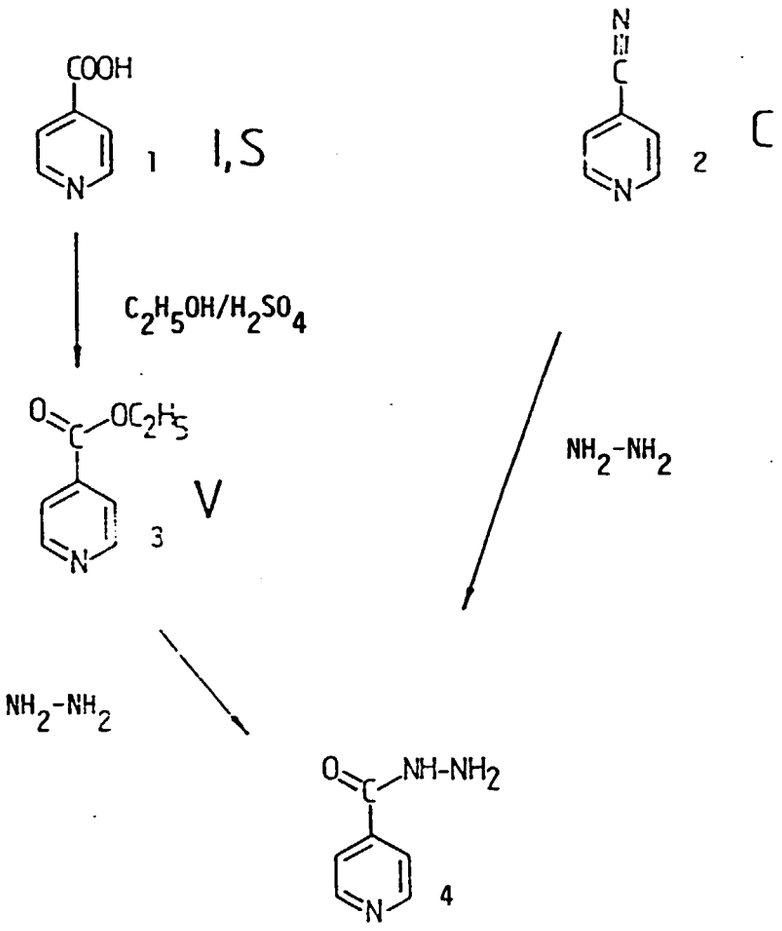
No proposal for starting material.

Evaluation: all offers according to one of the standard methods. All methods are 1 step reactions. Also (1) can be directly condensed with Hydrazin. The main question would be the economic evaluation (yields, availibility and prices) for the raw materials.

Technological value: basical methodes of condensation reactions of hydrazin with substituted pyridins.

B2

ISONIAZID



3.4.2.16. LIDOCAINE HYDROCHLORIDE (B3)

Process offered:

C	:	subcontracting from India not giving starting material
CL	:	0
I	:	Xilin = Lidocaine base (3) *)
S	:	2,6-Xylidine (1)
V	:	2,6-Xylidine (1)

All offers with poor process description.

Standard Synthesis: according to the reaction scheme from 2,6-Xylidine (1).

Proposed Starting Material: 2,6 Xylidine (1)

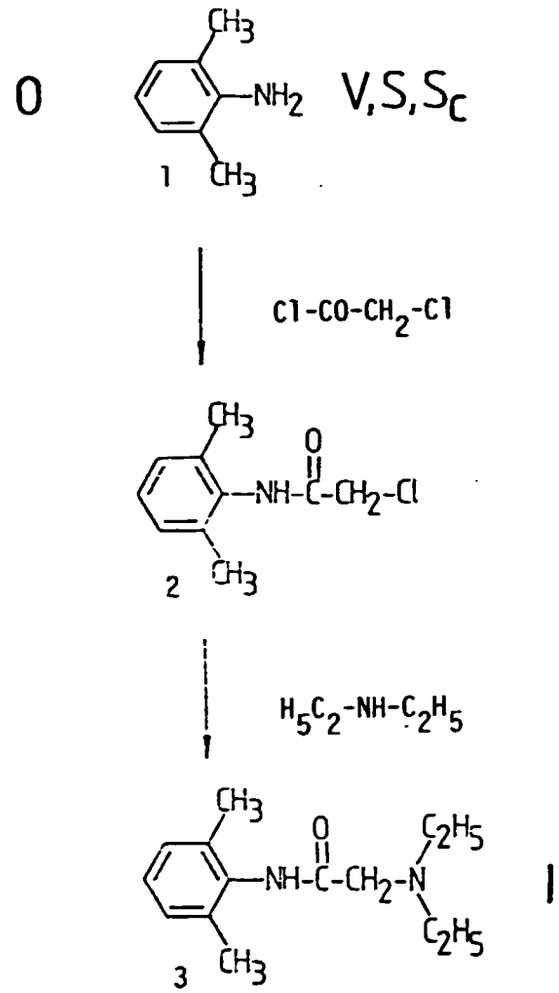
Evaluation: all offers are according to the standard synthesis

Technological value: the reactions in process are standard. For purification of the lidocaine base a high vacuum distillation is necessary. In similar reactions other local anesthetic substances may be obtained.

*) Offer was changed later - starting from 2,6-Xylidine

B3

LIDOCAINE HCl



3.4.2.17. NIACIN (B4)

Process offered:

C	:	3-Cyanopyridine (1) (without process-description)
CL	:	0
I	:	recrystallisation from feed grade (4)
S	:	3-Cyanopridine (1)
V	:	ß-Picolin (2)

All offers with poor process description.

Standard Synthesis: according to the reaction scheme from (1), (2) or (3).

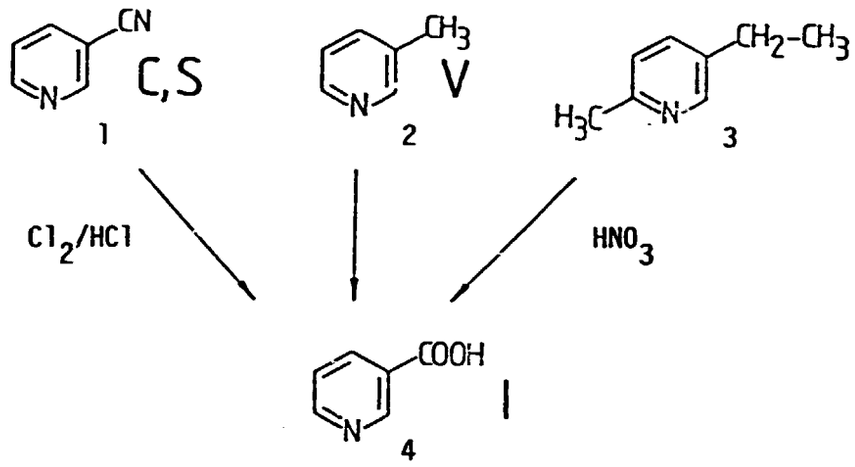
No proposal of starting material.

Evaluation: all offers according to one of the standard synthesis. All methods are 1 step reactions. The main question would be the economic evaluation (yields, availibility and price) for the raw-materials. No offered synthesis from MEP (3) with certainly good economic value. Also economic: recrystallisation from feed grade.

Technological value: basic oxidation and hydrolysis reactions.

B4

NIACIN



3.4.2.18. NIKETHAMIDE (B5)

Process offered:

C	:	Nicotinic Acid (1)
CL	:	0
I	:	0
S	:	Nicotinic Acid (1)
V	:	Nicotinic Acid (1)

Only VEGYTERV gave process description.

Standard Synthesis: according to the reaction scheme from Nicotinic Acid (1).

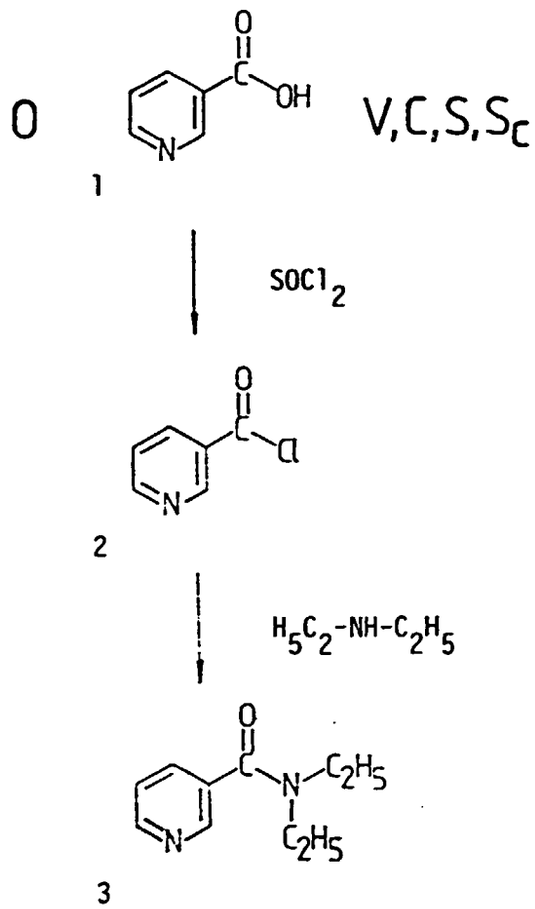
Proposed Starting Material: Nicotinic Acid (1).

Evaluation: all offers according to the standard synthesis.

Thechnological value: 2 very common synthetic methods leading to carboxylic acid-chlorides and amides.

B5

NICETHAMIDE



3.4.2.19. METRONIDAZOLE (C1)

Process offered:

C	:	subcontracted from India (no comments on starting material)
CL	:	0
I	:	0
S	:	offering without further comments
V	:	0

No process description is given.

Standard Synthesis: according to the reaction scheme from 2-Methylimidazole (1)

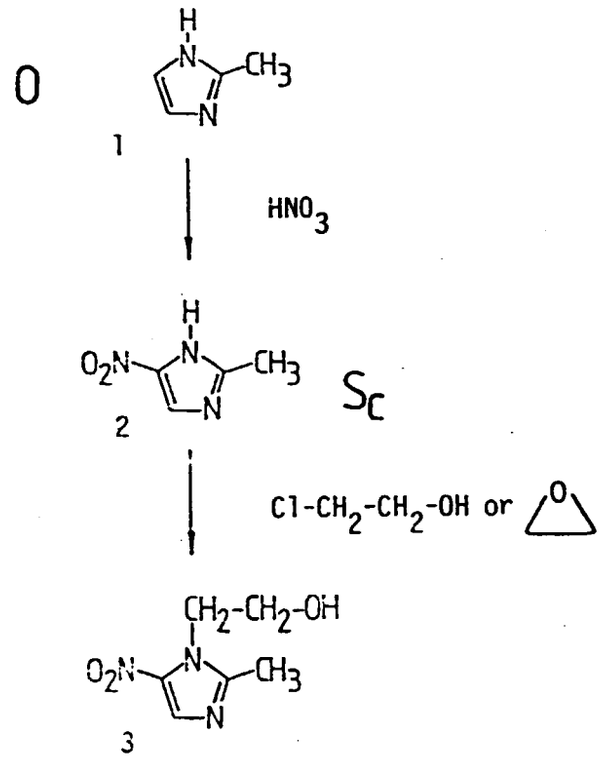
Poposed Starting Material: 2-Methylimidazole (1)

Evaluation: impossible
Sarabhai offered in Cuba starting from 2-Methyl-5-nitroimidazole (2).

Technological value: very useful synthetic methods (nitration, alkylation) commonly used.

C1

METRONIDAZOLE



3.4.2.20. SULFAMETHOXAZOLE (C2)

Process offered:

C	:	offered
CL	:	0
I	:	0
S	:	offered
V	:	0

All offers without process description.

Standard Synthesis: according to the reaction scheme from 3-Amino-5-methylisoxazole (2)

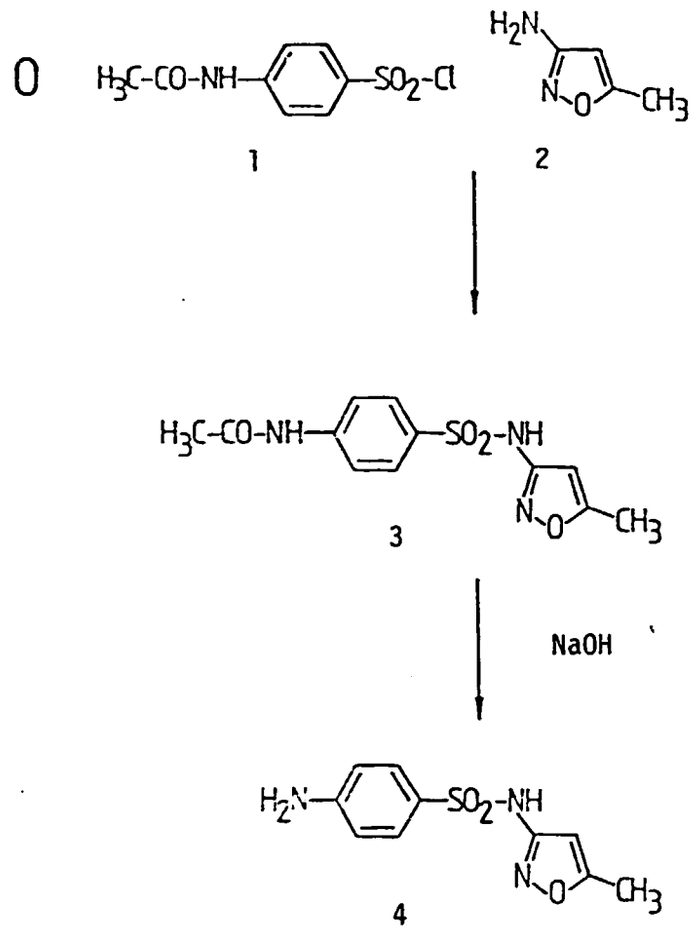
Proposed Starting Material: 3-Amino-5-methylisoxazole (2) + N-Acetyl-p-aminobenzenesulfonyl-chloride (1)

Evaluation: impossible

Technological value: a various number of sulfonamides may be prepared by this type of reaction.

C2

SULFAMETHOXAZOLE



3.4.2.21. TRIMETHOPRIM (C3)

Process offered:

C	:	offered
CL	.	0
I	:	0
S	:	offered
V	:	0

All offers without process description.

Standard Synthesis: according to the reaction scheme from 3,4,5-Trimethoxybenzaldehyde (1)

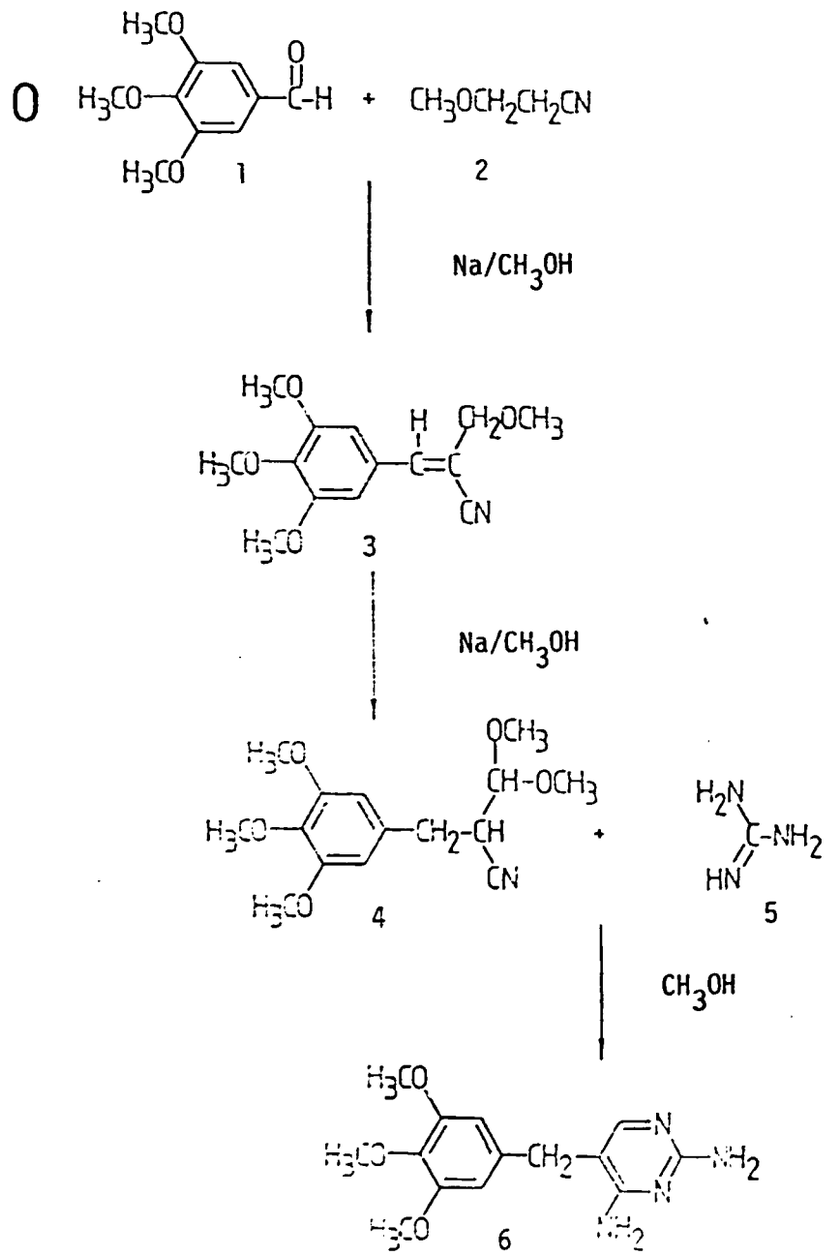
Proposed Starting Material: 3,4,5-Trimethoxybenzaldehyde (1) and ß-Methoxypropionitrile (2)

Evaluation: no comment

Technological value: modern types of unit processes

C3

TRIMETHOPRIM



3.4.3. COMMENTS ON COMPANY OFFERS

3.4.3.1. Cipla

The 9 technologies for which starting materials were given are corresponding to standard methods. No information concerning the rest of technologies could be obtained.

3.4.3.2. Chemie Linz

Only 2 technologies were offered: diazepam and propranolol. Both technologies correspond to standard processes.

3.4.3.3. Iprochim

Although this company was not to be considered for evaluation in this report the technologies were analysed. Out of 21 technologies 13 had been offered, all of them corresponding to standard processes, with exception of indometacin which uses N-methoxyphenyl-2-formylhydrazine as starting material. From the economic view an interesting proposal seems to be the recrystallisation of nicotinic acid from feed grade product. Furthermore Iprochim is the only company which gave a detailed offer for chlordiazepoxide.

3.4.3.4. Sarabhai and Sarabhai-Cuba

In principle the offer of Sarabhai supplemented by some

of the technologies from the Cuba project would have been the most complete offer concerning technologies. However on June 21st,1985 a telex was received indicating that technologies for chlordiazepoxid, diazepam, indometacin and nalidixic acid could not be provided for Iran, which seems disappointing especially with the technologies for chlordiazepoxide and nalidixid acid, which both had been rated best in their respective process analysis.

On the other hand it was indicated that technology for metronidazole, sulfamethoxazole and trimethoprim could be supplied, further details were however not indicated. The technologies offered were in good relation to standard methods, the starting materials for 3 of the products however seems to be very basic:

o-chlorobenzoic acid	for	clotrimazole
p-chlorobenzoic acid	for	mebendazole
phenol	for	oxyphenbutazone

3.4.3.5. Vegyterv/Chemokomplex

Two products, piperascat and trimetozine, which were offered instead of chlordiazepoxide and mebendazole were not evaluated.

Out of the remaining 16 technologies 15 are related to standard methods, although for the following compounds only last step technologies and in one case (nalidixic acid) only recrystallisation of the endproduct are given:

Clofibrate
Clotrimazole

Indometacin
Nalidixic acid
Propranolol

since some of these last but one step intermediates are not available on the international market these products should be manufactured from earlier intermediates.

The synthesis given for oxyphenbutazone from 4-hydroxyhydrazobenzene seems to be problematic because of very instable and sensitive intermediates due to the unprotected hydroxy group . All standard processes including a Hungarian patent (appendix P10) use protected hydroxyl groups.
In a series of cases the technologies offered by Vegyterv/Chemokomplex and Sarabhai are completely identical.

3.5. ECONOMIC EVALUATION OF PRODUCTS

3.5.1. GENERAL CONSIDERATION

An economic evaluation of the products can at present only be tentative for the following reasons.

There is until now not very much information concerning yield of the reaction steps of the various technologies offered.

Often neither consumption factors of raw materials nor of solvents are given.

The analyses were carried out as follows:

Prices for raw materials and endproducts were required directly from the supplyers and the economic input - output ratio was evaluated.

In cases where it seemed economically feasible rather early starting materials were chosen considering that besides economic aspects mainly know how should be transfered.

To obtain a more detailed analysis all materials and solvents should be also considered.

A detailed analysis of market prices for the raw materials and intermediates could not be finished within the short time given for this report. Upon request such a study could also be carried out.

3.5.2. MARKET PRICES OF END PRODUCTS

A revised list of world market prices (May/June 1985) of the end products was worked out in detail with each price checked several times.

Product		t/y	Price/ kg
Chlordiazepoxide	A1	1,5	55 US$
Clofibrate	A2	3,0	10 US$
Clotrimazole	A3	2,0	70 US$
Diazepam	A4	2,0	32 US$
Ethambutol	A5	10,0	40 US$
Indomet	A6	2,0	32 US$
Mebendazole	A7	3,0	40 US$
Nalidixi c Acid	A8	7,0	50 US$
Nicotinamide	A9	15,0	5,7 US$
Oxyphenbutazone	A10	10,0	35 US$
Paracetamol	A11	20,0	5 US$
Procaine Hydrochlorid	A12	8,0	8 US$
Propranolol	A13	2,0	16 US$
Diphenylhydantoin	B1	4,0	15 US$
Isoniazid	B2	5,0	10 US$
Lidocaine Hydrochlorid	B3	2,0	14 US$
Niacin	B4	15,0	5,5 US$
Nikethamide	B5	1,0	15 US$
Metronidazole	C1	7,0	20 US$
Sulfamethoxazole	C2	10,0	25 US$
Trimethoprim	C3	13,0	40 US$

The prices indicated by CIPLA for 4 of the products in their offer seem to be extremely low and should be rechecked.

Chlordiazepoxide	30.-- US$
Lidocaine.HCl	10.-- US$
Mebendazole	30.-- US$
Oxyphenbutazone	15.-- US$

3.5.3 ECONOMIC EVALUATION BASED ON INPUT/OUTPUT

3.5.3.1 CHLORDIAZEPOXIDE A1

Price of Product : US $ 55.- / Kg
Price of raw material ACB : US $ 11.-
Specific consumption:

Sarabhai	2,0
Literature	2,0

Factor used: 2,0
Result : Input 22.- / Output 55.-

Alternative raw material (not in Offer) : CCB US $ 20,50

3.5.3.2 CLOFIBRATE A2

Price of Product : US $ 10.- / Kg
Price of raw material p-Chlorophenol : US $ 3,30
Specific consumption:

Iprochim	1,25
Cipla	1,4
Sarabhai	1,0

Factor used : 1,3
Result : Input 4,30 / Output 10.-

Price of raw material Clofibrinic Acid :
Specific consumption:

Vegyterv	1,0

Factor used : 1,0
Result :

3.5.3.3 CLOTRIMAZOL A3

Price of Product: US $ 70.- / KG
Price of raw material O-Chlorobenzotrichlorid : US $ 2,70
Specific consumption:

Literature : 1,3
Literature : 1,6

Factor used: 1,6
Result : Input 4,32 / Output 70.-

(Not considered other raw materials)

3.5.3.4 DIAZEPAM

Price of Product : US $ 32.- / KG
Price of raw material MCB : US $ 20.-
Specific consumption:

Chemie Linz : 1,5
Sarabhai Cuba: 1,8
Literature: 1,5

Factor used: 1,5
Result: Input 30.- / Output 32.-

Price of raw material CMCB. : US $ 20.-
Specific consumption:

Literature : 1,5

Factor used: 1,5
Result: Input 30 / Output 32

3.5.3.5 ETHAMBUTOL A5

Price of Product: US $ 40.- / KG

Price of raw material D-2-Aminobutanol: US $ 33.-

Specific consumption:

Iprochim: 2,2

Literatur: 2,4

Factor used: 2,3

Result: Input 75.- / Output 40.-

Price situation still under Evaluation.

3.5.3.6 INDOMETHAZIN A6

Price of Product: US $ 32.- / KG

Price of raw material p-Anisidin: US $ 3,80

Specific consumption:

Sarabhai : 1,2

Factor used: 1,2

Result: Input 4,60 / Output 32.-

No other raw materials calculated.

Price of raw material N-P-Chlorobenzoyl -
N-P-Methoxyphenylhydrazin: US $ 24.-

Specific consumption:

Literature: 2,0

Factor used: 2,0

Result: Input 48.- | Output 32.-

3.5.3.7 MEBENDAZOLE A7

Price of Product: US $ 40.- | KG
Price of raw material 3,4 - Diaminobenzophenon: US $ 22,50|KG
Specific consumption:

None given by companies
Not clear from Cipla
None from Literature

Factor used: -
Result: -

3.5.3.8 NALIDIXIC ACID A8

Price of Product: US $ 50.- / KG
Price of raw material 2-Amino-6-Methylpyridine: -
Specific consumption:

Sarabhai : 1,6

Factor used: -
Result: -

3.5.3.9 NICOTINAMIDE A9

Price of Product: US $ 5,70 / KG
Price of raw material 3-Cyanopyridine : US $ 6,25
Specific consumption:

Cipla : 1,2
Sarabhai: 1,38

Factor used: 1,25
Result: Input 7,80 / Output 5,70

Price of raw material Nicotinic Acid Feed Grade: US $ 3,90
Specific consumption:

Iprochim: 1,88

Factor used: 1,88
Result : Input 7,33 / Output 5,7
Not offered: Price of Nicotinamide Feed Grade: US $ 4.-
Specific consumption : 1,2

3.5.3.10 OXYPHENBUTAZONE A10

Price of Product : US $ 35.- / KG
Price of raw material p-Aminophenol : US $ 4,20 / KG
Specific consumption: None given

Price of raw material Diethyl-N-Butylmalonate: US $ 7,75/KG
Specific consumption: None given

3.5.3.11 PARACETAMOL A11

Price of Product : US $ 5.- | KG
Price of raw material p-Aminophenol : US $ 4,20 | KG
Specific consumption:

Sarabhai : 1,0
Iprochim : 1,35

Factor used: 1,0
Result: Input 5.- | Output 5.-

Including solvents and acetic an hydride.

3.5.3.12 PROCAINE A12

Price of Product : US $ 8.- | KG
Price of raw material Benzocaine : US $ 10,7 | KG
Specific consumption:

Sarabhai : 1,17

Factor used: 1,17
Result: Input 12,1 | Output 8

3.5.3.13 PROPRANOLOL A 13

Price of Product : US $ 16.-|KG
Price of raw material ∝-Naphtol: US $ 7.- | KG
Specific consumption:

Cipla : 1,10
Iprochim: 1,45
Chemie Linz: 0,8

Factor used: 1,0
Result: Input 7.- | Output 16.-

3.5.3.14 DIPHENYLHYDANTOIN B1

Price of Product : US $ 15.-| KG
Price of raw material Benzoine : US $ 3.90|KG
Specific consumption:

Iprochim : 1,14

Factor used: 1,14
Result : Input 4,45 | Output 15.-

Price of raw material Benzil: -
Specific consumption: Sarabhai : 1,17
Factor used: -
Result: Input - | Output -

Price of raw material Benzaldehyde : US $ 1,60
Specific consumption: Cipla : 1,73
Factor used: 1, 75
Result : Input 2,80 | Output 15.-

3.5.3.15 ISONIAZID B2

Price of Product: US $ 10.- | KG
Price of raw material 4-Cyanopyridin: -
Specific consumption:

Cipla : 1,11

Factor used: -
Result : Input - | Output -

Price of raw material Isonicotinic Acid : US $ 11.- | KG
Specific consumption:

Iprochim : 1,35

Factor used: 1,35
Result: Input 14,85 | Output 10.-

Price of raw material Isonicotinic Acid Ethylester : -
Specific consumption:

Vegyterv : -

Factor used: -
Result: Input - | Output -

3.5.3.16 LIDOCAINE HCl B3

Price of Product : US $ 14.- | KG
Price of raw material 2,6 Xylidin: -
Specific consumption:

Sarabhai : 1,56

Factor used: -
Result: Input - | Output -

3.5.3.17 NIACIN B4

Price of Produkt : US $ 5,50 |KG
Price of raw material 3-Cyanopyridin : US $ 6,25
Specific consumption:

Cipla : 0.95

Factor used: 0.95
Result: Input 5,95 | Output 5,50

Price of raw material Niacin Feed Grade: US $ 3.90|KG
Specific consumption:

Iprochim : 1,20

Factor used: 1,20
Result: Input 4,7 | Output 5,5

Price of raw material ß-Picolin : -
Specific consumption:

Vegyterv : -

Factor used: -
Result: Input - | Output -

Price of raw material 5-Ethyl-2-Methyl-Pyridin: -
Specific consumption:

Nobel : 1,8

Factor used: 1,8
Result : Input - | Output -

3.5.3.18 NIKETHAMIDE B5

Price of Product: US $ 15.- | KG
Price of raw material Nicotinic Acid : US $ 3,9 | KG
Specific consumption:

Cipla : 0,63
Sarabhai: 0,9

Factor used: 0,9
Result: Input 3,50 | Output 15.-

3.5.3.19 METRONIDAZOLE C1

Price of Product : US $ 20.- |KG
Price of raw material 2-Methyl-5-Nitroimidazol: -
Specific consumption:

Sarabhai|Cuba: 1,15

Factor used: 1,15
Result: Input - | Output -

No Prices for 2-Methylimidazole.

3.5.3.20 SULFAMETHOXAZOLE C2

Price of Product : US $ 25.- / Kg
Price of raw material N-Acetyl-p-Amino-Benzene Sulfurylchloride:-
+5-Methyl-3-Amino-Isoxazol : US $ 41.-
Specific consumption:

Literature : 1,33 + 0,6

Factor used: 1,33 + 0,6
Result : Input - / Output -

3.5.3.21 TRIMETHOPRIM C3

Price of Product : US $ 40.- / Kg

Price of raw material 3,4,5-Trimethoxybenzaldehyd : -

ß-Methoxypropionitrile : US $ 1,90 / Kg

Specific consumption:

Literature : 1,4 + 0,7

Factor used: 1,4 + 0,7

Result : Input - / Output -

3.5.4. COMPARATIVE SUMMARY OF THE ECONOMIC EVALUATION

As stated in 3.1. process data for evaluation were far from complete, new data especially concerning material prices are still coming in and have been taken into account until the date of typing the report.

The products were divided into three groups:

3.5.4.1. PRODUCTS WITH ECONOMICALLY GOOD INPUT/OUTPUT RATIO

Chlordiazepoxide (A1)	from ACB
Clofibrate (A2)	from p-chlorophenol
Clotrimazole (A3)	from o-chlorobenzotrichloride
Diphenylhydantoin (B1)	from benzaldehyde
Indometacin (A6)	from p-anisidine
Niazin (B4)	from feed grade
Nikethamide (B5)	from nicotinic acid
Oxyphenbutazone (A10)	from p-aminophenol
Propranolol (A13)	from naphthol

3.5.4.2. PRODUCTS WITH ECONOMICALLY POOR INPUT/OUTPUT RATIO

Diazepam (A4)	from MCB
Paracetamol (A11)	from p-aminophenol

3.5.4.3. PRODUCTS WITH UNCERTAIN OR RATHER UNECONOMIC INPUT/OUTPUT RATIO

Ethambutol (A5)	from D-2-aminobutanol

Mebendazole (A7)	from 3,4-diaminobenzophenone
Nalidixic Acid (A8)	from 2-amino-6-methylpyridine
Nicotinamide (A9)	from 3-cyanopyridine
Procaine.HCl (A12)	from benzocaine
Isoniazid (B2)	from isonicotinic acid
Lidocaine.HCl (B3)	from 2,6-xylidine
Metronidazole (C1)	from methylimidazole
Sulfamethoxazole (C2)	from N-acetyl-p-aminobenzenesulfonylchloride
Trimethoprim (C3)	from 3,4,5-trimethoxybenzaldehyde

3.6. UNIT PROCESSES FORESEEN IN THE OFFERED TECHNOLOGIES

3.6.1. GENERAL CONSIDERATIONS AND RESULTS

All reactions steps which are discussed in the report were analysed with respect of the type of organic reaction applied. Reactions of similar type were listed together. Reaction steps mentioned in each of the offers as well as reaction steps of the "optimum" technology were marked in that list to check the versatility of reactions applied (appendix). The rather great versatility of tne unit processes can be seen from the list given for "optimum" combination of technology. It can be stated that most types of organic reaction are represented. Among the most important general types of organic reaction e. g. catalytic hydrogenation and reactions with organometallic compounds are missing in the offers.

3.6.2.

REACTIONS OF THE "OPTIMUM" COMBINATION OF TECHNOLOGIES

1. Aromatic Reactions

Friedel-Crafts acylation	
Friedel-Crafts alkylation	A3
Nitration	C1
Nucleophilic aromatic substitution	
Diazotization	A6

2. Carbonyl Reactions

Oxime formation	A1
Schiff base formation	A6
Enamine formation	A8
Knoevenagel condensation	C3
Strecker synthesis	
Benzoin condensation	B1

3. Ring Closure Reactions

Via ester formation	
Via amide formation	A4
Via hydrazide formation	A10
Via Schiff base formation	A4 A7
Fischer indole synthesis	A6
Via electrophilic aromatic substitution	A8
Aminal type	A1
Via condensation	B1

4. Amine Reactions

S_n-type amine formation	A1 A3 A10 B3
Amine formation by epoxide ring opening	A13
N-Alkylation	A5 A8 C1
N-Acylation	A11 B3

N-Tosylation	
N-Detosylation	
N-Deformylation	
5. Carboxyl Reactions	
Ester formation	A2 A12
Ester hydrolysis	A8
Direct amide formation	
Amide formation via acid chloride	B5
Amide hydrolysis	C2
Pinner reaction	
Acid chloride formation	B5
Hydrazide formation	
Nitrile hydrolysis	
6. Sulfonamide formation	C2
7. Ether formation	
O-Alkylation	A13
Clofibric acid synthesis	A2
8. Oxidation	A1 B1
9. Reduction	A6 A10
10. Rearrangements	A1 B1
11. Radical Chlorination	A3
12. Miscellaneous	
Condensation	A13
Hydrogenolysis (Debenzylation)	A10
Addition (Michael type)	C3

3.7. PROPOSAL FOR "OPTIMUM" CHOICE OF TECHNOLOGY

As a result of the whole analysis of the technologies given under 3.1. - 3.6. a list of "optimum" choice of technologies was set up in which a classification was made of all products considering all the aspects mentioned before.

3.7.1. CRITERIA FOR SETTING UP THE LIST OF "OPTIMUM" TECHNOLOGIES

From the table enclosed the results of application of the following criteria can be seen:

1. The percentage of value of endproduct was calculated and divided through the percentage of tons produced to give a figure on economic relevance.

2. Technological aspects were evaluated for each product resulting in positive marks for interesting technologies.

3. Evaluation of yields

4. Availability of starting materials

5. Evaluation of prices of starting materials

Concerning 3.4. and 5. additional information coming in could produce an even more precise result.

	Product		Ton/Y	US $ Price/KG	1000 US $ Total Value	3) % of total value	4) % of total prod.Volume	5) % Value/ % Tons	6) economy factor	7) Prod. factor	8) Evaluation
1	CHLORDIAZEPOXIDE	A1	1,5	55.-	82,5	2,7	1,1	2,5	2	5	2
2	CLOFIBRATE	A2	3	10.-	30.-	1,0	2,1	0,5	2	5	13
3	CLOTRIMAZOL	A3	2	70.-	140.-	4,6	1,4	3,3	1	5	1
4	DIAZEPAM	A4	2	32.-	64.-	2,1	1,4	1,5	4	3	7
	DIPHENYLHYDANTOIN	B1	4	15.-	60.-	2,0	2,8	0,7	2	1	14
	ETHAMBUTOL	A5	10	40.-	400.-	13,2	7,0	1,9	5 ?	4	18
	INDOMETACIN	A6	2	32.-	64.-	2,1	1,4	1,5	2	5	8
8	ISONIAZID	B2	5	10.-	50.-	1,7	3,5	0,5	5	3	16
9	LIDOCAINE HCl	B3	2	14.-	28.-	0,9	1,4	0,6	?	4	15
10	MEBENDAZOLE	A7	3	40.-	120.-	4,0	2,1	1,9	3 ?	?	5
11	NALIDIXIC ACID	A8	7	50.-	350.-	11,6	4,9	2,4	?	2	3
12	NIACIN	B4	15	5,50	82,50	2,8	10,5	0,3	4	3	19
13	NIKETHAMIDE	B5	1	15.-	15.-	0,5	0,7	0,7	2	4	11
14	NICOTINAMIDE	A9	15	5,70	85,50	2,8	10,5	0,3	4	2	20
15	OXYPHENBUTAZONE	A10	10	35.-	350.-	11,6	7,0	1,7	4 ?	3	6
16	PARACETAMOL	A11	20	5.-	100.-	3,3	14,0	0,2	4	2	21
17	PROCAINE	A12	8	8.-	64.-	2,1	5,6	0,4	5 ?	2	17
18	PROPRANOLOL	A13	2	16.-	32.-	1,1	1,4	0,8	2	3	12
19	METRONIDAZOLE	C1	7	20.-	140.-	4,6	4,9	0,9	?	3	10
20	SULFAMETHOXAZOLE	C2	10	25.-	250.-	8,3	7,0	1,2	?	3	9
21	TRIMETHOPRIM	C3	13	40.-	520.-	17,2	9,1	1,9	?	3	4
			142,5		3.027,50	100.-	100.-				

1) Price on international Market

3) % of 3.027.500 US $

4) % of 142,5 tons

5) Relation produced margins and amounts

6) Factor for margin 1=very economic 5=not economic

7) Factor for 1=low level of 5=high level of unit processes

8) Rank of the optimum unit processes

3.7.2. LIST OF "OPTIMUM" CHOICE OF TECHNOLOGY

1.	Clotrimazole	A3
2.	Chlordiazepoxid	A1
3.	Nalidixic Acid	A8
4.	Trimethoprim	C3
5.	Mebendazole	A7
6.	Oxyphenbutazone	A10
7.	Diazepam	A4
8.	Indometacin	A6
9.	Sulfamethoxazole	C2
10.	Metronidazole	C1
11.	Nikethamide	B5
12.	Propranolol	A13
13.	Clofibrate	A2
14.	Diphenylhydantoin	B1
15.	Lidocaine.HCl	B3
16.	Isoniazid	B2
17.	Procain.HCl	A12
18.	Ethambutol	A5
19.	Niazin	B4
20.	Nicotinamide	A9
21.	Paracetamol	A11

3.7.3. RECOMMENDATIONS

1. Paracetamol is a low price product on the international market. A proposed production level of 20 tons would occupy a considerable part of the plant capacity without having significant value as far as the technological aspects are concerned. Even a production level of 20 tons would not satisfy a significant percentage of Iranian annual consumption which is 280 tons. Single line production might be envisaged.

2. Niazin and Nicotinamide are both used as a vitamin for exactly the same indication (Nicotinic acid is taken up into the enzyme systems only after amidation, the vasomotoric effect is a minor indication.)

   It seems recommendable only to recrystallize those compounds starting from feed grade quality (about US$ 4,0 - 4,2 / kg)

3. Ethambutol: Hitherto a source of supply for D-2-aminobutanol at reasonable prices has not yet been located. Unless in case of manufacture in very good yields production does not seem promising.

4. Procaine Hydrochloride is also a low price product with rather expensive starting materials.

Since also the technological value of these 5 compounds does not seem to be very high, it is recommended not to take into consideration their manufacture in the proposed production level. Instead a semi-pilot plant level of synthesis should be envisaged for above mentioned compounds to develop know how for their production in the own plant.

4. EQUIPMENT

Equipment is a decisive factor of the project not only for reason of cost but also with respect of appropriateness, capacity and quality.

4.1. TYPES OF EQUIPMENT - SURVEY

Since some offers were rather vague concerning types of equipment to be used in the project, the requirements of the multi purpose plant concerning equipment were analysed independently. Equipment was divided into the following 12 groups:

Reactors	E1
Condensers and other parts connected to reactors	E2
High vacuum distillation unit	E3
Extraction	E4
Pumps	E5
Centrifuges	E6
Filters	E7
Dryers	E8
Balances	E9
Tanks	E10
Environmental protection	E11
Utilities	E12

For each group a choice was made among the different types on the market. Since the choice of equipment to a certain degree also depends on subjective experience series of appendices was prepared in which the criteria for recommendations are explained. Since it was the wish of Iran representatives to receive equipment from the Western European market also information concerning equipment needed specifically for the project was requested directly from equipment manufacturers.

Since it may be expected that Indian and Hungarian companies will use equipment from their country, especially reactors, standard prices for reactors of Indian and Hungarian origin on the Western European market were assessed and used as basis in cost analysis when required.

The appendices cited above do not appear in part 3 of the final report (appendices) but are contained in part 2 (2nd report).

4.2. UNIT OPERATIONS

An analysis of the equipment needed for the intended production reveals that most of the unit operations required for production of pharmaceutical chemicals can be done with proposed equipment such as heating, cooling, stirring, distillation in vacuo, centrifugation, filtration, extraction, recrystallisation and drying. To have an almost optimum choice of unit operations avialable only high-pressure autoclave, units for low-temperature reactions and rectification columns are missing. Establishing these units in the standard scale of multi-purpose plant is very expensive. Nonetheless it is proposed to supply this equipment in a small scale. To ensure that the opportunity to use these unit operations in research and development is given. This refers especially the autoclave, since the analysis of the technologies to be established, in several cases revealed that in the process of development use of catalytic pressure hydrogenation might result in improved technologies.

4.3. TRANSLATION TO THE INDUSTRIAL SCALE

4.3.1. BACK INTEGRATION OF TECHNOLOGY

As mentioned before some of the technologies offered start from basic raw materials, some from early intermediates, some from later intermediates and there are even technologies offered which are only recrystallisation of the endproduct.

Success in transfer of technology is closely connected to the capability of back integrating production processes, this means that as a result of research and development synthesis can be carried out starting from earlier stages.

Considering that translating to industrial scale from semi-industrial scale requires that the scaling-up gap of this transfer is not too wide, back integration also means that sufficient production capacity is available, to produce the first step in a scale which ensures that the back integrated synthetic process is not carried out in a scale which is too small for translation to industrial scale.

For this reason it seems advisable to have reactors of sufficient capacity to ensure that future developments in the plant will enable back-integration of technology.

4.3.2. SCALING-UP IN A MULTI-PURPOSE PLANT

The main aim of transfer of know-how in a chemical pilot scale plant is connected with the knowledge of carrying out chemical reactions in increasing scale and learning how to cope with with the problems arising in this scale up. This is much more important than the know how of carrying out different chemical reactions in principle, because this know how is present at least in laboratory scale in universities practically all over the world. Transfer of know how of scaling up has to consider also aspects of economic production for one simple reason: even if investment cost for equipment is neglected scaling up soon arrives at production levels where each batch of reaction will cause very high costs of input of chemicals. This renders the approach of the present project very promising to consider also questions of economic production of pharmaceuticals.

The production capacities given in the terms of references and also the opportunity to back-integrate technology according to the analysis carried out can only be achieved in a reasonable manner if an upper level of reactor capacity of 3000 l is established in the plant. Since it is impossible to scale a reaction up to that scale from laboratory scale in one step, it is proposed to establish a scale of production levels, which furthermore would be of a very great help for research and development and also for trouble shooting. The level proposed for this scaling up are 10 liters (research and trouble shooting), 100 liters (development and production in glass equipment), 500 liters (semi pilot scale for development and production) and 1500 - 3000 liters (last step of scaling up and production). Equipment for each of the steps of the scale should ensure all operations from reacting to drying can be carried out in the largest scale.

Trouble shooting which is necessary in regular production should be carried out in the low scales in close cooperation with the analytical laboratory. The 100 liter scale would provide an opportunity to establish equipment for new unit operations, such as catalytic hydrogenation, low temperature reactions or rectification, at reasonable cost so that the scope of opportunities to carry out own research and development is cosiderable widened.

4.4. TECHNICAL ANALYSIS OF PROPOSED EQUIPMENT

4.4.1. EQUIPMENT ACCORDING TO TERMS OF REFERENCES

Since neither terms of references nor offers referring to equipment according to the terms indicate detailed specifications this analysis cannot be regarded as sufficently detailed.

Concerning the question of layout the following can be stated: The proposed condensor surface of 4 m^2 for a 1000 l reactor is too small, 6 m^2 would be appropriate. Also 3 m^2 for 600 l and 1,5 m^2 for 200 l are too small. With respect that vacuum distillation shall be carried out in the latter a condenser surface of 3-4 m^2 would be appropriate. The capacity of the steam generator which is 500 kg/h is by far too small if the reactors in equipment are operated at once. A minimum capacity of 2500 - 3500 kg/h seems advisable to secure the supply of steam.

Concerning questions of material the following can be stated: The use of enamelled reactors indicates that protection from acid corrosion is required. With respect of this fact it does not seem reasonable that there are only stainless steel centrifuges. One of the three centrifuges ought to be halar coated and corrosion protected.

The use of rubber lined reactors does not seem appropriate, because on heating and cooling the rubber lining acts as insulator. It protects from corrosion by acids or bases, is however not suited for organic solvents. Therefore it would be advisable to use cheaper plastic tanks made of HDPE or PP.

The same comments as above also refer to rubber lined pumps. The use of corresponding plastic pumps can be recommended also because they are more versatile.

Also for storage of methanol, ethanol, mineral oil, sulfuric acid and bases plastic tanks can be used which are cheaper than steel tanks.

Finally Sparkler is a company name and not a filter type, so that this unit could not be analysed.

4.4.2. EXTENDED EQUIPMENT ACCORDING TO VEGYTERV ALTERNATIVE B

Among the 4 offers the extended Vegyterv alternative B is the only detailed proposal of equipment. A list of equipment given in the appendix was a great help in evaluation. The layout of combinations of equipment units is well coordinated. The following recommendations which result from our analysis refer mainly to the fact that the choice of equipment in a multi-purpose plant has to ensure maximum versatility as the processes to be carried out in future cannot be foreseen completely.

As far as the question of the material is concerned it can be said that in the case of several of the enamelled steel reactors different materials were used for reactors and condensers. The use of graphite in combination with glasslining would be useful, if there are specific advantages, such as less requirement of space, from the data provided this can however not be judged. The combination of enamelled steel with stainless steel (as given in G115, G119, G122, G201, G221, G226 and G224) however seems to be useless, with regard of a multi-purpose plant, because this results in the condensers, which may be exposed to acid or halogen corrosion, becoming the weakest point of the unit. In several other cases (G101, G210 and G249) this was taken into account.

A similar case of insufficient material combination occurs with the centrifuges S108, with 1 halar and 1 rubber coated receiver tank. Whenever organic solvents are to be involved in centrifugation the capacity of the halar receiver tank would be the limiting factor of the whole unit.

The use of PP and Teflon respectively as material for pumps is appropriate.

To enhance versatility of use of the tanks V103 and V220 GF polyester should be replaced by PP.

In case of the tanks 3, 4, 5, 8, 9, 12, 13 and 26 instead of steel PP should be used, in case given with an outside lining in GF polyester.

As far as questions of capacity of layout are concerned the filter area of 2 m^2 given for filterpresses S248 is too small. Large quantities of filtercake are to be expected in production so that very thick filterframes would be required.

The capacity of the steam generator which is 4t/h is to small. 6 - 7 t/h would be more appropriate preferable operated in 2 units to secure operation of at least a part of the production in case of shut-down.

Enamelled steel pressure filters S121, S206, S225 and S263 refer to the Lampert type filter which is built in several modifications with filter areas of 0,5 m^2. The proposed extensive use of this type of filter does not seem appropriate. The use of bag filters, which are much easier to handle, is certainly in many cases a better alternative.

Finally it can be stated that the equipment list is worked out carefully, only in few cases assessment could not be made due to lack of specification.

4.5. PRICES FOR EQUIPMENT AS GIVEN BY COMPANIES

4.5.1. EQUIPMENT ACCORDING TO THE TERMS OF REFERENCE

CIPLA	1.500.000 US$	TOTAL PRICE
REINIKAINEN	2.380.000 US$	TOTAL PRICE

VEGYTERV/CHEMOKOMPLEX

Equipment materials	1.737.200 US$	
Spare parts	34.700 US$	
Packing	52.100 US$	
Transporting	135.000 US$	
	1.959.000 US$	TOTAL PRICE

4.5.2. OTHER PROPOSALS FOR EQUIPMENT

REINIKAINEN	1.615.000 US$	Reduced equipment for 12 products

VEGYTERV/CHEMOKOMPLEX: Extended equipment

Equipment materials	2.520.400 US$	
Spare parts	50.500 US$	
Packing	75.700 US$	
Transporting	176.600 US$	
	2.823.200 US$	TOTAL PRICE

4.6. ANALYSIS OF PROPOSED EQUIPMENT FROM VIEWPOINT OF COST

The calculation of proposed equipment is based on Western European with prices ex works. Costs of piping are not included. Since the specifications given were in many cases not sufficiently exact, a special reserve A was calculated for that reason. Some units of equipment for which specifications were entirely or almost entirely missing had to be estimated (reserve B), the percentage for this differing very much because of the lack of specifications in the terms of reference equipment. A reserve for spare parts was also foreseen.

Terms of reference equipment		Extended equipment Vegyterv
878.200 US$	Equipment	2.472.740 US$
118.000 US$	Laboratory equipment	110.000 US$
125.000 US$	Reserve A	125.000 US$
300.000 US$	Reserve B	200.000 US$
45.000 US$	Spare Parts	60.000 US$
1.466.200 US$		2.967.740 US$

As an alternative for both offers a cheaper version was worked out in which Western European equipment was combined with Eastern European reactors (standard prices in Western Europe, ex work) and also change in material (plastic instead of steel) was made were appropriate. In some cases also cheaper versions of Western European equipment were selected.

Terms of reference equipment		Extended equipment Vegyterv
827.300 US$	Equipment	1.968.540 US$
118.000 US$	Laboratory equipment	110.000 US$
100.000 US$	Reserve A	100.000 US$
300.000 US$	Reserve B	200.000 US$
45.000 US$	Spare parts	50.000 US$
1.390.300 US$		2.428.540 US$

Although a comparison to the prices of the offers cannot be made without considering some more factors (e.g. packing, transport and piping), it can be seen that for term of reference equipment complete supply from the Western European market would not pose any price problem. As far as the extended version of Vegyterv/ Chemokomplex is concerned the reduced cost version would give considerable savings compared to complete supply from Western European sources.

4.7. LIST OF "OPTIMUM" EQUIPMENT INCLUDING ESTIMATE OF COST

As stated already under point 2.1. a list of equipment including standard prices to assure production of the compounds of the "optimum" list of technology was set up independently from the offers to establish a framework for quick evaluation. On the other hand it could thus be followed the wish of the Iranian delegation to assess the feasibility of using equipment from Western European sources.

The equipment indicated was selected to secure production of the 18 drugs of the terms of reference in the production levels proposed there. For Metronidazole and Trimethoprim, 7 and 13 tons/year were chosen which correspond to half of the annual consumption in Iran, for Sulfamethoxazole a production level of 10 tons/year was envisaged. All prices are standard prices ex works requested directly from reputated manufacturors in Western Europe.

4.7.1. REACTORS

4	3000 l	enamelled steel	
6	3000 l	stainless steel	
2	1600 l	enamelled steel	
5	1600 l	stainless steel	1 of them oil heated
1	1250 l	enamelled steel	
1	500 l	enamelled steel	

Standard Price: 346.800 US$

4.7.2. CENTRIFUGES

2	1250 l	halar coated
5	1250 l	stainless steel

Standard Price: 488.000 US$

4.7.3. DRYERS

2	paddle dryers, discotherm (continuous, discontinuous)
5	tray dryers, each 30 trays
1	vacuum tray dryer, 30 trays
1	fluid bed dryer

Standard Price: 414 000 US$

4.7.4. FILTERS

3	filter presses	7 m^2, 10 m^2, 13 m^2, PVDF, heated
3	bag filter	each 1 m^2, in pairs

Standard Price: 67.000 US$

4.7.5. PUMPS

6	excentric worm pumps	PVDF/SS	10 m^3/h	6 bar
2	excentric worm pumps	Teflon	10 m^3/h	6 bar
18	centrifugal pumps	PP	10 m^3/h	1 bar
4	centrifugal pumps	teflon	10 m^3/h	1 bar
12	double diaphragm pumps	Teflon	10 m^3/h	0,5 bar
15	centrifugal pumps	SS	10 m^3/h	1 bar
2	water ring pumps		60 m^3/h	
4	water ring pumps		100 m^3/h	
1	water ring pump		30 m^3/h	
1	rotary gear pump		50 m^3/h	0,01 mbar
2	steam jet pumps			0,2 - 0,5 bar

Standard Price: 149.700 US$

4.7.6. CONDENSERS

1	4 m^2	glass
1	6 m^2	glass
2	8 m^2	glass
3	8 m^2	SS
4	12 m^2	glass
4	12 m^2	SS

Standard Price: 81.200 US$

4.7.7. TANKS

Corresponding to version Vegyterv B.

Standard Price: 131.000 US$

4.7.8. VESSELS AND RECEIVERS

5	3000 l	PE	
3	2000 l	PE	
3	1500 l	PE	
4	600 l	Halar	
14	600 l	SS	
7	250 l	PP	vacuum buffer
6	500 l	enamelled steel	
6	500 l	SS	
5	300 l	SS	
3	300 l	glass	
2	200 l	glass	
2	100 l	glass	
3	3000 l	SS	
2	1500 l	SS	

Standard Price: 192.050 US$

4.7.9. BALANCES

6	300/600 kg	ex electr.,	SS
3	300/600 kg	electr.	SS
2	150 kg	electr.	
2	50 kg	electr.	

Standard Price: 46.600 US$

4.7.10. LABORATORY EQUIPMENT

Corresponding to version Vegyterv B.

Standard Price: 110.000 US$

4.7.11. UTILITIES

Corresponding to version Vegyterv B.

But: point 1: 5000 kg/h 12 bar

Standard Price: 262.600 US$

4.7.12. MISCELLANEOUS

2	scrubbers (20.000 m^3/h)
1	mill including separator
1	compressor (250 m^3/h, 8 bar)
1	high vacuum distillation

Standard Price: 134.300 US$

4.7.13. SUMMARY

1.	Reactors	346.800 US$
2.	Centrifuges	488.000 US$
3.	Dryers	414.000 US$
4.	Filters	67.000 US$
5.	Pumps	149.700 US$
6.	Condensers	81.200 US$
7.	Tanks	131.000 US$
8.	Vessels and Receivers	192.050 US$
9.	Balances	46.600 US$
10.	Laboratory equipment	110.000 US$
11.	Utilities	262.600 US$
12.	Miscellaneous	134.300 US$
	Total	2.423.250 US$
	Reserve for unforseen units	150.000 US$
	Reserve for spare parts	60.000 US$
	Standard Price for "optimum" equipment from Western European market	2.633.250 US$

A comparision shows that the price of 2.633.250 US$ for "optimum" equipment is lower than the price of 2.967.740 US$ for Vegyterv equipment B. Both figures are based on Western European equipment standard prices. The lower total price in spite of higher production capacity is due to differences in the layout of both plants. The list of "optimum" equipment given in this chapter reveals the differences in the choice of equipment which are considered to be reasonable improvements and should be discussed in detail before making final decision.

Finally it may be stated that of course also for the "optimum" list of equipment a cheaper version could be set up by using reactors of Hungarian origin whereever feasible without loss of efficiency and versatility.

4.8. SPARE PARTS

It was the wish of the Iranian delegation to have spare parts for 2 years included in the equipment. Since terms of guarantee granted by equipment suppliers will as a rule not be a 2 years overall guarantee this question has to be considered more in detail. With this respect it seems necessary to distinguish between parts which underlie normal wear and tear within 2 years, such as seals, gaskets, bearings etc., and parts which from the standpoint of statistics might break within a two year period. It will pose no problem to foresee a two years reserve for the parts which underlie normal wear and tear. It is however difficult to solve the problem of spare parts for the latter group. One opportunity which is the more economical from the point of investment is to keep reserve funds for procurement of broken parts. The disadvantage of this simple approach is the danger of prolonged shut-downs. Especially in the case of equipment in developing countries therefore the better approach seems to be to make a careful analysis of the parts which might break by statistic chance and to make a choice of items to be kept in reserve in the plant. This means e.g.: If glass equipment used in production (e.g. condensers) one unit of each size should be kept in reserve because glass repair may take some time if repair is complicated. As far as units of equipment are concerned which are subjected to corrosion, a choice of parts which are in direct contact with the medium should be kept in stock.

4.9. WORKSHOP

It is obvious that a unit of the size of the proposed plant requires considerable skilled work and workshop. The question of equipping this workshop is closely related to the infrastructure at the site. Skilled work required is very broad from: metal, glass and plastic works, as well as simple masonry, qualified knowledge in electrotechnics and basic knowledge in electronics. Whenever such a skill is not presented in the existing infrastructure it has to be taken into the activities of the workshop to secure quick repair. As far as training of workshop staff is concerned, broad and specialized skills are required. It seems advisable not to have specialists for each single field, but rather to provide a specific training for the staff concerning techniques required in the plant.

As far as equipment of the workshop is concerned it can be seen from all offers that this question has hitherto been rather neglected. To secure efficiency it may even be necessary to provide a lot of equipment , such as turning lathe, welding machines (also using protective gas for welding of stainless steel), welding equipment for plastics, boring and milling machines etc.. Therefore it seems advisable to study this subject more in detail before making final investment decisions, and to set up a workshop equipment according to the actual requirements.

4.10. ANALYTICAL LABORATORY EQUIPMENT

It was regarded as beyond the scope of the present report to make a detailed assessment of the list of analytical equipment. It is however pointed out that it would be advisable to check on the one hand the analytical procedures given in the reference pharmacopoeas product by product and to make on the other hand an assessment which units of equipment are needed in addition to secure efficient research and development activities.

5. TECHNOLOGY VERSUS EQUIPMENT ASSESSMENT

In chapter 3. evaluation of technology was discussed, in chapter 4. an assessment of equipment is presented. In this chapter an attempt is made to relate offered technology and offered equipment in such a way that reasonable production can be carried out taking into account the capacities which are required.

The importance of sufficient capacity was pointed out at the May meeting at UNIDO headquarters and the wish to have 20 - 30% reserve capacity was given.

5.1. METHOD OF EVALUATION

1. The reaction volume (included volume for work-up) was estimated for each production step of each product.

2. A total annual production volume was calculated from that.

3. The total capacity of all reactors was determined 90% of which was regarded as working volume.

4. Dividing 2. through 3. gives the number of reac[illegible]cupancy.

5. A number of 260 working days per year was taken as the basis.

6. According to practical experience only 30% of the working days/year is realistic for reactor occupance.

This method of evaluation has been already applied for the choice of optimum equipment in 4.7.: In that case assessment

of the total reaction volume for all 21 products had given 2400 m^3/year. Adding 30% reserve capacity gave 3200 m^3/year. The number of reactor occupancy is 78 (260 days x 0.3). This gave a reactor working volume of 40 m^3 so that a total reactor capacity of 43 m^3 was regarded to be suited provided the selection of reactor size and number is appropriate

Following this method of evaluation both alternatives of equipment which had been offered in the project were analysed.

5.2. PROPOSAL FOR PRODUCTION IN EQUIPMENT OF TERMS OF REFERENCE

The reactor working volume of this equipment is about $9m^2$. Considering a reactor occupancy number of 78 an annual reaction volume of 700 m^3 results, which by far will not be sufficient to reach the capacities proposed for the products in the terms of reference if suitable technologies are applied.

To secure reasonable production it seems advisable to follow the findings given in 3.7.3. by eliminating Ethambutol, Paracetamol Procain Hydrochloride, Niazin and Nicotinamide from the production programme for reasons of capacity and economy. Also the suggestion to take up into the production programme Metronidazole, Sulfamethoxazole and Trimethoprim could only be followed on a rather limited production scale.

5.3. PROPOSAL FOR PRODUCTION IN EXTENDED VEGYTERV EQUIPMENT B

Analysis of production of all 18 drugs which were indicated by Vegyterv according to the proposed technologies an annual reaction volume of about 1500 m^3 / year was calculated.

On the other hand the working volume of the reactors is about 35 m^2. From this and the reactor occupancy number of 78 results an annual reaction volume of about 2700 m^3 / year, so that it can be stated that the capacity of equipment is suited for the requirements of production easily.

Considering that many of the VEGYTERV technologies such as Clofibrate, Clotrimazole, Indometacin, Nalidixic Acid, Oxyphenbutazone and Propranolol are last step reactions. The capacity of this equipment alternative would be sufficent to integrate more basic technologies, as well as the production of the newly proposed drugs Metronidazole, Sulfamethoxazole and Trimethoprim. It seems however doubtful if above that 30 % reserve capacity is given.

6. ENVIRONMENTAL PROTECTION AND RELATED ASPECTS

6.1. GENERAL REMARKS

A chemical unit which has the size of the multi-purpose plant is certainly a factor which will have considerable impact on the surrounding environment. Therefore the wish of the Iranian delegation in the May-meeting at UNIDO headquarters to consider questions of environmental protection is of utmost importance. This problem was not significantly pointed out in the terms of reference and also the offers did not contain relevant information on this topic. Upon the request in the questionnaire Vegyterv/ Chemokomplex indicated several measures of environmental protection mainly in connection with the proposed alternative of extended equipment.

Measures to achieve environmental protection as well as measures which guarantee safety at work if possible should not be taken as single measures but within the frame of a complete concept. First prerequisite with this respect are legal specifications indicating critical values which have to be regarded. If there are not yet corresponding detailed regulations in Iranian law, useful specifications should be set up from other sources, e.g. from the experience of countries with existing regulations such as Austria.

Only when the critical values to be obtained are fixed reasonable planning of measures to be taken can set in because the layout of environmental protection units largely depends on the critical values which may not be exceeded. Since environmental measures might result in considerable investment, the conceptual frame-

work ought to be set up most urgently so that detailed planning can be carried out together with the detailed planning of the plant itself.

In the following some brief comments are given on some of the relevant topics.

6.2. EFFLUENT TREATMENT

Effluent treatment should be done in a way that assures that there are no significant changes of the biotope. The effluent water should be neutralised, solvents of higher or lower specific gravity should be separated from the water. Neutralisation is to be carried out in a way that the effluent is enriched with air, also sedimentation of solid particles has to be provided. In case given also basins for precipitation or biological purification have to be planned. The operation of the effluent treatment unit should be automated to a great extent.

6.3. CHEMICAL WASTE TREATMENT

The main quantities of chemical waste will be the mud of the effluent treatment unit, mother liquors and distillation residues.

To keep quantities of solvents to be treated small solvents should be recovered. With respect to the prospected 20 - 30 % reserve capacity this can either be done in existing units which are not occupied or in solvent recovery units which can be operated automatically. 1 or 2 of this units would secure a quick return of investments because of reduced cost of waste treatment and saving in the purchase of solvents.

The residues of solvent recovery together with the mud from the waste water treatment and other waste are to be burnt in an incinerator, especially of rotary tube furnace type. The heat obtained from this incinerator can be used for heating and thus allow a lower capacity of the steam generator.

6.4. AIR POLLUTION

Air could be polluted with vapors of acids, bases and solvents. Acids and bases can be removed using a gas purification plant in which acids are washed out with bases and vice versa. NO_x and vapors of solvents should be removed through catalytic incineration. The choice of gas purification depends on the quantity of effluent air but also on the layout of the production units (open vessels, solvents through piping etc.). Adsorption on active carbon is another type of purification, which however is more tedious.

6.5. STORAGE OF CHEMICALS

Also storage of chemicals is subjected to an increasing number of regulations. To avoid fire hazards solvents should be stored separately according to their flash point. In storage facilities for liquids having a flash point below 50° C only exlosion protected electrical installations should be used. Specific construction should be considered to avoid exposure of tanks to the sun and to protect the ground from leaking solvents.

6.6. FIRE HAZARDS

To enable instant measures in case of fire, it is necessary to provide a sufficient number of fire extinguishers ABC of sufficient capacity in each room regardless of its size. With respect to the size of the plant also provision of 50 kg powder extinguishers should be made. An extinguisher car (about 250 kg) would even in case of more severe fire hazards allow an efficient action through company staff, which however in this case has to be thoroughly trained.

6.7. SAFETY AT WORKING PLACE

Also with respect of safety at working place existing regulations must be observed carefully. Apart from protection of workers through suited dress including items from gloves to gas masks, permanent ventilation through exhaustion is necessary. Flexible tubes connected to the exhausters allow punctual exhaustion at a specific point of danger.

7. SUMMARY OF THE REPORT - FINDINGS

(worked out jointly with UNIDO staff)

The present report has considered the evaluation of the offers received by UNIDO from 4 companies, Cipla, Reinikainen, Sarabhai and Chemokomplex according to UNIDO terms of reference.

In order to identify the scope of the project based on the objectives specified by the Iranian Government and UNIDO, the following actions were taken in addition following the terms of reference of a contract which was set up between UNIDO and the consultant.

Data and information have been supplied on the technical and economic aspects of the project, including particulars regarding process, starting raw materials, design, equipment specifications, layout and other details.

The situation relating to the technologies for the production of the 18 drugs specified in the terms of reference has been examined from the standpoint of patent, unit processes and economic evaluation thereof, equipment prices, suitability and availability in international markets and the technical and economic evaluation of such equipment.

Recommendations have been made regarding the possible integration of the offers with a view to formulating optimum design, flexibility, unit processes and an appropriate level of technology.

Enviromental protection and safety aspects of the personals/tenders have been examined.

This report cannot be a final decision making force, it is only giving

evaluation of different offers and their alternatives based on which the recipient country has to make the final decision as to which alternative should be chosen. It will try to point out the different consequences in development of technology, transfer of know how, economic translation and development of research and development capability. Based on this the consultant likes to present the major technical and economical points as follows:

Technology Development: In the original terms of reference by UNIDO technology of 18 drugs had been proposed. A revision of these technologies by the Iranian Government resulted in a reduction to 13 drugs and 3 new drugs. In the present report the totality of all 21 drugs has been analysed. First an analysis of standard production processes for these drugs was carried out. This basic analysis has been compared with the technology received from the different companies (chapter 3.). Among the criteria which were applied for evaluation special consideration was put to the question of starting materials, which were classified either as raw material, intermediates or late intermediates.

The result of comparative evaluation of technologies is given in the report (chapter 3.7.3.). In short it can be said that as a whole Sarabhai has offered the greatest number of appropriate technologies, also the offer of Chemokomplex/Vegyterv is rather complete as far as number is concerned, however 6 of the technologies are only late stage technologies. At this point it must be stated that a detailed comparision of technologies of similar value could not be carried out, because of lack of information from some companies.

Unit Processes: An assessment of all the unit processes involved in all technologies was made and the result related to the company offers (chapter 3. 6.). An analyis of unit operations required to carry out all the unit processes revealed that the layout of equipment according to the terms of reference as offered by Cipla,Reinikainen and Chemokomplex/Vegyterv provide for all the required unit processes.

Economic Translation of Technology to the Industrial Level: Economic translation is the translation of a given technology, the economics of which have been justified in the semi-industrial level, to the industrial level.

Capacity requirements of a pilot plant for economic translation cannot be generalized. The capacity from which each individual product is transferred to industrial scale depends on its market size. There is a wide range of market size for the 16 drugs required by the Iranian Government. Therefore it seems necessary to accomodate the design of the pilot plant to a capacity which also allows translation of products with a big market size.

To have a basis for assessment of equipment in the different offers an "optimum" design and layout of equipment for synthesis transfer and back integration of all 21 drugs has been established by the consultant, based on a choice of "optimum" technologies (see chapter 3.7. and 4.7.). This "optimum" equipment has given the possiblity to evaluate all the offers.

According to this evaluation equipment proposed according to the terms of reference of UNIDO does not give the possibility of back integration of all technologies required by Iranian Government, because the design of equipment is based on the technology which is transferred today with identified level of technology, some from basic materials, some intermediates, some even almost final products. Bearing in the mind that back integration of technology requires more steps, more processes and greater batches this layout cannot give on one hand this back integration and on the other hand the guarantee for production of all the 18 drugs as required.

Evaluation of alternative B of Chemokomplex/Vegyterv offer revealed that this equipment could give the possibility of back integration of all drugs as well as unit processes and required capacity of equipment are concerned. The main difference of this alternative compared to the "optimum" version is that there is no reserve capacity which might be used for adding new drugs without replacing others. However the same offer without additional equipment could come close to the "optimum" choice by a somewhat revised design.

Patents: Patents are great in importance in transfer of technology especially when technology is going to be put into industrial production. Therefore an assessment of the situation concerning patents has been made (chapter 3. 3.). Before making final recommendations however first of all the patent situation in Iran has to be known, secondly further clarification of the offering companies should be given not only concerning infringements referring to the drugs themselves but also to the processes for their preparation.

Economics of the offers according to terms of reference: Terms of reference by UNIDO allocated 2,12 million US$ for subcontract. The different offers were compared taking into account quality of equipment quality of technology and assurance of availability from the international market. Among these offers Chemokomplex/Vegyterv alternative A is the lowest, Sarabhai has only offered technology and services, Cipla and Reinhaiden offers are high.

Further economic evaluation is not useful before decision is taken, which products, which technologies and which level have to be considered.

As already discussed before the consultant has compared equipment according to UNIDO terms of reference to alternative equipment

the basis of the international market. All single units of equipment are available in the international market and can be supplied by manufacturers with detailed specifications. Nevertheless the final price of equipment cannot be singled out because engineering companies will have to provide engineering and performance guarantee for the entire pilot plant. Of course provision has to be made for these services and overheads. Therefore indicative prices given by the consultant should not be taken as final price for the project to be put into operation.

According to this logic, the lowest offer with its limits as given before is alternative A of Chemokomplex/Vegyterv who offered mainly equipment of Hungarian origin.

According to the findings in this report it seems advisable to procure certain parts of the equipment from the international market and integrate it suitably with the rest. This refers mainly to units which are not manufactured in Hungary in a standard which meets the requirements of best design and layout.

8. RECOMMENDATIONS

(worked out jointly with UNIDO staff)

8.1. TECHNOLOGY

As far as it can be judged from data available Sarabhai offers suited technologies for most drugs. Therefore this offer may be considered best as a whole concerning technology. For several drugs also technology offered by Cipla or Vegyterv may be considered best. Efforts should be made to ask the main contractor to integrate and take responsibility for all technologies.

It should be noted that technology, equipment and engineering design should be coordinated to ensure the realization of the objectives of the project. These should not be seen as separate entities.

8.2. UNIT PROCESSES

Both the terms of reference and the offers evaluated provide for all the required unit processes. However, if this project is to be oriented towards research and development, flexibility and reserve capacity, the alternative B of the Vegyterv/Chemo-komplex offer or the "optimum" design worked out by the consultant has to be considered.

8.3. ECONOMIC TRANSLATION

The equipment proposed in the terms of reference does not ensure economic translation of all the 18 drugs. It can be estimated that it can provide for a maximum of 13 drugs if proper selection is

made. If all 18 drugs proposed in the terms of reference or the 13 + 3 drugs according to the revised list of Iranian Government are to remain in the project, a higher capacity design such as alternative B of the Chemokomplex/Vegyterv offer or the consultant's optimum version has to be considered.

8.4. ECONOMICS

In the first instance the alternative A of the Chemokomplex/ Vegyterv offer, which is also according to the terms of reference is the lowest offer. For further evaluation however more detailed specifications concerning this alternative should be provided by the company.

8.5. FURTHER RECOMMENDATIONS

A series of other recommendations concerning specific questions, such as spare parts, workshop, equipment for trouble shooting, equipment to secure maximum unit operations, analytical laboratory equipment and aspects of environmental protection are given in the report.

8.6. PREREQUISITES FOR FINALISATION OF RECOMMENDATIONS

The consultant recommends that the final decision should be taken only after clarifying the following points:

- Final group of drugs
- Is the pilot plant to be oriented towards research and development, is it to be flexible and to give the possibility of back-integration or is this unit meant only for technologies as they are received now ?
- Is there a possibility of expanding the budget ?
- Extent to which environmental measures are to be taken

Based on the answers to above questions further clarifications based on the findings of the report and further answers from the companies can be provided by the consultant to enable finalisation of the recommendations.

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PART 2

2ND REPORT

ABOUT SERVICES RELATING TO THE PHARMACEUTICAL CHEMICALS MULTI-PURPOSE PLANT IN IRAN

SUGGESTIONS FOR CHANGES IN EQUIPMENT

UNIDO CONTRACT NO. 85/39
PROJECT NO.DP/IRA/83/014
ACTIVITY CODE:DP/02/32.1

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SUGGESTIONS FOR CHANGES IN THE LAYOUT OF EQUIPMENT

In the meeting of June 25th, 1985 a list of 13 drugs was set up to be synthesized in the multi-purpose pilot plant. The consultant was asked to suggest changes in the layout of the equipment for producing these drugs and to give estimation of additional cost of equipment.

In the present report first a survey on the unit processes is given, which are roreseen in the course of syntheses for the 13 drugs. Next a compilation of reaction schemes for all these drugs is given from which the chosen technologies can be seen and which also includes additional information on Sarabhai technologies obtained on June 25th, 1985.

Then follows a list of types and numbers of equipment units for the main parts of equipment followed by the cost estimation. At last a survey of types of equipment is given.

As far as the choice of source of technology is concerned first of all criteria given in the main report were applied. Whenever the information available did not allow to make a decision from a technical point of view among similar technologies offered, the choice was made according to the wish of the Iranian delegation.

UNIT REACTIONS OF 13 DRUGS ACCORDING TO CHOICE MADE AT MEETING ON JUNE 25TH, 1985:

1. Aromatic Reactions

Friedel-Crafts acylation	A3	(A7)
Friedel-Crafts alkylation	A3	
Nitration	C1	(A7)
Nucleophilic aromatic substitution	(A7)	
Diazotization	A6	(A10)

2. Carbonyl Reactions

Oxime formation	A1
Schiff base formation	A6
Enamine formation	
Knoevenagel condensation	C3
Strecker synthesis	
Benzoin condensation	

3. Ring Closure Reactions (C2)

Via ester formation		
Via amide formation	A4	
Via hydrazide formation	A10	
Via Schiff base formation	A4	A7
Fischer indole synthesis	A6	
Via electrophilic aromatic substitution	(A8)	
Aminal type	A1	(C1)
Via condensation		

4. Amine Reactions

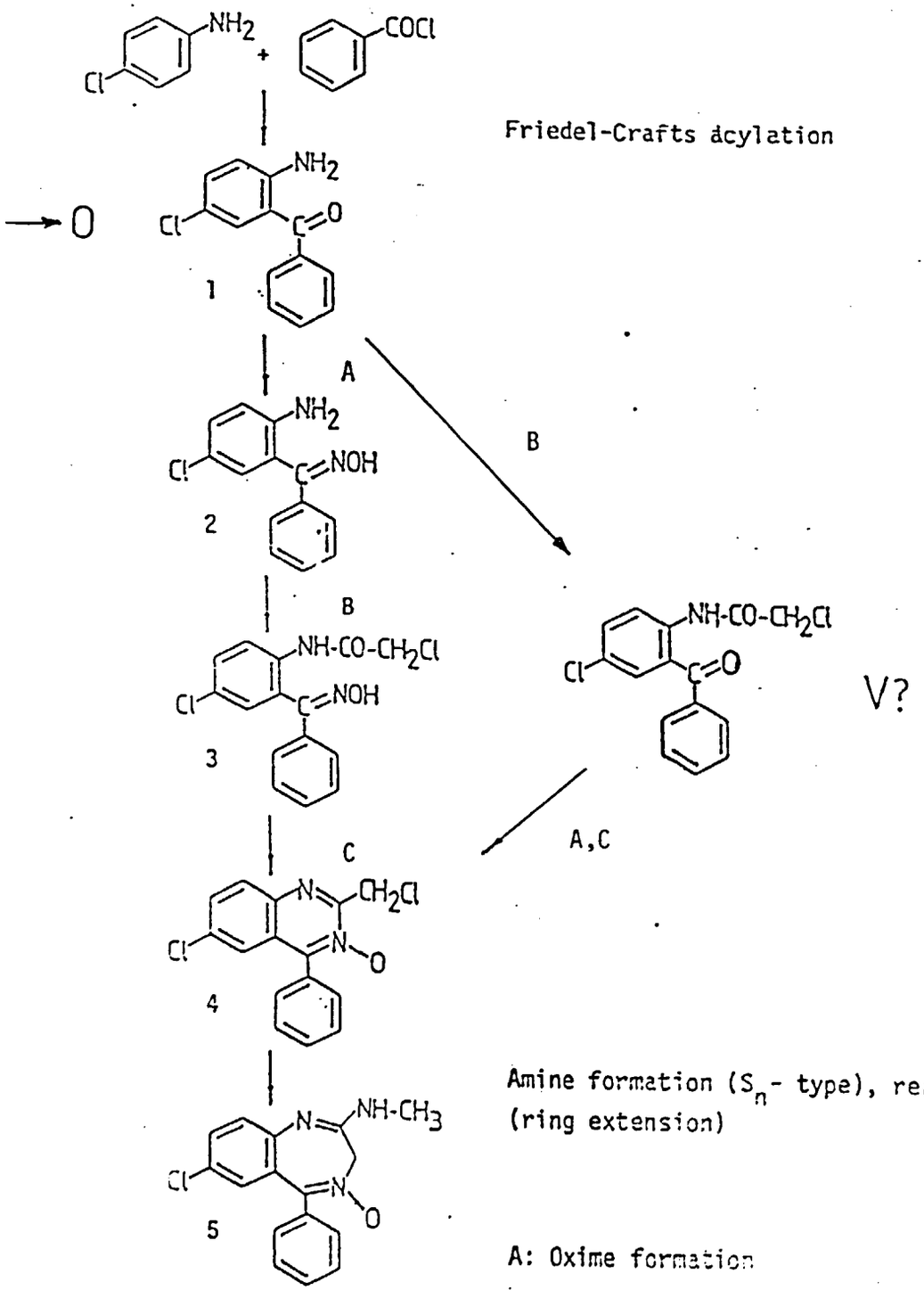
S_n-type amine formation	A1	A3	A13
Amine formation by epoxide ring opening	A13		
N-Alkylation		(A6)	C1
N-Acylation		(A7)	

N-Tosylation	
N-Detosylation	
N-Deformylation	
5. Carboxyl Reactions	
Ester formation	A2 A12
Ester hydrolysis	(A8)
Direct amide formation	
Amide formation via acid chloride	
Amide hydrolysis	C2
Pinner reaction	
Acid chloride formation	A3 (A7)
Hydrazide formation	
Nitrile hydrolysis	
6. Sulfonamide formation	C2
7. Ether formation	
O-Alkylation	A13 (A10)
Clofibric acid synthesis	A2
8. Oxidation	
9. Reduction	A6 (A7) (A10?)
10. Rearrangements	A1
11. Chlorination	A3
12. Miscellaneous	
Condensation	
Hydrogenolysis (Debenzylation)	(A10)
Addition (Michael type)	C3
Aromatic Hydroxylation	(C3?)

PROPOSED REACTION PATHWAYS

A1

CHLORDIAZEPOXIDE



Amine formation (S_n- type), rearrangement (ring extension)

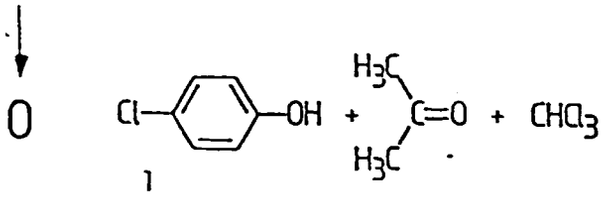
A: Oxime formation

B: N-Acylation

C: Ring closure reaction (C-N-condensation type)

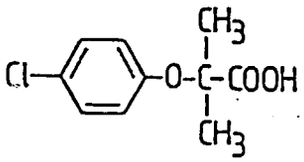
A2

CLOFIBRATE



1

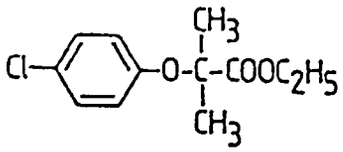
Condensation



2

V

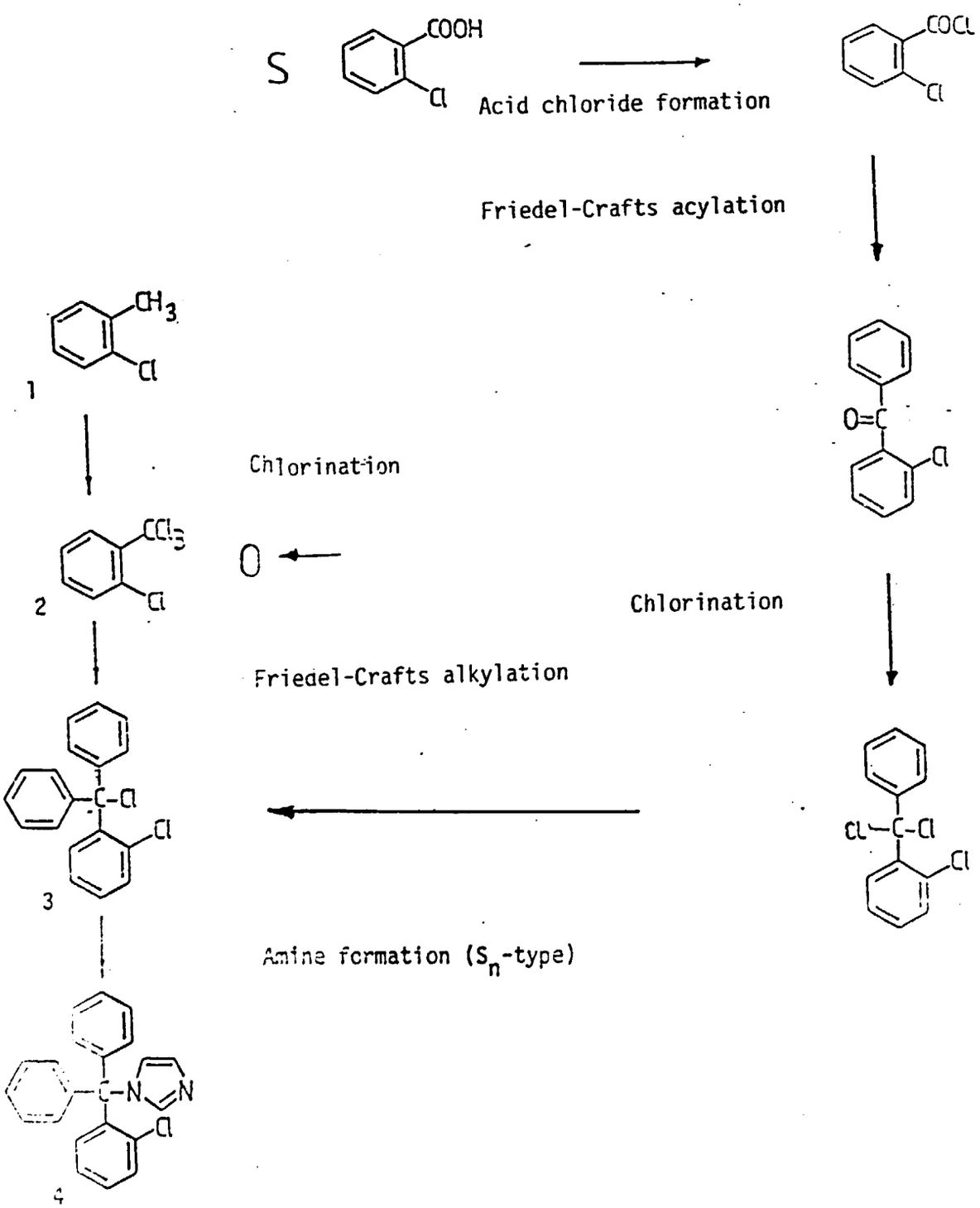
Ester formation



3

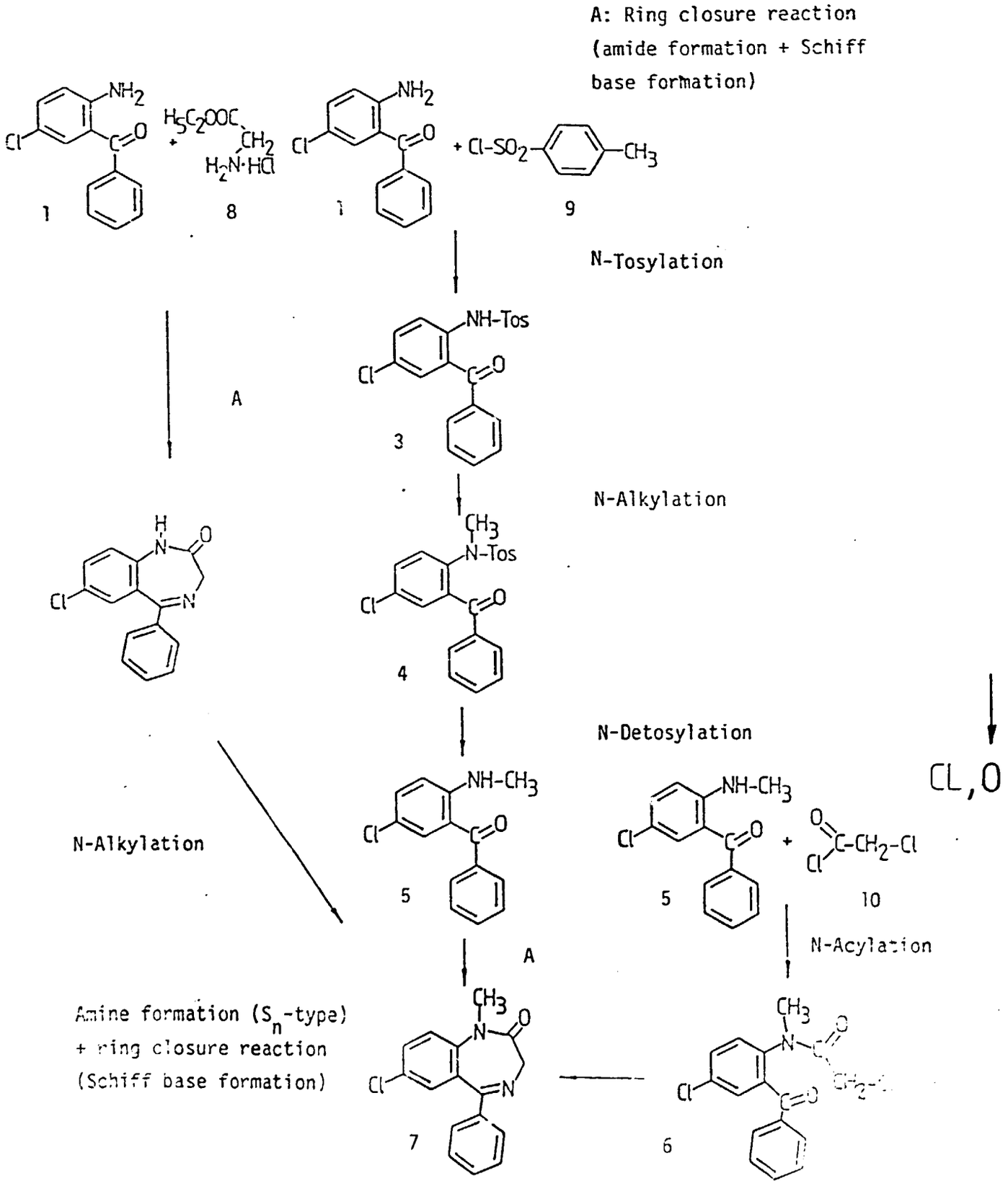
A3

CLOTRIMAZOL



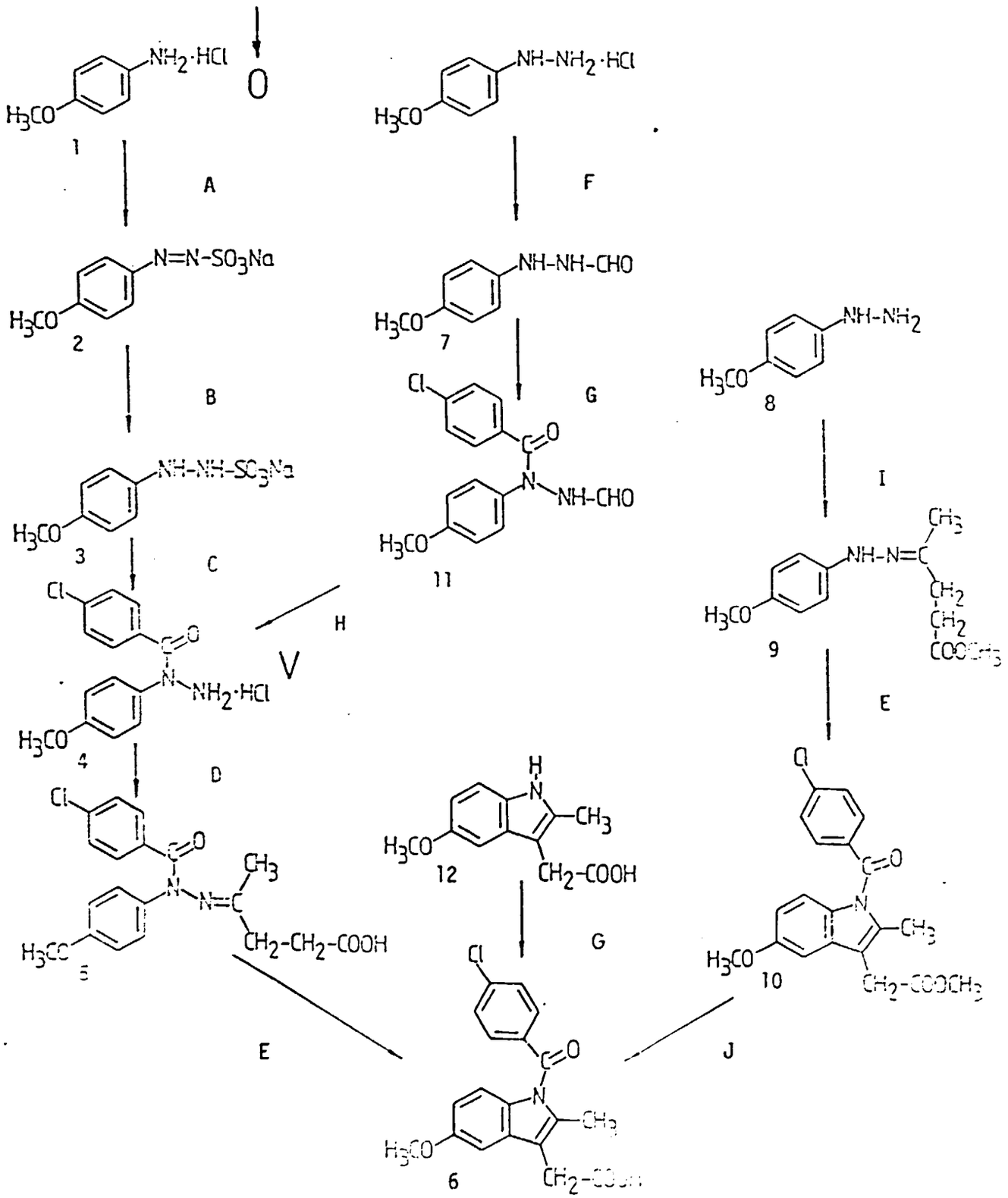
A4

DIAZEPAM


A: Ring closure reaction (amide formation + Schiff base formation)
1
8
1
9
N-Tosylation
A
3
N-Alkylation
4
N-Detosylation
N-Alkylation
5
5
10
N-Acylation
A
Amine formation (S_n-type) + ring closure reaction (Schiff base formation)
7
6

A6

INDOMETACIN



A: Diazotization

B: Reduction

C: N-Acylation

D: Condensation (Schiff base formation)

E: Ring closure reaction (Fischer Indole synthesis)

F: N-Acylation (formylation)

G: N-Acylation

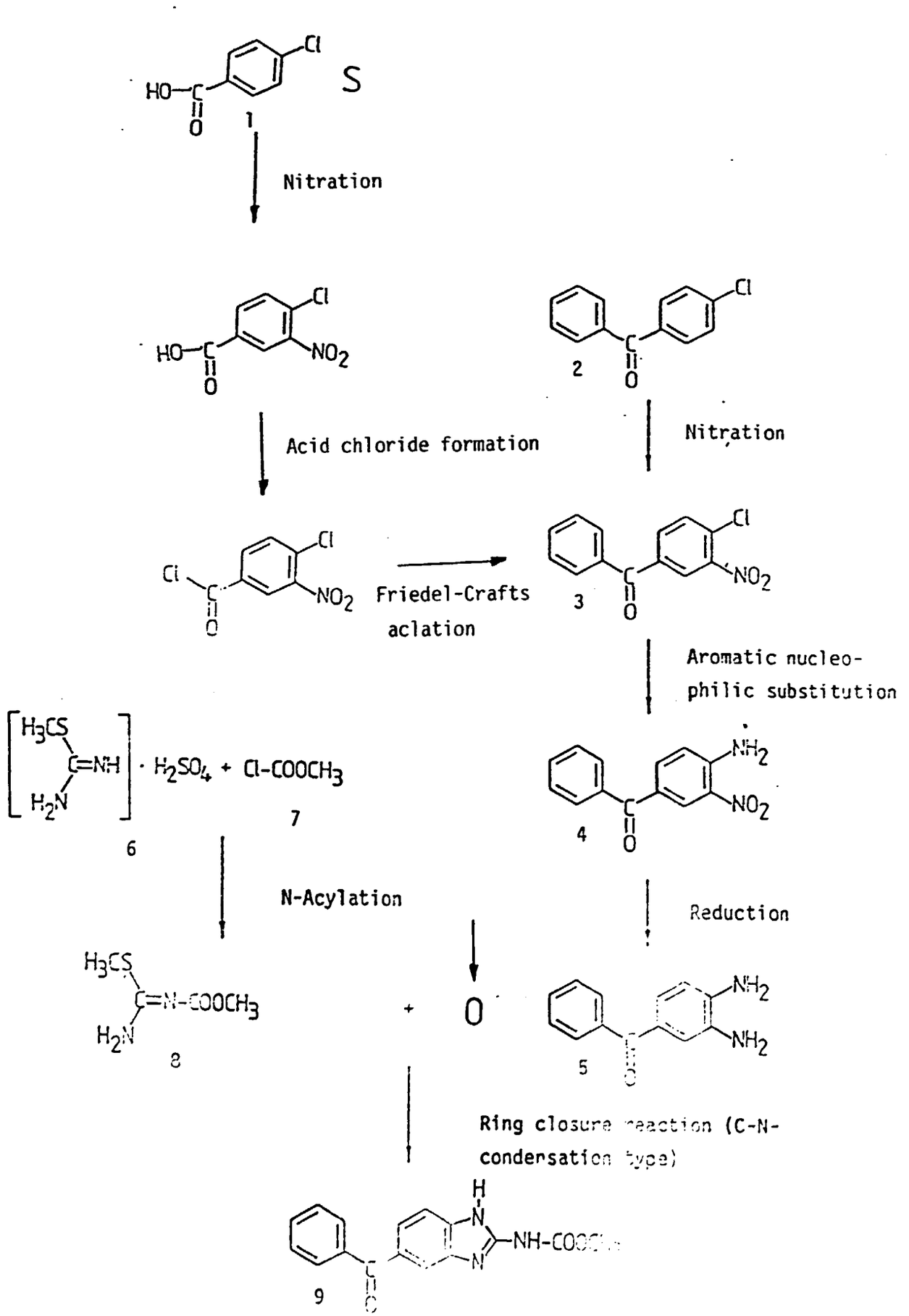
H: Hydrolysis (deformylation)

I: Condensation (Schiff base formation)

J: Ester hydrolysis

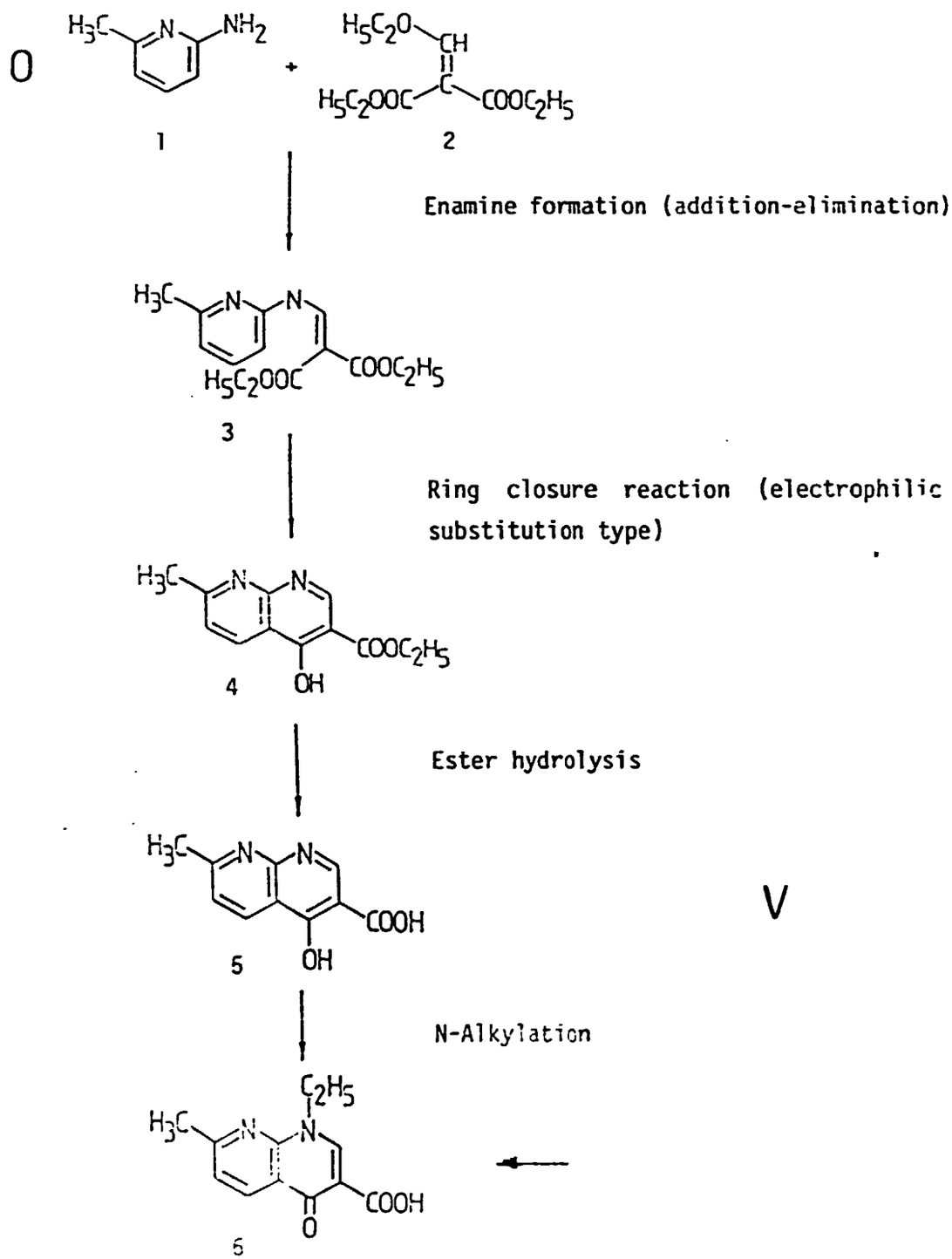
A7

MEBENDAZOLE



A8

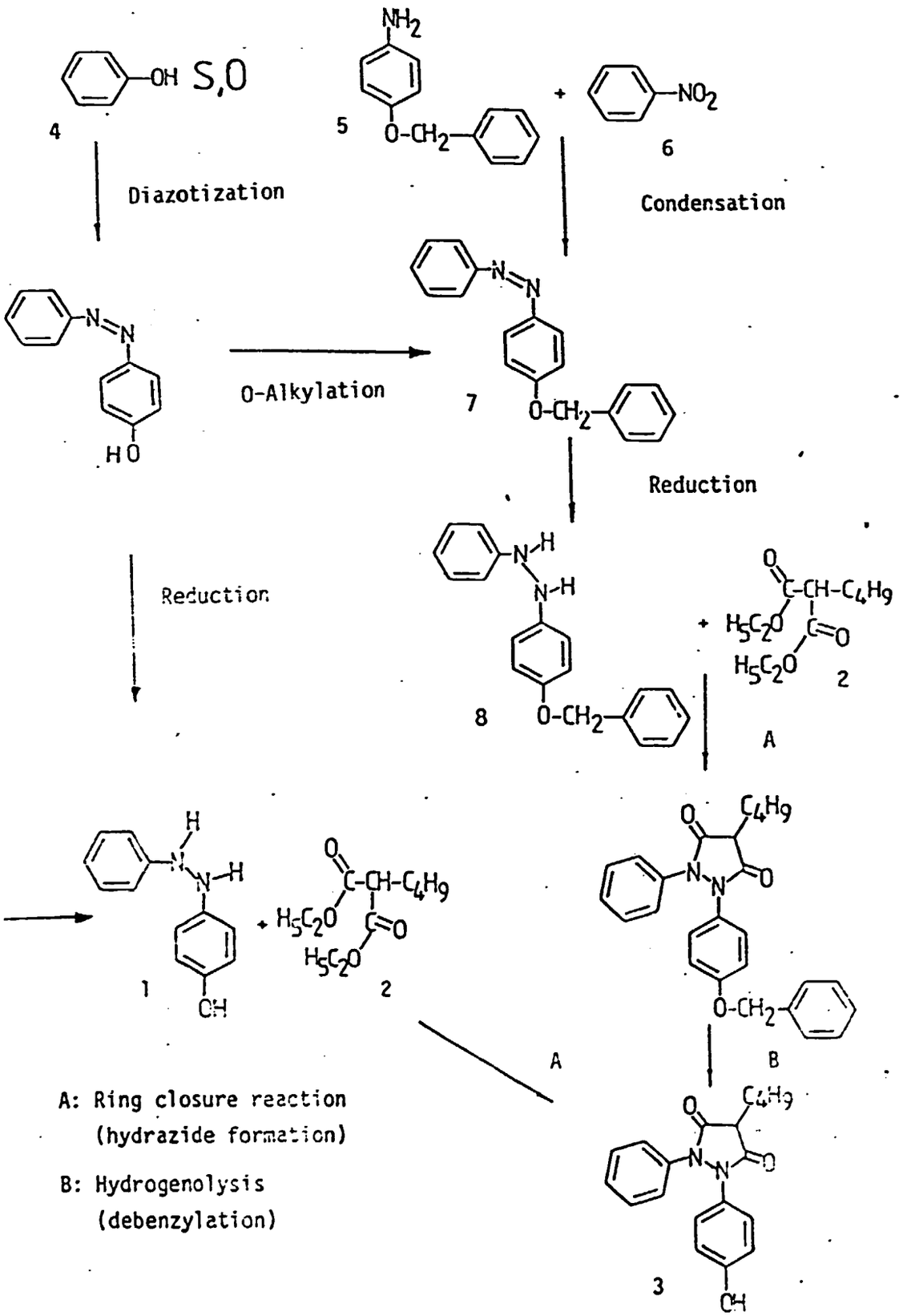
NALIDIXIC ACID



V

A10

OXYPHENBUTAZONE

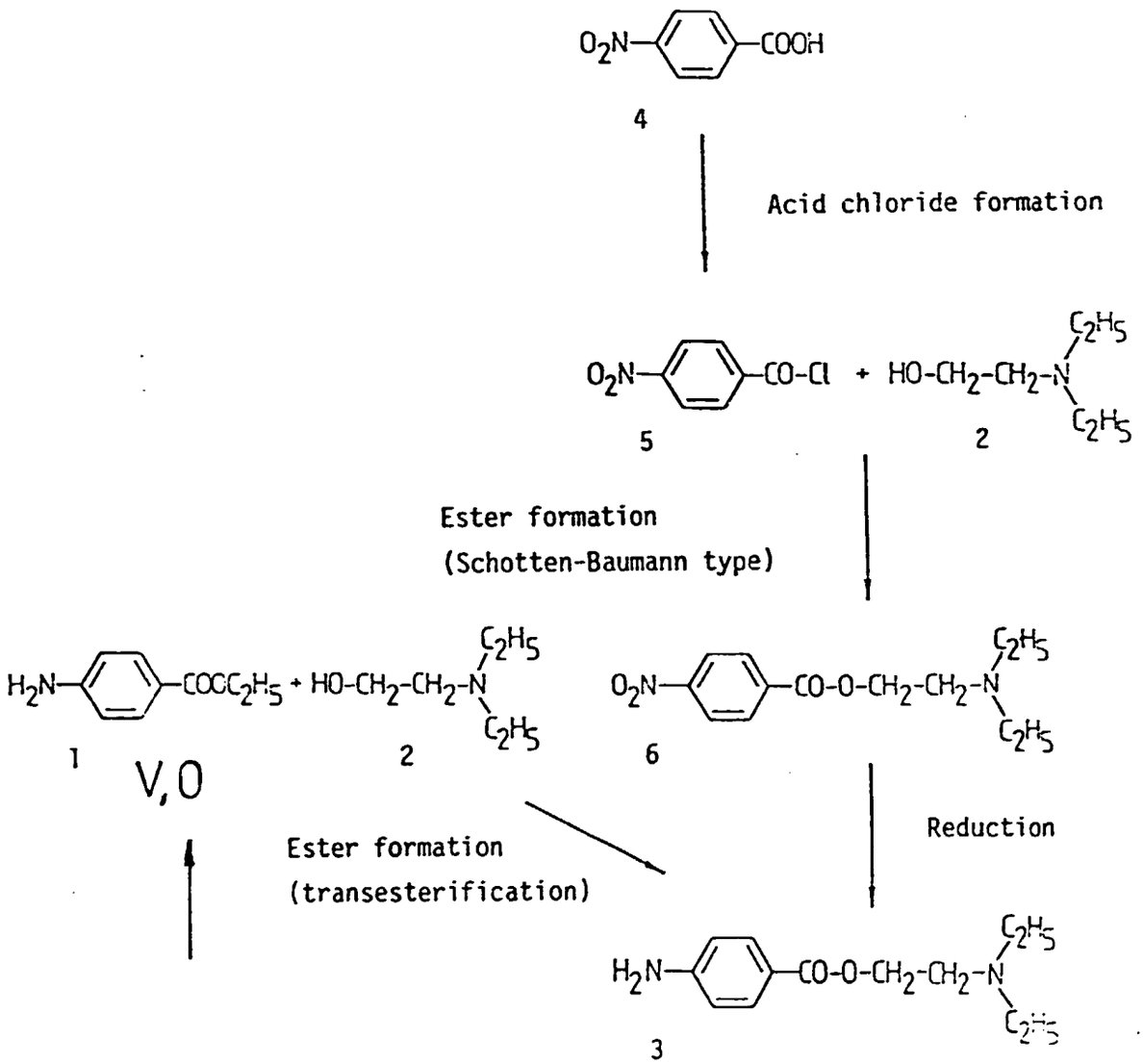


A: Ring closure reaction
(hydrazide formation)

B: Hydrogenolysis
(debenzylation)

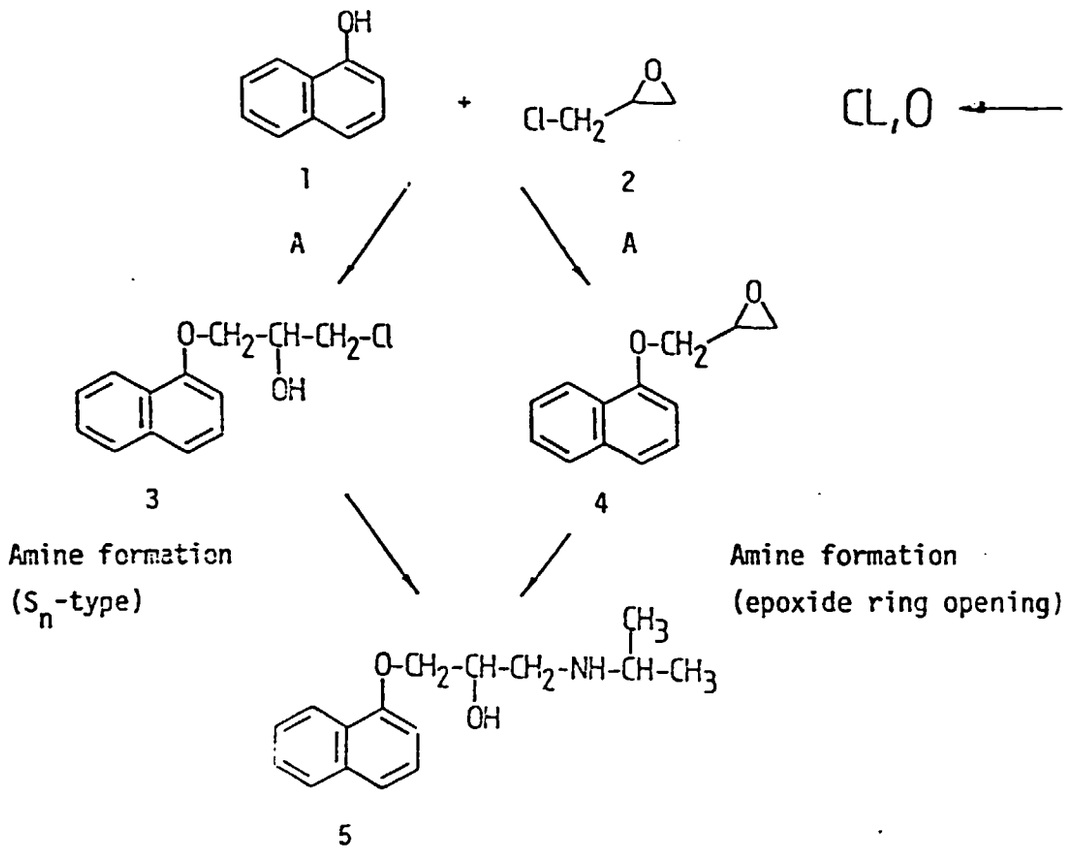
A12

PROCAINE HCl



A13

PROPRANOLOL

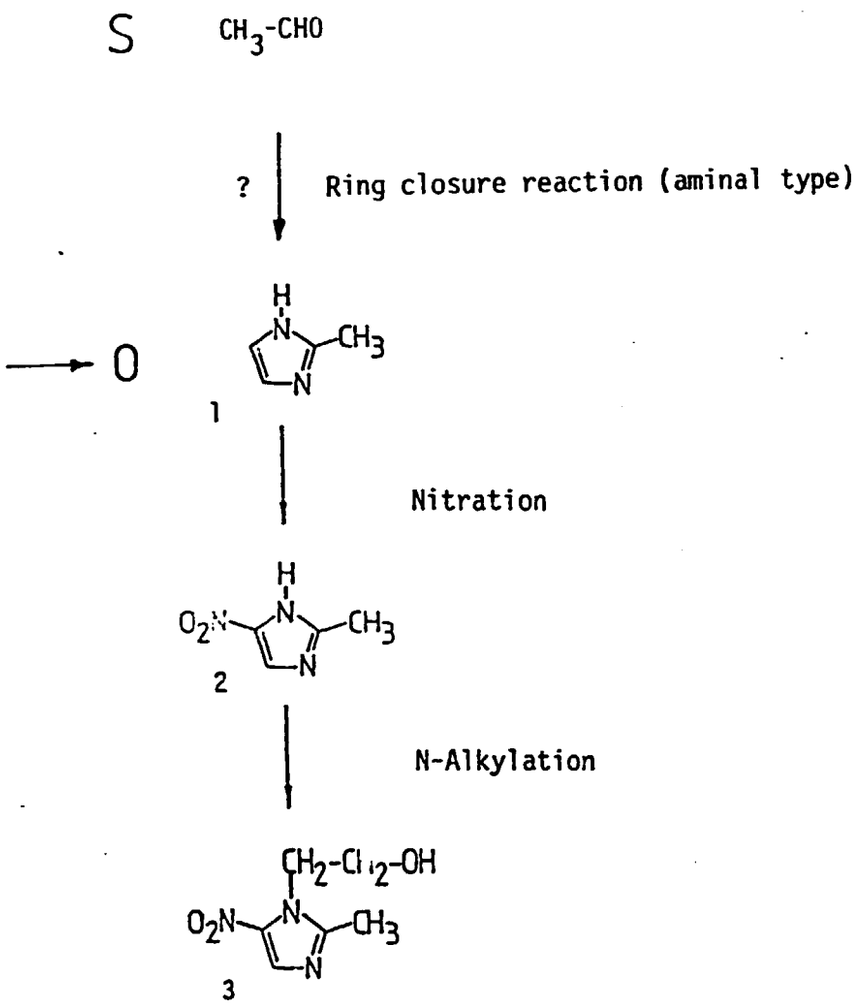


A: O-Alkylation

Cl

METRONIDAZOLE

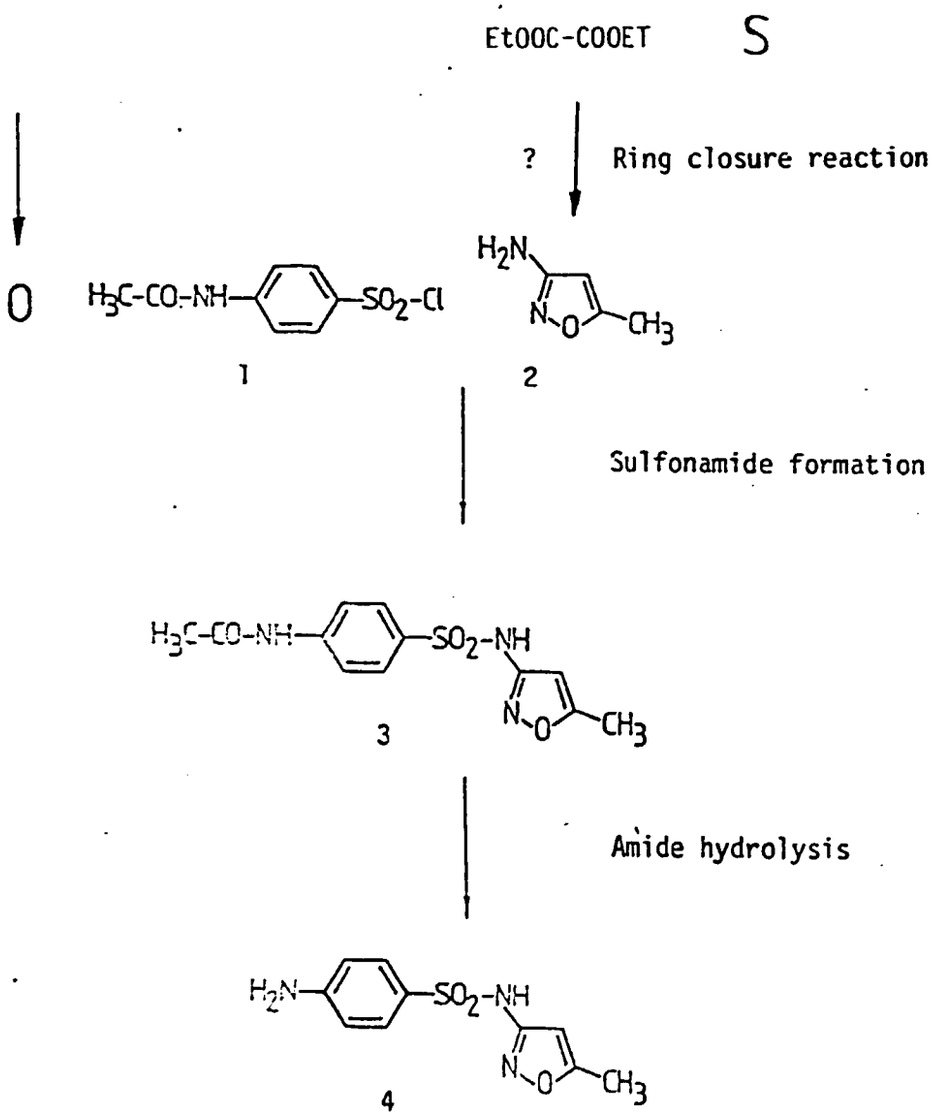
TYPES OF CHEMICAL REACTION



C2

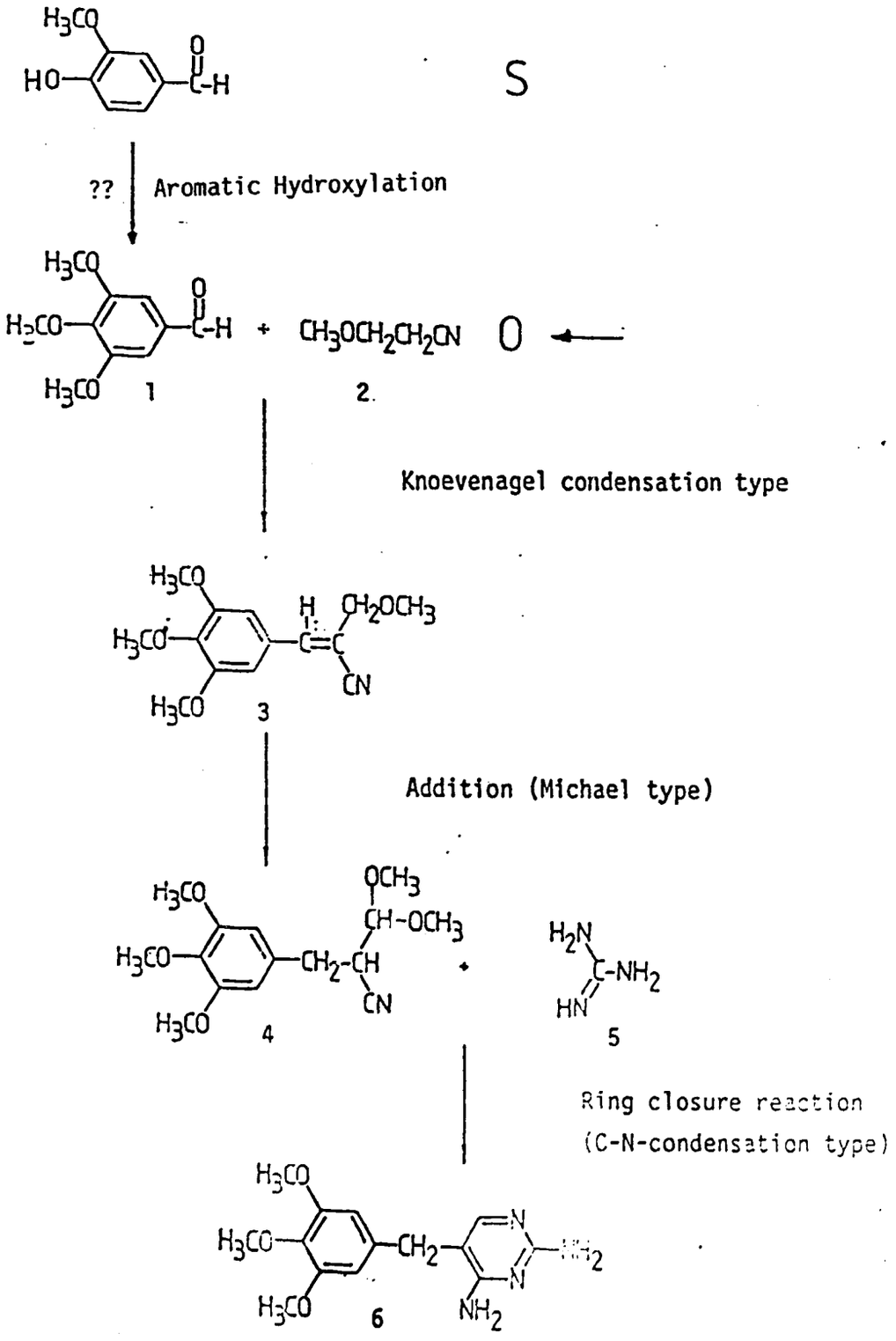
SULFAMETHOXAZOLE

TYPES OF CHEMICAL REACTION



C3

TRIMETHOPRIM



LIST OF EQUIPMENT

1. REACTORS

2 or 3	1	3000 l	enamelled steel	
	4	3000 l	stainless steel	
	1	1600 l	enamelled steel	cr
	2	1600 l	stainless steel	1 of them oil heated
	2	1250 l	enamelled steel	cr
	1	500 l	enamelled steel	
	1	1250 l	stainless steel	
	1	500 l	stainless steel	

2. CENTRIFUGES

1	1250 l	halar coated
4	1250 l	stainless steel

3. DRYERS

1	paddle dryers, discotherm
2	tray dryers, each 30 trays
1	fluid bed dryer

4. FILTERS

2	bag filter	each 1 m^2, in pairs
2	bag filter	each 0,5 m^2

5. PUMPS

3	excentric worm pumps	SS	10 m^3/h	6 bar
1	excentric worm pump	Teflon	10 m^3/h	6 bar
3	centrifugal pumps	PP	10 m^3/h	1 bar
1	centrifugal pump	teflon	10 m^3/h	1 bar
2	double diaphragm pumps	Teflon	10 m^3/h	0,5 bar
5	centrifugal pumps	SS	10 m^3/h	1 bar
1	water ring pump		200 m^3/h	
1	water ring pump		100 m^3/h	
1	rotary gear pump		50 m^3/h	0,01 mbar

6. CONDENSERS

2	4 m^2	glass
3	6 m^2	glass
3	8 m^2	glass
5	12 m^2	glass

7. TANKS

Dimension and number Vegyterv B, other material

8. VESSELS AND RECEIVERS

3	3000 l	PE	
2	1500 l	PE	
2	600 l	Halar	
8	600 l	SS	
2	250 l	PP	vacuum buffer
3	500 l	enamelled steel	
4	500 l	SS	
3	300 l	SS	
1	300 l	glass	
4	200 l	glass	
4	100 l	glass	

9. BALANCES

4	300/600 kg	ex electr.,	SS
3	300/600 kg	electr.	SS
1	150 kg	electr.	
1	50 kg	electr.	

10. LABORATORY EQUIPMENT

Corresponding to terms of reference

11. UTILITIES

Corresponding to version Vegyterv B.

But: point 1: 4500 kg/h 12 bar

12. MISCELLANEOUS

2	scrubbers (20.000 m^3/h)
1	mill including separator
1	compressor (250 m^3/h, 8 bar)
1	high vacuum distillation

ESTIMATION OF ADDITIONAL EQUIPMENT COST

With respect of short time available the estimation had to be rather rough. It is, as the estimations in the main report, based on prices for equipment units on the Western European market and can therefore only be indicative.

The estimation is based on an assessment of equipment required for each reaction step of synthesis of the 13 drugs. According to this a required reactor capacity of 24 m^3 was chosen.

Estimated additional cost of equipment compared to terms of reference equipment as indicated on page 98 of the main report:

480.000 US$

Percentage $\sim$ 33%

The production levels used in this estimation were those of the terms of reference. For the drugs, which were introduced later, production levels given in the main report (p.100) were taken.

SURVEY ON TYPES OF EQUPIMENT

A survey on different types of equipment to be used in a multi-purpose plant is given on the following pages. This survey deals mainly on the question of choice of specifically suited units and the question of materials.

REACTORS

Reactors are classified according to their construction material.

Steel reactors regardless the type of material e.g. 4571 or 4301 cannot be used for storage and reacting of acids, such as hydrochloric acid, hydrobromic acid etc., because even highly alloyed steel e.g. Hastelloy is resistant towards acids of this type only at low concentrations of acid and low temperatures. These reactors are mainly suited for reactions with bases and organic media.

Enamelled steel reactors are suited for reactions in acidic media. As far as enamel is concerned different types of enamel exist:

Standard glass lining is very well suited for use in acidic media with exception of hydrofluoric acid. It can however only be used to limited extent in the presence of bases.

Base resistant enamel which is useful for reactions in bases exhibits only about 50 % of resistance towards acids compared to standard enamel.

Crystal enamel is the third type of lining material. Its main advantages are good mechanical and corrosion resistance.

Enamel lined reactors as a rule have a bottom drain with an enamel valve. In case of emptying liquid together with solid compounds great mechanical ware of the valve can occur on closing the valve. Due to mechanical strain of the enamel in this case the use of a teflon lid seems advisable

Heating of the reactors is effected either by internal heating elements, by double coating or halftube coils surrounding the coating. Internal heating may be effected by electric heating elements or by heating elements through which a heating medium is passed. The disadvantage of electrical heating lies in the high surface temperatures of the elements which can lead to decompositions at the surface. Elements which contain a heat carrier require considerable space and therefore reduce the free space in the reactor. Double coating is an economical way of heating with steam being well suited as heating medium. Double coating is less suited for liquid media because there is a strong tendency of unequal heating because of imperfect circulation of the medium. In this case and also if cooling with liquids is required it seems preferable to use half tube coils, because this type guarantees an organized circulation of the medium over the whole heating or cooling area.

CONDENSORS AND OTHER PARTS CONNECTED TO REACTORS

The material used for these parts has to meet the requirements of reaction conditions. In a multi purpose plant it does not seem advisable to use different materials for reactor and condensor. Condensors and the other parts are available in the following materials: steel, glass lined, and glass. Glass seems to be an exceptional material for this purpose. Although base resistance is lower than that of steel, this does not play a role regarding the thickness of the material used for the condensors and the size of the reactors used in the process. There are however significant advantages of glass parts such as condensors. It can be seen what is going on in the apparatus. Also cleaning is easier because contaminations are seen easily (of special importance in multi purpose plants). As a rule glass parts cost less. Special equipment can be constructed in glass more easily and cheaper. Damages are seen easier than with other materials. Standard parts render setting up of a reactor unit simpler than glass lining. The disadvantage is the danger of fractures which can be avoided by careful installation (no tensions) and treatment.

The vessels used for collecting filtrates can equally be made of steel, enamel, and glass. Use of glass for this purpose is however limited to a maximum volume of 400 l.

HIGH VACUUM DISTILLATION UNIT

Among the different methods for vacuum distillation vacuum short path distillation seems to be the most careful way for distilling thermally unstable compounds. In the process the material to be distilled is brought to a heated surface. The distance between this surface and the cooler is very small so that exposure to heat is limited very much. The distillation units can be used in a continuous process so that relatively small units give sufficient capacity.

EXTRACTION

GENERAL REMARKS

In principle there are continous and discontinuous processes. The discontinuous process can be done in suited stirred reactors. The relatively small contact surface between the phases results in prolonged operation time. The advantage lies in the fact that this method can be carried out in units which are part of the project equipment anyway. As soon as capacity questions arise the occupation of different units for the purpose of extraction has to be examined.

CONTINUOUS EXTRACTORS

There are three process groups for continuous extraction: mixer settler , column extraction and mixers which are adapted to continuous extraction

Mixer settler consist of a mixing chamber and a settling chamber in one unit. Several units can be installed in serial operation to achieve the required efficiency.

As far as column extraction is concerned a great exchange surface is obtained by different internal structures e.g. pulsed columns, columns with moving internal structures, columns with rotors. Column mixers, such as Graesser-contactor have specially shaped mixing elements and settling chamber from which the extract can be removed.

The choice of extracting system depends from capacities envisaged and the specific problems of each process. The cost of extraction systems differ considerably especially when comparing discontinuous with continuous process.

PUMPS

GENERAL REMARKS CONCERNING THE OFFERS

Except for water ring pumps in none of the offers the type of pump is indicated. Since pumps are used for different purposes in a multi purpose plant the main fields of application are discussed separately concerning advantages and disadvantages of different types.

PUMPS FOR FILTRATION UNDER PRESSURE

For filtration under pressure gear wheel pumps , rotary piston pumps and eccentric worm pumps are well suited in principle. With reference to the envisaged production removal of active carbon and filter aids will be the main application. Both compounds can cause considerable abrasion. The construction material of gear wheel pumps and rotary piston pumps usually is alloy steel (DIN 4571 or less alloy) so that with reference to the application extreme abrasion has to be expected. As far as eccentric worm pumps are concerned rotor stator combinations are commercially available in alloy steel and different plastics such as PP, PE, PVDF, or ECTF respectively which results in a reduced mechanical wear and prolonged lifetime due to the elasticity of the material.

Another aspect to be considered-especially in a multi purpose plant-is a great versatility in the use of the pumps. The use of plastics in eccentric worm pumps enables the application for acids, bases and organic solvents. The choice of suitable plastic materials also allows thermal stress caused by the medium in hot filtration.

PUMPS FOR FILLING AND EMPTYING OF REACTORS

Mainly drum pumps , centrifugal pumps and diaphragm pumps are used for filling and emptying reactors. Drum pumps provide optimum flexibility since they are not heavy and simple in handling. They are profitable because pump shafts of different materials are available and can be used with the same motor. The disadvantage of this type of pump is the low unit output and the little altitude of pumping which excludes them for the present project. Centrifugal pumps meet the requirements of quantity and altitude of pumping. They are commercially available in different materials with PP being especially recommendable with respect of chemical resistance and price. It must however be considered that PP is not suited for elevated temperatures. For this purpose selected use of teflon pumps can be recommended with the greater chemical resistance being an additional aspect. For certain types of application diaphragm pumps can be considered useful, especially for transport of liquids with relatively great content of solids. These pumps are available in different materials, including teflon. With respect to the fact that the production area has to be explosion protected, an additional advantage of the diaphragm pumps is that as a rule they are supplied for compressed air drive and thus can be used saving cost and maintenance. Compressed air diaphragm pumps with constant air pressure are also suited for adding fluid chemical to a reaction.

Another type of pumps are the peristaltic pumps . These simple pumps are also suited for transport of liquids with great content of solids. Caused by the material of the flexible tube (standard: rubber, but also other elastomers available) this type of pump is not suited for highly corrosive liquids.

VACUUM PUMPS

The water ring pump is the most widely used type of vacuum pump and is available on the market for all dimensions foreseen in the project. The materials used for these pumps are stainless steel and grey cast iron. The great quantity of water usually renders also aggresive vapors harmless for thepumps. The disadvantage is the limited vacuum of about 20mm which can be achieved only in the most favourable cases using additional injectors. A further disadvantage is the relatively high consumption of electrical current in case of greater units (ca. 7 kW for 350 m^3/h).

The steam jet pump can be found in the market made of different metallic and ceramic materials. For chemical purpose ceramic steam jet pumps are ideally suited for their indifference towards corrosion. Since steam is foreseen in the project also the operational medium is available. These pumps are versatile and furnish a vacuum of about 1 mm.

If an ever better vacuum is required, rotary gate valve pumps can be used which even in relatively great units an endvacuum of 0,1 - 0,01 mm can be reached. This type of pump meets the requirements of the high vacuum distilltion planned in the project.

CENTRIFUGES

GENERAL REMARKS CONCERNING THE PROJECT

The relatively great number of different products within the project and their differing production quantities may result in the choice of different types of centrifuges.

CENTRIFUGES FOR EJECTION AT BOTTOM

These centrifuges have a ploughing device which peels the product from the wall of the centrifuge, where it is collected on the filter material, transports it to the bottom of the centrifuge and ejects it. This type of centrifuge is well suited in case of the same product being collected in the centrifuge with constant thickness of the layer because the ploughing device need not be adjusted each time. Also purification is a little tedious because of the bottom ejection. This type of centrifuge is well suited for products which are manufactered in large quantities because emptying and refilling of this centrifuge can be done quickly. This type of centrifuge is also suited for automated process control.

CENTRIFUGES FOR EMPTYING AT TOP

These centrifuges have a perforated drum which is covered by a filter bag. The centrifuged product may be carried out by hand or lifted out together with the filter bag, if there is a lifting device. Compared to the type discussed first another construction of the drum as well as another type of filter bag is required. Centrifuges for emptying at top are well suited for products which are manufactured in small quantities and where different products have to be filtered in consecutive runs. The simpler design of these centrifuges results in prolonged time for emptying, but purification is easier on the other hand.

TURN FILTER CENTRIFUGES

This type of centrifuge remains closed as well during filling and emptying. For emptying the filter fabric is turned out of the drum and the precipitate is thrown from the filter by centrifugal force. Thus there is almost no loss of tome by emptying. This type is well suited for products to be manufactered in large quantities and can be used in an automatic process. Purification is especially easy because of the horizontal position of the drum.

CONSTRUCTION MATERIALS FOR CENTRIFUGES

All centrifuges are available in stainless steel (DIN 4571) or coated with different materials. Halar and rubber coatings are approved coating materials. Halar coating is poreless and exhibits practically the same resistance as teflon. Rubber is used for coatings where the filter medium is mainly acid and no organic solvents are used.

FILTERS

PRESSURE FILTERS

ENAMELLED PRESSURE FILTERS

There are different types of construction of these filters They all consist of a closed compartment and a built in filter plate. Compared to other types the disadvantage of this type is the rather tedious process of emptying. These filters are not well suited for filtration of filter aids such as carbon and hyflo.

BAG FILTERS

Bag filters consist of a vertical tube with lid in which the filter bag (available in different materials: plastics, natural fibre) is mounted. The filter cake remains in the bag. Emptying is done in a quick and simple manner by opening the lid, removing the filter bag and turning it. The capacity can be easily adjusted by parallel arrangement of several filters with several units being operated by one pump. This type is well suited for the project.

FILTER PRESSES

Between steel frames, frames with filter fabric (made of different materials) are mounted. The product is collected in the cavities between the plates and can easily be removed. This type of filter is available in a wide range of capacities. It is well suited for the project.

All types of filter discussed here can be heated.

DRYERS

TRAY DRYERS

This type consists of an insulated case in which the product is spread on trays and dried by passing heated air. These dryers are suited for thermically stable compounds only unless they are constructed for vacuum operation. They are suited for relatively small batches only. These dryers require a long time for loading, since this is done by hand. The use of tray cars will reduce this time to almost zero, since the trays are loaded with material outside and there is only an exchange of tray cars. This drying process requires a relatively long time, but the simple design of these dryers renders purification quick and simple. Beside others this type of dryer would be suited for the present project.

DRYERS IN WHICH THE MATERIAL TO BE DRIED IS MOVED

PLATE DRYERS

These dryers operate with vacuum or without. drying and emptying proceeds continously, with the product being rolled around on plates, which can be heated according to requirement. With proceeding of the drying process the product is moved from top to bottom over several levels of plates. This type is suited for drizzling products only which are produced in great quantities and is suited for this project only limited.

PADDLE DRYERS

In the classic models of this type of dryer the product is moved by rotating paddles. Improved dryers consist of a heated horizontal tube in which the product is moved by heated discs. The dryer is practically self purifying and also suited for drying in vacuo. It can be operated as well continously as in batch and is suited for pastous and viscid products also. This type is suited for the project.

FLUID BED DRYERS

This type of dryer is mainly useful for dizzling materials because otherwise the fluid bed, in which the product is dried by the surrounding air flow, cannot be built up. There also types which process mud and pastous materials but they are designed for very great capacities which exceed the requirements of the present project.

CONE DRYERS

After corresponding modifications these devices originally designed as mixers are offered also as dryers They are also suited for drying in vacuo. They are mainly suited for drying powder and granulates. In great capacity cone dryers the top cannot be removed so that drying has to be done by installed spray heads and special instruments. This type of dryers is suited for the project to a limited extent.

BALANCES

MECHANICAL BALANCES

The main type of mechanical balances are sliding poise and pointer reading balances The precision parts of both types are made of steel and therefore susceptible to corrosion. Mainly in production areas corrosion can occur because the balances as a rule are standing in a hole in the floor to adjust the weighing-platform to the floor level which is necessary to enable quick weighing. Humidity which collects in the hole and aggressive vapors lead to increased corrosion and high rate of repair. In other areas the use of mechanical balances is recommendable mainly for price reasons. It has however to be considered the regular adjustment of the balances, which is rather complicated has to be carried out by trained personell.

ELECTRONIC BALANCES

The advantages of electronic balances is that they are less susceptible to corrosion and self- adjusting. Their weighing platforms are more flat. Therefore they can be built in more easily. Furthermore costs of maintenance are low. It has however to be considered that in explosion-protected areas also balances must be explosion protected which results in substantially higher prices.

TANKS

Tanks usually are made of steel, glass lined steel or plastics. With the normal temperature range plastic tanks can be used for many purposes such as mixing, storing and precipitating as well as steel or glass lined steel tanks. There are two main types of plastic: HDPE and PP. Both are well suited for long term use with inorganic acids, alcohols, ethers and partially ketones. Plastic tanks are not suited for long term use such as storage with aromatic and chlorinated hydrocarbons. In case of short term use with subsequent cleaning as it is the rule in a batch operated plant there is no restriction in use. Since these tanks are much cheaper compared to steel and glass lined tanks. Their use in the project is strongly recommended although they do not appear in any of the offers.

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PART 3

APPENDICES

UNIDO CONTRACT NO. 85/39

PROJECT NO.DP/IRA/83/014

ACTIVITY CODE:DP/02/32.1

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PATENTS

1967-1985

APPENDICES P1 - P21

The patents cited were obtained through a computer-assisted search of literature in Chemical Abstracts based on a combination of the compound name with the term preparation. For this reason the search may not be exhaustive in the case of some of the compounds.

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A1

CHLORDIAZEPOXIDE

PATENTS

1967-1985

ANALYSIS OF THE ABSTRACTS OF PATENTS

The preparation of chlorodiazepoxide from 2-amino-5-chlorobenzophenon oxime is described in patents A1.1, A1.2, A1.4 and A1.5 with the reaction with chloroactetylchloride being carried out in presence of zink chloride or in acetic acid (A1.4.) respectively.

In the patents A1.13. and A1.14. a process is claimed for the last step. In A1.14. a special separation and purification process is described which yields 87% chlorodiazepoxide in a minimum purity of 93.3%.

An alternative process for the preparation of 2-chloromethyl-6-chloro-4-phenylquiazolin-3-oxide is claimed in A1.17., according to which this compound is obtained in 2 steps from 2-chloroacetylamino-5-chloro-benzophenone by reaction with thionyl chloride and hydroxylamine chloride.

In A1.17. a process is described for the purification of chlorodiazep-oxide using formation of a complex with zink chloride and decomposition with water.

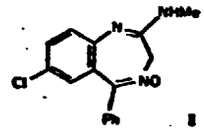
ABSTRACTS OF PATENTS

A1

CHLORDIAZEPOXIDE

Preparation

A1.1. 53386t 1,4-Benzodiazepine derivatives. Gallardo, Antonio, S. A. Span. 383,444 (Cl. A 61*k*, C 07*d*), 16 Feb 1973, Appl. 383,444, 07 Sep 1970; 7 pp. Benzodiazepine (I) was prepd. in



I

90% yield by addn. of $ClCH_2COCl$ to a soln. of 2-amino-5-chlorobenzophenone oxime in the presence of $ZnCl_2$, followed by amination with $MeNH_2$ at −5 to −10°.

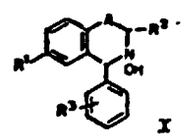
A1.2. 32115p 1,4-Benzodiazepine derivatives. Kycia, Henryk; Lenkowski, Przemyslaw; Surgiewicz, Janusz; Rolak, Hanna; Lasocka-Tatar, Barbara; Roszkowska, Danuta; Sobolew, Marek; Bartkiewicz, Boguslaw (Tarchominskie Zaklady Farmaceutyczne "Polfa") Pol. 66,212 (Cl. C 07*d*), 14 Oct 1972, Appl. 22 May 1968; 4 pp. 1,4-Benzodiazepine derivs. (I;

I III

R = halo, NO_2; A = NHCO, N:CNHME) were obtained by heating 2,5-$H_2N(R)C_6H_3C(Ph)$:NOH (II) (α, β, or mixt.) with $ZnCl_2$ and haloacetyl halogenide in a monocarboxylic aliphatic acid with 2–4 C atoms; the resulting 2-halomethyl-4-phenylquinazoline 3-oxide (III; R = H, X = halo) was treated either with alc. soln. of $MeNH_2$ or aq. alc. KOH. Thus, 25 part II (R = Cl) and 30 parts $ZnCl_2$ were added to 75 parts AcOH: to this soln. 30 part $ClCH_2COCl$ were added during 30 min at 30–55 to give 51 parts III (R = X = Cl), which, added to 100 parts 25% $MeNH_2$ at −5° and kept for 12 hrs at room temp., gave 19 parts I (R = Cl, A = N:CNHMe) m. 237–9° (MeOH).

A. Janowski

A1.3. 118349x 5-Phenyl-1,4-benzodiazepines and their derivatives. Sternbach, Leo H.; Metlesics, Werner (Hoffmann-La Roche, F., und Co., A.-G.) Swiss 507,965 (Cl. C 07*d*), 15 Jul 1971, US Appl. 01 Dec 1963; 4 pp. Benzodiazepines (I) are prepd.



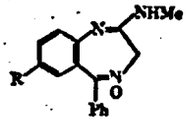
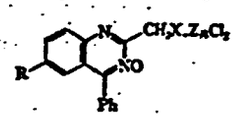
I

Thus, 5,2-$Cl(O_2N)C_6H_3CH$:NOH reduced catalytically in alc. over PtO_2 and the corresponding 2-amino compd. condensed with $ClCH_2COCl$ in Et_2O gave 5,2-$Cl(ClCH_2CONH)C_6H_3CH$:NOH, cyclized by refluxing 7 hr in C_6H_6 with $BF_3.Et_2O$ to 6-chloro-2-chloromethylquinazoline 3-oxide. This stirred with $MeNH_2$ in MeOH gave 7-chloro-2-(methylamino)-3*H*-1,4-benzodiazepine 4-oxide. This in THF treated with PhLi in 7:3 C_6H_6-Et_2O and the product isolated gave I [A = N:C(NHMe) R^1 = Cl, R^2 = R^3 = H], oxidized with HgO in 10:1 Me_2CO H_2O at 20° to 7-chloro-2-(methylamino)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide. Similarly, 7-chloro-1,3-dihydro-2*H*-1,4-benzodiazepine-2-one 4-oxide treated with PhLi in aq. Me_2SO gave I [A = NHCO R^1 = Cl, R^2 = R^3 = H], dehydrogenated with $SOCl_2$ in refluxing $CHCl_3$ to 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one, methylated by treatment of the Na deriv. with Me_2SO_4 to give 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one.

C. L. Zirkle

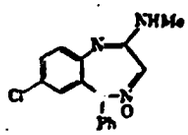
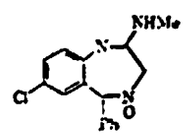
A1.4. 125747h 2-Methylamino-5-phenyl-7-chloro-3H-1,4-benzodiazepine 4-oxide. Heidrich, Hans J.; Hendel, Juergen; Roehnert, Helmut; Henker, Siegfried (VEB Arzneimittelwerk Dresden) Ger. Offen. 2,037,276 (Cl. C 07d), 04 Mar 1971, Ger. (East) Appl. 08 Aug 1969; 8 pp. Pure title compd. (I) was prepd. by stirring a soln. of crude I with aq. $CHCl_3$ and filtration of the cryst. ppt. or by reaction of 5,2-Cl(H_2N)C_6H_3C(:NOH)Ph (II) with $ClCH_2COCl$ in $CHCl_3$ soln. Thus, $ClCH_2COCl$ was added to tech. II in HOAc at <30° within 2 hr, the mixt. was stirred 16 hr at 35°. HOAc was distd. in vacuo, the residue dissolved in $CHCl_3$, filtered, the filtrate treated 2 hr at 25–30° with 43–5% aq. $MeNH_2$ and $CHCl_3$, and the ppt. digested with aq. $CHCl_3$ to give 75% pure I. KHPG

A1.5. 90539w 7-Halo-5-phenyl-2-methylamino-3H-1,4-benzodiazepine 4-oxides. Kycia, Henryk; Surgiewicz, Janusz; Lasocka-Tatar, Barbara; Bartkiewicz, Boguslaw; Lenkowski, Przemyslaw; Rolak, Hanna; Roszkowska, Danuta; Sobolew, Marek (Grodziskie Zaklady Farmaceutyczne "Polfa") Ger. Offen. 1,924,451 (Cl. C 07d, A 61k), 05 Feb 1970, Pol. Appl. 22 May 1968; 14 pp. The title compds. (I), sedatives and soporifics, are produced by treating a 2-aminobenzophenone oxime (II) with a haloacetyl halide in the presence of, e.g., $ZnCl_2$ to give III, which is then treated with $MeNH_2$. Thus, to 75 wt. parts cold AcOH was added 25 parts 2-amino-5-chlorobenzophenone oxime and 30 parts $ZnCl_2$, followed by addn. of 30 parts $ClCH_2$-


(I)

(III)

COCl at 30–5° within 30 min to yield 51 parts III (X = R = Cl), m. 210–12°. This was added at −5° to a 25% soln. of $MeNH_2$ in MeOH to give 19 parts I (R = Cl), m. 237–9°. Similarly prepd. was III (X = Br, R = Cl), m. 200–4°, and I (R = Br), m. 242–4°. J. M. Grasshoff

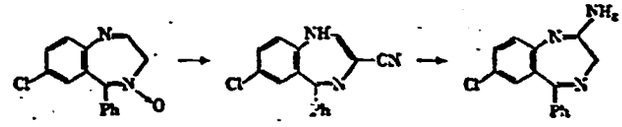
A1.6. 31854x 7-Chloro-2-(methylamino)-5-phenyl-5H-1,4-benzodiazepine 4-oxide and its transformation into 7-chloro-2-(methylamino)-5-phenyl-3H-1,4-benzodiazepine 4-oxide. Moeller, Torben T.; Nedenskov, Poul; Rasmussen, Henning B. (Hoffmann-La Roche, F., and Co. A.-G.) Ger., Offen. 1,803,911 (Cl. C 07d, A 61k), 02 Oct 1969, Dan. Appl. 19 Oct 1967; 7 pp. A mixt. of the title compds. (I) and (II), useful as psychostimulants and


(I)

(II)

sedatives, is prepd. by oxidn. of 7-chloro-2-(methylamino)-4-hydroxy-5-phenyl-4,5-dihydro-3*H*-1,4-benzodiazepine (III). I may be isomerized to II in basic soln. Thus, 4.35 g $K_4Fe(CN)_6$ and 1.11 g $NaHCO_3$ in 34 ml H_2O was mixed with 2 g III in 50 ml Me_2CO and the mixt. kept 16 hr in the dark to give 2.28 g I–II. Crystn. from EtOH gave 70% I, m. 210–12°. When the mixt. of I and II was refluxed 7 hr in a soln. of 1.08 g NaOEt in 50 ml 96% EtOH, 1.26 g II, m. 236°, was obtained. Ten ml aq. soln. contg. 1.305 g NaOCl was added at −2° to −5° to a mixt. of 0.5 g III, 0.5 g HOAc, and 15 ml Me_2CO to give 0.33 g I and 0.11 g II. P. Nedenskov

A1.7.

78030z Benzodiazepine derivatives. Field, George F.; Sternbach, Leo H. (Hoffmann-LaRoche, F., und Co., A.-G.) S. African 67 06,817 17 Jun 1968, US Appl. 15 Dec 1965; 13 pp. To a cooled mixt. of 13.5 g. 7-chloro-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (I), in 100 ml. MeOH was added 2.5 g. NaCN and the mixt. stirred 10 min., 3 ml. AcOH was added and

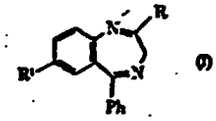


(I) (II) (III)

the mixt. stirred 30 min. to yield 7-chloro-5-phenyl-1*H*-1,4-benzodiazepine-3-carbonitrile (II), m. 211–13° (MeOH). To a refluxing mixt. of 2.3 g. II in 50 ml. MeOH was added, first 3 ml., then after 25 min., 6 ml. 3*N* NaOH and heating continued 35 min. to yield, after cooling overnight, 2-amino-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine (III), m. 236–40° (aq. MeOH and Me_2CO). III was acetylated in pyridine and Ac_2O to give 2-acetamido-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine (IV), m. 200–204° (decompn.) (AcOEt). To a soln. of 1.5 g. IV in 50 ml. dry $HCONMe_2$ was added 365 mg. of a 50% dispersion of NaH in oil, the mixt. stirred 10 min., 0.5 ml. MeI added, the mixt. stirred 3 hrs., dild. with ice water, and extd. with CH_2Cl_2 to yield 7-chloro-2-(*N*-methylacetamido)-5-phenyl-3*H*-1,4-benzodiazepine (V), (2 recrystns., undepressed on admixt. of authentic material) m. 160–4°. An ice-cold soln. of V in Me_2Cl_2 was treated with freshly prepd. Ac_2O_2 and allowed to stand overnight at 25° to yield crude 7-chloro-2-(*N*-methylacetamido)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide which was placed on a column contg. 90 g. basic Al_2O_3. Elution with AcOEt gave 7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide, m. 235–7° (CH_2Cl_2–Et_2O). III, IV, and V are sedatives, muscle relaxants, or anticonvulsants. Barbara H. Weil

A1.8.

68441v 2-Amino-5-phenyl-3H-1,4-benzodiazepine sedatives. Sternbach, Leo H.; Earley, James V.; Fryer, Rodney I. (Hoffmann-La Roche, F., und Co., A.-G.) S. African 68 01,075, 10 Sep 1968, US Appl. 03 Mar 1967; 22 pp. A soln. of 75 g. 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (Ia) in 250 ml. $HCONMe_2$ was satd. with $MeNH_2$ at 10°, the mixt. placed in a pressure vessel, the vessel charged with 67 atm. N_2, heated at 150° 24 hrs., cooled, and vented to the atm., the soln. poured into 4 l. H_2O, the mixt. adjusted to pH 6 with HCl and filtered, the ppt. dissolved in 1 l. CH_2Cl_2, the soln. extd. with 250 ml. portions of 3*N* HCl thrice, the acid exts. combined, washed with 250 ml. CH_2Cl_2, basified with NH_4OH, and extd. with 3 250 ml. portions of CH_2Cl_2, the exts. combined, washed with H_2O, dried, and filtered, the filtrate evapd., the residue boiled with 3 150 ml. portions of benzene, and the benzene fractions combined, concd., and cooled to give pale yellow I (R = MeNH, R^1 = Cl) m. 248–9° (MeOH–CH_2Cl_2). A soln. of 5 g. Ia, 30 ml. pyrrolidine, and 0.1 g. *p*-$MeC_6H_4SO_3H.H_2O$ in 100 ml.



(I)

PhMe was stirred and refluxed 22.5 hrs. with a water remover, the mixt. evapd. in vacuo, the residue extd. with Et_2O–3*N* HOAc, the acid layer filtered, and the filtrate basified with dil. NaOH to give I (R = 1-pyrrolidinyl, R^1 = Cl) (iso-PrOH). A soln. of 5 g. Ia in 125 ml. dry tetrahydrofuran (THF) was added to a soln. of 15 g. $MeNH_2$ in 100 ml. dry THF, a mixt. of 1.8 g. $TiCl_4$ in 50 ml. THF added over 20 min. at 0°, the mixt. stirred at room temp. 4 hrs., kept overnight, and filtered, the filtrate evapd. to dryness, the residue dissolved in 500 ml. CH_2Cl_2, and the soln. washed once with 200 ml. dil. NH_4OH and twice with 100 ml. satd. NaCl soln., dried, and evapd. to give I (R = MeNH, R^1 = Cl) (THF–hexane). Similarly prepd. was I (R = MeNH, R^1 = NO_2). Similarly prepd. I (R^1 = Cl) 4-oxides were (R given): MeNH, Me_2N, iso-PrNH, piperidino, NH_2. To a suspension of 25 g. 7-chloro-1,3,4,5-tetrahydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one dissolved in 300 ml. dry THF under an N atom. was added a soln. of 30 g. $MeNH_2$ in 300 ml. dry THF, the mixt. cooled in an ice bath, a soln. of 12 g. $TiCl_4$ in 100 ml. benzene added over 10 min. with stirring, the mixt. kept 4 hrs. at room temp., 20 ml. H_2O added, the soln. filtered, the ppt. washed with THF, and the combined filtrates evapd. to dryness to give 7-chloro-4,5-dihydro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine (II), m. 175–80° (MeOH–Et_2O). A soln. of 1.2 g. diethyl malonate in 10 ml. dry benzene was added to a soln. of 2 g. II in 50 ml. dry benzene and the soln. refluxed 1 hr., cooled, extd. with 50 ml. dil. NH_4OH, the benzene dried and evapd. to give I (R = MeNH, R^1 = Cl). VNPZ

A1.9. 37854c Benzodiazepine derivatives. Archer, Giles A.; Sternbach, Leo H. (Hoffmann-La Roche, F., und Co., A.-G.) Fr. 1,507,878 (Cl. 3 07d, A 61k), 29 Dec 1967, US Appl. 19 Jan 1966; 5 pp. Quaternary quinazoline derivs. react with primary amines to give the corresponding title compd. Thus, 1 g. (6-chloro-4-phenyl-2-quinazolinylmethyl)trimethylammonium 3-oxide iodide (II) was reacted 19 days at 25–3° with ~ 20 ml. $MeNH_2$ in a closed tube and worked up to give 7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide, m. 256–8°, (Me_2CO). II is prepd. by reacting 5.0 g. 6-chloro-2-dimethylaminomethyl-4-phenylquinazoline 3-oxide in 50 ml. MeOH with 5.0 ml. MeI at room temp.; II m. 201–3°, (decompn.). Also prepd. were 1-(6-chloro-4-phenyl-2-quinazolinylmethyl)-1-methylhexahydroazepinium N_3-oxide iodide, m. 205–7° (decompn.); 7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide, m. 234–7°; 7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine 3-oxide, m. 235–7°; 6-chloro-4-phenyl-2-piperidinomethylquinazoline 3-oxide, m. 151–3°; and 6-chloro-2-morpholino-4-phenylquinazoline 3-oxide, m. 159–61° decompn). Anita Mangels

A1.10. 106759u 7-Chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine N⁴-oxide. Takacsik, Tiberiu; Kosztin, Peter; Popa, Valer; Mathe, Eniko (Romania, Ministry of the Chemical Industry) Rom. 49,035 (Cl. C 07d), 23 Mar 1968, Appl. 16 Nov 1966; 2 pp. The title compd. (I) was prepd. from 2-chloromethyl-4-phenyl-6-chloroquinazoline N^3-oxide and 30% $MeNH_2$ soln. in MeOH. Thus, 31.5 kg. $MeNH_2$ soln. was cooled to 0–5° and 13.5 kg. 2-chloromethyl-4-phenyl-6-chloroquinazoline (II) was added during 15–20 min. under stirring at <15°. The reactor was closed and the reaction mixt. was heated to 48–50°, when the pressure attained 0.4–0.6 atm. After 4 hrs., the suspension was cooled to −5 to −8°, and stirred at this temp. 26–32 hrs., when I crystd. The crystn. was completed when the mother soln. reached a concn. <2.5%. The end. of the crystn. of I was detd. polarographically by comparing the filtered soln. with a standard soln. prepd. from 0.05 g. I in 60 ml. AcOH brought to 100 ml. with distd. water. The crystd. product was filtered off and washed with 2–5 l. Me_2CO cooled to 0° and then with 2–10 l. distd. water. Thus, 88–91% I, m. 231–5°, was obtained. Marcel M. Gregorian

A1.11. 105261t Derivatives of 5-phenyl-7-chloro-3H-1,4-benzodiazepine. Aktieselskabet Grindstedvaerket. Fr. 1,482,641 (Cl. C 07d, A 61k), May 26, 1967; Brit. Appl. June 9, 1965; 6 pp. A mixt. of 6 g. 5-chloro-2-nitrobenzaldehyde, 3.9 g. $HC(OMe)_3$, 0.08 g. NH_4Cl, and 4 ml. MeOH refluxed 90 min. gave 92% 5-chloro-2-nitrobenzaldehyde dimethyl acetal (I), $b_{0.1}$ 86°, n_D^{25} 1.5356. I (12.18 g.) was hydrogenated at 4 atm. on 5 g. Ni in the presence of 300 mg. KOAc in 150 ml. MeOH to give 10.6 g. 5-chloro-2-aminobenzaldehyde dimethyl acetal (II). Acylation of the crude II by AcOH–$ClCH_2CO_2H$ mixed anhydride (from 4.95 ml. $ClCH_2COCl$ and 5.25 g. KOAc in 100 ml. Cl_2C:CHCl) in 10 ml. Cl_2C:CHCl gave 14.55 g. 2-dimethoxymethyl-α,4-dichloroacetanilide (III). III, 7 g. NH_4OH.HCl, 150 ml. MeOH, and 40 ml. H_2O were boiled 5 min. to give 9.05 g. 2-(*N*-chloroacetylamino)-6-chlorobenzaldoxime (IV), m. 202–3° (decompn.) (1:2 C_6H_6–Me_2CO). A soln. of 6.9 g. IV in 200 ml. HOAc was satd. with anhyd. HCl at 60–70°. The mixt. was concd. to 3–4 ml. and extd. with 500 ml. CH_2Cl_2 and 30 ml. *M* Na_2CO_3. The dried org. layer was concd. to 50 ml. and dild. with 50 ml. Et_2O and 50 ml. petroleum ether, giving 5.17 g. 6-chloro-2-chloromethylquinazoline β-oxide (V), m. 188° (decompn.) (3:1:1 CH_2Cl_2–Et_2O–petroleum ether). V (1 g.), dissolved in 9 ml. 25% methanolic $MeNH_2$ at 5° for 30 min., then chilled to −15°, gave 0.5 g. 7-chloro-2-methylamino-3*H*-1,4-benzodiazepine 4-oxide (VI), m. 240°. Addn. of PhMgBr (from 15.84 g. PhBr) in 140 ml. Et_2O to 11.2 g. VI in 500 ml. tetrahydrofuran at 60° gave 8.3 g. 2-methylamino-4-hydroxy-5-phenyl-7-chloro-4,5-dihydro-3*H*-1,4-benzodiazepine (VII), m. 181–3° (Et_2O). Oxidn. of 1.5 g. VII by HgO g. 0.70 g. 2-methylamino-5-phenyl-7-chloro-3*H*-1,4-benzodiazepine 4-oxide (VIII), m. 242°. Treatment of 4.03 g.

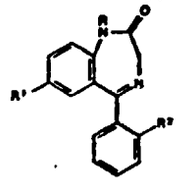
IV in 30 ml. MeOH with 16.3 ml. *N* NaOH for 15 min. under N gave 2.7 g. 7-chloro-3*H*-1,4-benzodiazepine-2(1*H*)-one 4-oxide (IX), decomp. 235° (3:5 EtOH–H_2O). [illegible] PhMgBr (from 1.84 g. PhBr) in 20 ml. Et_2O to [illegible] ml. tetrahydro[illegible] 50–60° gave 4-hydr[illegible]-chloro-1,2,[illegible]-*H*-1,4-benzodiazepin[illegible] m. 214–20° (d[illegible] 50% HOAc). VIII is a [illegible] L. R. Caswell

A1.12. 105006x 1,4-Benzodiazepines. Aktiebolaget Grindstedvaerket. Neth. Appl. 6,608,039 (Cl. C07d), Dec. 12, 1966; Brit. Appl. June 9, 1965; 14 pp. A mixt. of 6 g. 3-chloro-6-nitrobenzaldehyde, 3.9 g. 98% trimethyl orthoformate, 0.03 g. NH_4Cl, and 4 ml. MeOH was refluxed 90 min., filtered, and evapd. in vacuo, the residue added to Et_2O, the ppt. filtered off, the filtrate evapd., and the residue distd. to give 92% 3-chloro-6-nitrobenzaldehyde dimethyl acetal (I), $b_{0.1}$ 86°, n_D^{25} 1.5355. I (12.18 g.) and 300 mg. AcOK in 150 ml. MeOH was shaken 5 hrs. over 5 g. Raney Ni at 4 atm. H at room temp., the mixt. filtered, the filtrate evapd. in vacuo at 60°, 150 ml. Et_2O added to the residue, the ppt. filtered off, the filtrate dried and evapd. in vacuo, the residue dissolved in 10 ml. C_2HCl_3, a soln. of 5.25 g. AcONa and 4.95 ml. $ClCH_2COCl$ in 100 ml. C_2HCl_3 added, the whole stirred overnight at room temp. and filtered, the filtrate evapd., and the residue in 100 ml. Et_2O washed with 6% $NaHCO_3$ and dried over $MgSO_4$, the Et_2O evapd. in vacuo to give 14.55 g. yellow oil which was dissolved in 150 ml. MeOH and the whole refluxed. A soln. of 7 g. $NH_2OH.HCl$ in 40 ml. H_2O was added, the whole stirred and refluxed 5 min., 30 ml. H_2O added, and the whole was cooled to −20° to ppt. 9.05 g. 4′-chloro-6′-formyl-2-chloroacetanilide oxime (II), m. 202–3° (decompn.) formyl-2-chloroacetanilide oxime (II) m. 202–3° (decompn.) (12 C_6H_6–AcOEt). II (6.9 g.) in 200 ml. glacial AcOH was satd. at 60–70° with dry HCl, the soln. kept overnight at room temp. and concd. to 3–4 ml., and the residue worked up to give 5.17 g. 6-chloro-2-(chloromethyl)quinazoline 3-oxide (III), m. 188° (decompn.) (3:1:1 CH_2Cl_2–Et_2O-petroleum ether). III (1 g.) was dissolved at −5° in 9 ml. 25% $MeNH_2$ in MeOH and the whole heated 30 min. at 5°, cooled to −15° and kept overnight

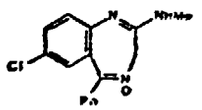
CHLORDIAZEPOXIDE

Purification

A1.13. 101: 191976j **Purification of 1,4-benzodiazepines.** Lewandowska, Maria Bozena; Morawski, Bogdan; Zarecka, Barbara; Parszewska, Halina; Tomaszewska, Irena (Tarchominskie Zaklady Farmaceutyczne "Polfa") Pol. PL 122,616 (Cl. C07D243/24), 05 Apr 1984, Appl. 221,252, 07 Jan 1980; 4 pp. Title compds. (I) (R = H, alkyl; R^1 =



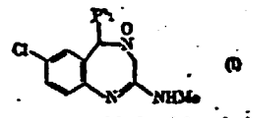
I



II

Cl, NO; R^2 = H, Cl) or II were purified by complexing them with $ZnCl_2$ in an org. solvent, then decompg. the complex with H_2O.

A1.14. 59300a Separation and purification of 7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine N⁴-oxide. Curan, Constantin; Cotschownian, Agiton; Bernstein, Aurelia (Romania, Ministry of the Chemical Industry) Rom. 48,926 (Cl. C 07*d*), 05 Nov 1967, Appl. 17 Apr 1965; 2 pp. The title compd. I was obtained by the reaction of 2-chloromethyl-4-phenyl-6-chloroquinazoline N³-oxide (II) with $MeNH_2$ in MeOH. After sepg. the reaction product by cooling at room temp. 16 hrs. and distg. the excess MeOH soln. of $MeNH_2$ or by filtration of the suspension, the purification of the obtained residue or ppt. was carried out by extg. the impurities with toluene and water. For example, to 3261 g. 20% $MeNH_2$ soln. in MeOH cooled at 10° was added in portions with stirring 964 g. II of min. purity 95% over 30 min., at 30°, the mixt. heated at 43–6° 1 hr., the mixt. stirred 16 hrs. at room temp., and excess MeOH soln. of $MeNH_2$ distd. under low pressure at 30–5°. PhMe(0.5 l.) was added to the residue, toluene-MeOH azeotrope distd. at low pressure, 1 l.



(I)

toluene and 1 l. water were added with stirring to the 2nd residue, the suspension filtered, and the ppt. washed with toluene and water until the wash toluene was only light yellowish and the distd. water did not contain Cl^- to give 74 g. 99.4%-pure I, m. 235–6°. By concg. the toluene obtained after washings, an addnl. quantity of 99.3%-pure I was obtained, the total yield of I being 87%. Marcel M. Gregorian

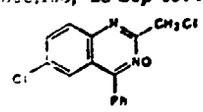
CHLORDIAZEPOXIDE

Miscellaneous

A1.15. 6240m Analgesic. Miller, Joseph Alvin, Jr. (Lilly, Eli, and Co.) Ger., Offen. 1,910,986 (Cl. A 61*k*), 18 Sep 1969, US Appl. 04 Mar 1968; 14 pp. An improved analgesic is obtained by mixing α-*d*-4-dimethylamino-3-methyl-1,2-diphenyl-2-butyl propionate (I) or a pharmaceutically acceptable salt, in an amt. which, in the presence of 7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (II) or 7-chloro-1,2-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (III) or their salts, is active as an analgesic. In general, the active oral dose of I is 0.5–30 mg./kg. body wt. of the animal. Preferably, the prepn. contains 1 wt. part II or III and 1–10 wt. parts I. Thus, I.HCl and II are tested on rats (s.c.), (Robbins test method, 1955). The uv. reaction time of the controls is about 4 sec (compd., amt. in mg/kg. and reaction time in sec given): control, —, 4.22; II, 2.0, 4.25; II, 10.0, 4.25; I.HCl and II, 7.5 and 2.0, 8.50; I.HCl and II, 7.5 and 8.0, 10.43. Harry De Moor

A1.16. 42344m Sustained release or enteric small cuboidal dosage forms. Gaunt, William E. U.S. 3,449,489 (Cl. 424-31; A 61k), 10 Jun 1969, Appl. 21 Oct 1965; 7 pp. Small cuboidal dosage forms of a variety of medicaments are provided which can be either sustained release or enteric in nature. The biol. active agent is dissolved in a volatile solvent or solvent mixt. with a film former or a film forming polymer and the soln. is cast onto a flat surface, the solvents evapd. and the remaining flexible film cut into strips and then transversely to form the cuboidal particles which are clear, transparent and glass-like. Thus, 10 g. of pentapiperide Me sulfate (I) and 10 g. of poly(vinyl acetate)-phthalate copolymer (II) were dissolved in 50 cc. of a mixt. of 80 parts of CH_2Cl_2 and 20 parts of MeOH, 20 g. of Al acetyl salicylate (III) was dissolved in 50 cc. of the same solvent mixt. The two solns. were mixed and poured into a shallow tray of approx. 250 $cm.^2$ area. The solvent was permitted to evaporate slowly and when the film weighed about 50 g., it was removed from the dish and cut into approx. 0.05 in. cubes. The remaining solvent was removed in the oven at 60°. On testing the release characteristics of these cubes using the rotating bottle technic of Souder and Ellenbogen, the following data were obtained. After gastric exposure for 1 hr., the % cumulative release was 18.5. After gastric exposure for 1 hr. and intestinal exposure for 1 hr., the % cumulative release was 25.0. After 1 hr. gastric plus 3 hrs. intestinal exposure, the % cumulative release was 35.0%. After 1 hr. gastric plus 7 hrs. intestinal exposure the % cumulative release was 45.5%. Different film formers gave different release characteristics. Using 9 parts I and 24 parts III with 12 parts of cellulose acetate phthalate (IV) or with 6 parts IV and 6 parts II, the following results were obtained. In the former case, the % cumulative release was 25.0, 57.5, 87.5 and 97.5% under the conditions described above. In the latter case, the figures were 17.5, 42.5, 67.5 and 90.0% resp. The following medicaments were also used; vitamin B_{12}, phendimetrazine-HCl, valethamate bromide, isothipendyl hydrochloride, chlorpheniramine maleate, methamphetamine-HCl, castor oil, chlordiazepoxide, Na *O,O*-dimethyl 2,2,2-trichlorohydroxyethylphosphonate and hexylresorcinol. The following film formers were also used; white wax-free shellac, refined gum sandarac, cellulose acetate succinate, poly(vinylpyrrolidinone), cellulose acetate propionate and cellulose acetate diethylaminoacetate. The following plasticizers were used; di-Et phthalate and tri-Bu acetylcitrate. The following salts were used; dibasic Al acetate, Al abietate, Al acetylsalicylate, Al laurate and Al octoate. The following solvents and solvent mixts. were used; H_2O, $CHCl_3$, iso-PrOH and EtOH. The rate of soln. of the film formers is more important in the release of the drugs than the soly. of the drugs themselves.

A1.17. 85: 33063f 6-Chloro-2-chloromethyl-4-phenylquinazoline-3-oxide and intermediates. Nakanishi, Susumu; Martin, Wayne E. (Pfizer Inc.) U.S. 2,932,323 (Cl. 260-251Q; C07D), 13 Jan 1976, Appl. 503,103, 23 Sep 1974; 4 pp. Chlorination of



I

2,4-(Bz)ClC$_6$H$_3$N:HCOCH$_2$Cl by $SOCl_2$ in refluxing $CHCl_3$ gave 2,4-(Bz)ClC$_6$H$_3$N(O)(CH$_2$Cl)Cl, which underwent cyclization with $NH_2OH.HCl$ in pyridine at room temp. to give the title compd. I.

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A2

CLOFIBRATE

PATENTS

1967-1985

APPENDIX P2

ANALYSIS OF THE ABSTRACTS OF PATENTS

In the patents A2.2. and A.2.4. the preparation of clofibrate is described according to the standard process, with A2.4. being an improvement of A2.2. (same inventor). The yield of clofibric acid is 38-89%, the subsequent ester formation yields 94%.

In A2.3. clofibrate is obtained from clofibric acid by ester formation with ethyl acetate. Patent A2.1. proceeds from sodium-4-chlorophenoxide and 2-chloroisobutyric acid.

ABSTRACTS OF PATENTS

A2

CLOFIBRATE

Preparation

A2.1. 86: 155332a Ethyl α-(4-chlorophenoxy)isobutyrate. Takasu, Itaru; Hiramoto, Takashi; Yokoo, Hiroshi; Takahashi, Hiroshi; Satoh, Kazuo (Daicel Ltd.) Japan. Kokai 76,125,337 (Cl. C07C69/67), 01 Nov 1976, Appl. 75/48,963, 22 Apr 1975; 7 pp. 4-$ClC_6H_4OCMe_2CO_2Et$ (I) was prepd. by treatment of an alakalai metal 4-chlorophenoxide with Me_2CXCO_2Et (II; X = halo). Low-boiling impurities were removed by distg. off the excess II and treating the residue with an alkali metal ethoxide. Thus, a mixt. of 64.3 g 4-ClC_6H_4OH and 80 g 25% NaOH in PhMe was dehyrated via the PhMe-H_2O azeotrope and the resulting 4-ClC_6H_4ONa as a slurry in PhMe treated with 113 g II (X = Cl), the excess evapd., and the residue stirred with 20.7 g 10% EtONa-EtOH for 1 h at 80° C with distn. of EtOH to give 91.3 g I. The product did not contain low-boiling impurities and only 6 ppm 4-ClC_6H_4OH, compared with 0.32% low-boiling impurities and 180 ppm 4-ClC_6H_4OH without the EtONa treatment. S. Okuda

A2.2. 126245s p-Chlorooohenoxyisobutyric acid and its derivative. Andreescu, Gheorghe (Fabrica Chimica "Sintoform") Rom. 52,802 (Cl. C 07c), 20 Dec 1971, Appl. 59,502, 27 Mar 1969; 2 pp. p-Chlorophenoxyisobutyric acid (I) is prepd. from p-chlorophenol, acetone, NaOH, and $CHCl_3$. $CHCl_3$ is added at 40° and the reaction is effected at 40–5° to yield 88–9% I. The Et ester is obtained from EtOH and the acid (94% yield). The Na salt is obtained by neutralization with NaOH in ethanol soln. G. Thirot

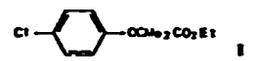
A2.3. 59244e Ethyl α-(p-chlorophenoxy)isobutyrate. Giermasinski, Jakub; Kycia, Henryk; Sobolew, Marek (Grodziskie Zaklady Farmaceutyczne "Polfa") Ger. Offen. 2,112,546 (Cl. C 07c, A 61k), 18 Nov 1971, Pol. Appl. 16 Mar 1970; 5 pp. Title compd. (I), useful as a pharmaceutical for the blood circulation system, was prepd. by esterification of p-$ClC_6H_4OCMe_2CO_2H$ (II) with AcOEt. Thus, 21.4 parts II was refluxed 8 hr with AcOEt and H_2SO_4 to give 22 parts pure I.

A2.4. 33945j Preparation of p-chlorophenoxyisobutyric acid and its derivatives. Andreescu, Gheorghe (Institutul de Cercetari Chimco-Farmaceutice) Rom. 52,886 (Cl. C 07c), 26 Aug 1971, Appl. 13 Oct 1969; 2 pp. Addn. to Rom. 52,802. In the extn. of p-chlorophenoxyisobutyric acid (I) the expensive and high-boiling solvents of the parent patent are replaced by C_6H_6, PhMe, and xylene at 20–30° and the I Na salt is obtained in Me_2CO instead of EtOH medium. Thus, to p-chlorophenol in Me_2CO, contg. NaOH is added $CHCl_3$, the soln. kept 5 hr at 40–2°. Me_2CO excess is removed and I is pptd. with dil. HCl and extd. from the aq. soln. with C_6H_6 at 20–30°. A 9% soln. of Na_2CO_3 is added to the benzene layer and after the extn. with H_2O of the Na salt, I is pptd. with HCl in 88–9% yield. Boiling with EtOH and H_2SO_4 yields I Et ester. The Me_2CO soln. of I was treated with a concd. aq. soln. of NaOH at 20–30°, yielding 98–9% Na salt. Jana Russu

CLOFIBRATE

Miscellaneous

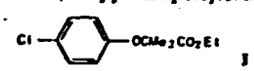
A2.5. 86: 60525k **Solid preparations containing ethyl α-p-chlorophenoxyisobutyrate.** Watanabe, Sumiko (Ishii, Hideki) Japan. Kokai 76,104,026 (Cl. A61K9/14), 14 Sep 1976, Appl. 75/26,049, 05 Mar 1975; 3 pp. Liq. *clofibrate* (Et α-*p*-chlorophenoxyisobutyrate)(I) [637-07-0] is mixed with powd. inorg. substances (such as Mg silicate, anhyd. silicic acid, and active C) to form powd. I. Thus, I 3g and Mg silicate were mixed to give a powder. The powder can be granulated with a binder.



I

K. Sempuku

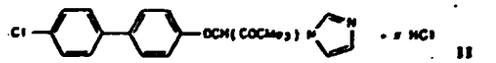
A2.6. 86: 34276k **Solid preparations containing ethyl α-p-chlorophenoxyisobutyrate.** Watanabe, Sumiko (Ishii, Hideki) Japan. Kokai 76,104,024 (Cl. A61K9/14), 14 Sep 1976, Appl. 75/26,047, 05 Mar 1975; 3 pp. Liq *clofibrate* (Et α-*p*-chlorophenoxyisobutyrate)(I) [637-07-0] is mixed with powd. carbohydrates such as D-*sorbitol* [50-70-4], *amylose* [9005-82-7], *β-cyclodextrin* [7585-39-9], or *dextrin* [9004-53-9] to produce powd. I. The powder may be granulated with a binder. Thus, 3g I and 9% D-sorbitol were mixed to give powd. I.



I

K. Sempuku

A2.7. 84: 169551a **Azole antimycotics as cosmetic agents.** Buechel, Karl H.; Plempel, Manfred (Bayer A.-G.) Ger. Offen. 2,430,039 (Cl. A61K), 08 Jan 1976, Appl. P 24 30 039.8, 22 Jun 1974; 44 pp. Imidazole and triazole compds. showing antimycolytic activity against *Pityrosporum ovale* were prepd. and used in shampoos and hair care compns. For example, 409 g *4'-chloro-4-hydroxybiphenyl* [28034-99-3] was treated with 260 g *α-chloropinacolone* [13547-70-1] to give 513 g *1-[4'-(4''-chlorophenyl)phenoxy]-3,3-dimethyl-2-butanone* (I) [58732-36-8]. I (650 g) was treated with 280 g *imidazole* [288-32-4] to give *1-imidazol-1-yl-1-[4'-(4''-chlorophenyl)phenoxy]-3,3-dimethyl-2-butanone-HCl* (II) [58949-85-2]. II inhibited growth of *P. ovale* cultures at concns. <1 mcg/ml when examd. after 3 days. A lig. shampoo compn. contg. 50.0% monoethanolammonium lauryl sulfate, 3.5% oleic acid diethanolamine, 45.5% H_2O, 1.0% antimycolytic, and desired amts. of perfume, dye, or preservatives was prepd.



II

A2.8. 89: 42336v **Aminated halophenoxy compounds useful in the treatment of lipid equilibrium disorders.** Laboratorios Funk S. A. Span. 439,155 (Cl. C07C), 16 Oct 1977, Appl. 01 Jul 1975; 26 pp. *p*-Halophenoxyisobutyric acid amine salts or amides were prepd. for use as hypolipemics and antiatherosclerotics (no data). Thus, clofibric acid salts with imidazole or $Et_2NCH_2CH_2OH$ were prepd. by reaction of the components in ether-ethanol. The amide *p*-$ClC_6H_4OCMe_2CONHR$ (R = 2-pyridyl) was prepd. by oxidation of clofibric acid chl

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A3

CLOTRIMAZOLE

PATENTS

1967-1985

APPENDIX P3

ANALYSIS OF THE ABSTRACTS OF PATENTS

The patents for the preparation of clotrimazole belong mainly to three companies: A3.3. - A3.15. to Kyowa Hakko Kogyo Co., the patents A3.17. - A3.28. to Sumitomo and the patents A3.29. and A3.31. - A3.36. to Bayer.

Among these patents the reaction of o-chlorotritylchloride with imidazole which is frequently reacted as a complex metal salt is protected in the following patents: A3.16., A3.17., A3.22., A3.23., A3.27., A3.29., A3.30., A3.32., A3.33. and A3.35.

In the patents A3.1. - A3.5., A3.13. - A3.15., A3.18. - A3.21., A3.24., A3.26., A3.28. and A3.36. o-chlorotriphenylcarbinole reacts with imidazole in the presence of acidic catalysts.

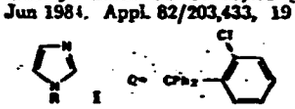
ABSTRACTS OF PATENTS

A3

CLOTRIMAZOLE

Preparation

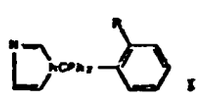
A3.1. 101: 171250q 1-(O-Chlorotrityl)imidazole. Kotobuki Seiyaku K. K. Jpn. Kokai Tokkyo Koho JP 59 95,275 [84 95,275] (Cl. C07D233/62), 01 Jun 1984. Appl. 82/203,433, 19 Nov 1982; 2 pp.



I

The title compd. [I, R = Q (II)] was prepd. by reaction of HOQ with AcCl and treatment of the product with I [R = Ac (III), cyano]. Thus, 0.47 g AcCl in 3 mL CH_2Cl_2 was added to 1.47 g HOQ in 17 mL CH_2Cl_2 at room temp., the resulting mixt. refluxed for 1 h, 0.66 g III and 1.66 g K_2CO_3 were added, and the resulting mixt. was refluxed for 3 h to give 1.01 g II.

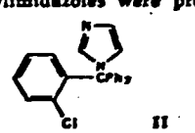
A3.2. 101: 130591r N-(Triphenylmethyl)imidazoles. Biernat, Jan; Luboch, Elzbieta (Politechnika Gdanska; Instytut Przemyslu Farmaceutycznego) Pol. PL 116,755 (Cl. C07D233/62), 30 Jun 1981, Appl. 208,869, 03 Aug 1978; 3 pp. Title compds. (I) (R = H,



I

Cl) were prepd. Thus, 20 mL pyridine, then 11.8 mL $Cl_2P(O)OEt$ were added to 14 g imidazole in 30 mL MeCN, the mixt. was stirred a few min, 18.8 g 2-$ClC_6H_4CPh_2OH$ were added, and the whole was refluxed 5 h to give 56% I (R = Cl).

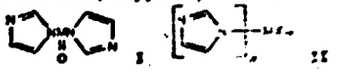
A3.3. 101: 23472y 1-Triphenylmethylimidazoles. Kyowa Hakko Kogyo Co., Ltd. Jpn. Kokai Tokkyo Koho JP 58,193,471 [83,193,471] (Cl. C07D233/62), 18 Nov 1983, Appl. 82/80,807, 13 May 1982; 4 pp. 1-Triphenylmethylimidazoles were prepd. by reaction of



II

triphenylmethanols with imidazole (I) in the presence of heteropoly acid catalysts. Thus, a mixt. of 5.9 g (2-ClC_6H_4)Ph_2COH, 10 mL AcOH, 10 g $H_3PMo_{12}O_{40}$, and 6.8 g I in trichloroethane was kept 12 h at 110° to give 72.5% imidazole II. Similarly prepd. was 1-triphenylmethylimidazole. K. Sempuku

A3.4. 100: 209827c 1-Triphenylmethylimidazoles. Kyowa Hakko Kogyo Co., Ltd. Jpn. Kokai Tokkyo Koho JP 59 16,879 [84 16,879] (Cl. C07D233/62), 28 Jan 1984, Appl. 82/124,374, 15 Jul 1982; 3 pp.



I II

1-Triphenylmethylimidazoles were prepd. by reaction of triphenylmethanols with activated imidazoles I (X = Se, O) or II (X = halo; n = 0–3; m = 1–4; m + n = 4). Thus, 2.55 g (2-ClC_6H_4)Ph_2COH was added to a mixt. of 7 g imidazole and 1.06 g $SeOCl_2$ in MeCN and the whole refluxed 8 h to give 58% 1-(o-chlorophenyldiphenylmethyl)imidazole. Also, 1-tritylimidazole was prepd. K. Sempuku

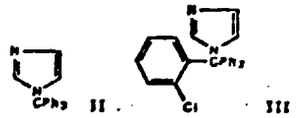
A3.5. 100: 209322x 1-(Triphenylmethyl)imidazoles. Kyowa Hakko Kogyo Co., Ltd. Jpn. Kokai Tokkyo Koho JP 58,216,164 [83,216,164] (Cl. C07D233/62), 15 Dec 1983, Appl. 82/100,159, 11 Jun 1982; 3 pp. 1-(Triphenylmethyl)imidazoles were prepd. by reaction of triphenylmethanols with 1-unsubstituted imidazoles in the presence of $(XSO_2)_2O$ (I, X = halo) or $(XSO_2O)_2$. Thus, 1.2 g I (X = F) was added to 2.95 g (o-chlorophenyl)diphenylmethanol in CH_2Cl_2 at −10°, 3.4 g imidazole added 1 h later, and the whole let react 30 min to give 63.8 % 1-[(o-chlorophenyl)diphenylmethyl]imidazole. Also, prepd. was 1-(triphenylmethyl)imidazole. K. Sempuku

A3.6. 100: 209821w 1-(Triphenylmethyl)imidazoles. Kyowa Hakko Kogyo Co., Ltd. Jpn. Kokai Tokkyo Koho JP 58,216,166 [83,216,166] (Cl. C07D233/62), 15 Dec 1983, Appl. 82/100,161, 11 Jun 1982; 3 pp. 1-(Triphenylmethyl)imidazoles were prepd. by reaction of triphenylmethanols with 1-unsubstituted imidazoles in the presence of RSO_2OR^1 (I; R, R^1 = aryl, alkyl). Thus, 3.4 g I (R = F_3C, R^1 = Me) was added to a mixt. of 2.95 g (2-ClC_6H_4)Ph_2COH and 3.5 g imidazole in trichloroethane and the whole let react 7 h at 90° to give 52 % 1-[(o-chlorophenyl)diphenylmethyl]imidazole. Also, prepd. was 1-(triphenylmethyl)imidazole. K. Sempuku

A3.7. 100: 209820v 1-(Triphenylmethyl)imidazoles. Kyowa Hakko Kogyo Co., Ltd. Jpn. Kokai Tokkyo Koho JP 58,216,165 [83,216,165] (Cl. C07D233/62), 15 Dec 1983, Appl. 82/100,160, 11 Jun 1982; 3 pp. 1-(Triphenylmethyl)imidazoles were prepd. by reaction of triphenylmethanols with 1-unsubstituted imidazoles in the presence of $XOSC_2X^1$ (I, X, X^1 = halo). Thus, 1.5 g I (X = X^1 = F) was added to 2.95 g (2-ClC_6H_4)Ph_2COH in CH_2Cl_2 at −40°, 3.4 g imidazole added 1 h later, and the whole let react 30 min to give 60.9 % 1-[(o-chlorophenyl)diphenyl]imidazole. Also prepd. was 1-(triphenylmethyl)imidazole. K. Sempuku

A3.8. 100: 209319b 1-(Triphenylmethyl)imidazoles. Kyowa Hakko Kogyo Co., Ltd. Jpn. Kokai Tokkyo Koho JP 58,216,163 [83,216,163] (Cl. C07D233/62), 15 Dec 1983, Appl. 82/100,158, 11 Jun 1982; 3 pp. 1-(Triphenylmethyl)imidazoles were prepd. by reaction of triphenylmethanols with 1-unsubstituted imidazoles in the presence of anhyd. HNO_3, NO_2, N_2O_4, or their mixts. Thus, 15 mL liq. H_2SO_3 and then 1 g NO_2 were added to 2.95 g (2-ClC_6H_4)Ph_2COH in CH_2Cl_2 at −30°, 3 g imidazole was added 1 h later, and the whole let react 1 h to give 56 % 1-[(o-chlorophenyl)diphenylmethyl]imidazole. Also, 1-(triphenylmethyl)imidazole was prepd. K. Sempuku

A3.9. 100: 209813v 1-Triphenylmethylimidazoles. Kyowa Hakko Kogyo Co., Ltd. Jpn. Kokai Tokkyo Koho JP 58,198,470 [83,198,470] (Cl. C07D233/62), 18 Nov 1983, Appl. 82/80,808, 13 May 1982; 3 pp. 1-Triphenylmethylimidazoles were prepd. by reaction of



II III

triphenylmethanols with imidazole (I) in the presence of $(COX)_2$ (X = halo). Thus, refluxing a mixt. of Ph_2COH 2.6, I 2.04, and $(COCl)_2$ 1.3 g in MeCN 12 h gave 65.1% imidazole II. Similarly prepd. was III. K. Sempuku

A3.10. 100: 121075v 1-(Triphenylmethyl)imidazoles. Kyowa Hakko Kogyo Co., Ltd. Jpn. Kokai Tokkyo Koho JP 58,189,167 [83,189,167] (Cl. C07D233/62), 04 Nov 1983, Appl. 82/72,864, 30 Apr 1982; 3 pp. 1-(Triphenylmethyl)imidazoles were prepd. by reaction of triphenylmethanols with imidazole (I) in the presence of concd. HNO_3, fuming HNO_3, HSCN, or their salts. Thus, 15 mL liq. H_2SO_3 (inorg. solvent) and 5.2 g fuming HNO_3 were added to 2.6 g Ph_3COH in CH_2Cl_2 at −20°, the whole was kept 0.5 h, 3.1 g I added, and the whole kept 1 h at −20° to give 63.4% 1-[(o-chlorophenyl)diphenylmethyl]imidazole. Also prepd. was 1-(triphenylmethyl)imidazole.

K. Sempuku

A3.11. 100: 121073u 1-(Triphenylmethyl)imidazoles. Kyowa Hakko Kogyo Co., Ltd. Jpn. Kokai Tokkyo Koho JP 58,170,765 [83,170,765] (Cl. C07D233/62), 07 Oct 1983, Appl. 82/53,243, 31 Mar 1982; 3 pp. 1-(Triphenylmethyl)imidazoles were prepd. by reaction of triphenylmethanols with imidazole (I) in the presence of concd. H_2SO_4 or fuming H_2SO_4. Thus, reaction of 6.81 g I with 5.2 g Ph_3COH in CH_2Cl_2 contg. 5.21 g fuming H_2SO_4 at room temp. for 15 min gave 72% 1-(triphenylmethyl)imidazole. Also, prepd. was 1-[(o-chlorophenyl)diphenylmethyl]imidazole. K. Sempuku

A3.12. 100: 121073t 1-(Triphenylmethyl)imidazoles. Kyowa Hakko Kogyo Co., Ltd. Jpn. Kokai Tokkyo Koho JP 58,170,764 [83,170,764] (Cl. C07D233/62), 07 Oct 1983, Appl. 82/53,242, 31 Mar 1982; 3 pp. 1-(Triphenylmethyl)imidazoles were prepd. by reaction of triphenylmethanols with imidazole (I) in the presence of SO_3. Thus, reaction of 5.45 g I with 5.21 g Ph_3COH in CH_2Cl_2 contg. 3.20 g SO_3 at room temp. for 15 min gave 78% 1-(triphenylmethyl)imidazole. Also, prepd. was 1-[(o-chlorophenyl)diphenylmethyl]imidazole. K. Sempuku

A3.13. 100: 121072s 1-[(O-Chlorophenyl)diphenylmethyl]imidazole. Kyowa Hakko Kogyo Co., Ltd. Jpn. Kokai Tokkyo Koho JP 58,170,767 [83,170,767] (Cl. C07D233/62), 07 Oct 1983, Appl. 82/53,245, 31 Mar 1982; 3 pp. 1-[(o-Chlorophenyl)diphenylmethyl]imidazole (I) was prepd. by reaction of (o-ClC_6H_4)Ph_2COH (II) with imidazole (III) in the presence of $MeSO_3H$ (IV). Thus, refluxing a mixt. of II 0.29, III 0.14, IV 0.1 g in PhMe for 4 h under azeotropic removal of formed H_2O gave 96% I. K. Sempuku

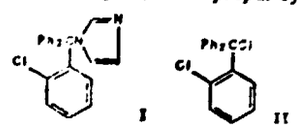
A3.14. 100: 121070q 1-(Triphenylmethyl)imidazoles. Kyowa Hakko Kogyo Co., Ltd. Jpn. Kokai Tokkyo Koho JP 58,170,765 [83,170,765] (Cl. C07D233/62), 07 Oct 1983, Appl. 82/53,244, 31 Mar 1982; 3 pp. 1-(Triphenylmethyl)imidazoles were prepd. by treating triphenylmethanols with imidazole (I) in the presence of $ClSO_3H$ (II) or FSO_3H. Thus, reaction of 6.81 g I with 5.21 g Ph_3COH and in CH_2Cl_2 contg. 2.8 g II at room temp. for 15 min gave 75.1% 1-(triphenylmethyl)imidazole. Also, prepd. was 1-[(o-chlorophenyl)diphenylmethyl]imidazole. K. Sempuku

A3.15. 100: 85701k N-Substituted imidazoles. Kyowa Hakko Kogyo Co., Ltd. Jpn. Kokai Tokkyo Koho JP 58,180,474 [83,180,474] (Cl. C07D233/62), 21 Oct 1983, Appl. 82/62,242, 14 Apr 1982; 3 pp. The title compds. I (R = Ph, o-ClC_6H_4) were prepd. by reaction

I

of imidazole with Ph_2CROH in the presence of MX_n (M = Mo, W, Zr, Ge, Ta; X = halo; n = 4-6). Thus, 2.73 g $MoCl_5$ was added to 5.44 g imidazole in 250 mL Cl_3CMe at 0-10°, the resulting mixt. stirred at the same temp. for 1 h, 2.60 g Ph_3COH added, and the resulting mixt. refluxed for 5 h to give 2.0 g I (R = Ph).

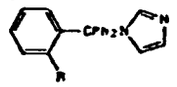
A3.16. 97: 162984d Diphenyl(2-chlorophenyl)imidazolylmethane. Kotobuki Seiyaku K. K. Jpn. Kokai Tokkyo Koho JP 82,120,571 (Cl. C07D233/62), 27 Jul 1982, Appl. 81/7,261, 21 Jan 1981; 2 pp. Title compd. (I) was prepd. by treating II with



I II

trimethylsilylimidazole (III) or 1,1-carbonyldiimidazole. Thus, heating 0.73 g II with 1.5 g III in $ClCH_2CH_2Cl$ at 75-80° 3 h gave 0.84 g I.

A3.17. 94: 139312a 1-(Triphenylmethyl)imidazoles. Sumitomo Chemical Co., Ltd. Jpn. Kokai Tokkyo Koho 80,130,954 (Cl. C07D233/61), 11 Oct 1980, Appl. 79/38,934, 30 Mar 1979; 3 pp. 1-(Triphenylmethyl)imidazoles I (R = H, Cl) were prepd. by



I

reaction of (tributylstannyl)imidazole with (2-RC_6H_4)CPh_2Cl (II). Thus, a mixt. of 680 mg imidazole and 2.98 g $(Bu_3Sn)_2O$ in C_6H_6 was refluxed 3 h with removal of H_2O, 2.22 g II (R = H) added, and the whole refluxed 3 h to give 83% I (R = H).

K. Sempuku

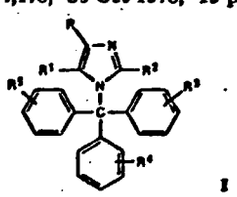
A3.18. 94: 65678n 1-Triphenylmethylimidazoles. Sumitomo Chemical Co., Ltd. Jpn. Kokai Tokkyo Koho 80 66,563 (Cl. C07D233/62), 20 May 1980, Appl. 78/141,409, 15 Nov 1978; 3 pp. 1-Triphenylmethylimidazoles were prepd. by reaction of triphenylmethanols with 1-unsubstituted-imidazoles in the presence of H_2SO_3 esters. Thus, a mixt. of di-Ph sulfite 4.68, imidazole 1.4, and Ph_3COH 4.68 g in MeCN was refluxed 5 h to give 72.4% 1-triphenylmethylimidazole. Also, 1-[o-(chlorophenyldiphenylmethyl]imidazole was prepd.

K. Sempuku

A3.19. 94: 30752e 1-Triphenylmethylimidazoles. Sumitomo Chemical Co., Ltd. Jpn. Kokai Tokkyo Koho 80 53,274 (Cl. C07D233/62), 18 Apr 1980, Appl. 78/126,499, 14 Oct 1978; 6 pp. 1-(Triphenylmethyl)imidazoles were prepd. by reaction of org. trivalent P compds. having one or two 1-imidazolyl groups with triphenylmethanols. Thus, 1.4 g imidazole was added to 1.57 g $(EtO)_2PCl$ in $CHCl_3$ with ice cooling and the mixt. kept 1 h at 0–15° to give 1.9 g diethoxy(1-imdazolyl)phosphine, which was dissolved in $CHCl_3$, 2.03 g Ph_3COH added, and the whole kept 3 h at 0–20° to give 1.37 g 1-(triphenylmethyl)imidazole. Also prepd. was 1-[(*o*-chlorophenyl)diphenylmethyl]imidazole.

K. Sempuku

A3.20. 94: 15728h N-Tritylimidazole compounds. Agui, Hideo; Saji, Ikutaro; Nakashita, Mitsuo (Sumitomo Chemical Co., Ltd.) Eur. Pat. Appl. 10,565 (Cl. C07D233/62), 14 May 1980, Japan. Appl. 78/134,178, 30 Oct 1978; 19 pp. Imidazoles I (R,



I

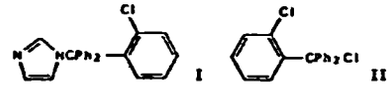
R^1, R^2 = H, alkyl, Ph; R^3, R^4, R^5 = H, alkyl, electro-neg. moiety) were prepd. Thus, refluxing 2-$ClC_6H_4CPh_2OH$ with imidazole in the presence of $(PhO)_2POH$ in pyridine gave 71.8% I (R–R^4 = H, R^5 = 2-Cl).

A3.21. 94: 15724d 1-Tritylimidazole derivatives. Sumitomo Chemical Co., Ltd. Jpn. Kokai Tokkyo Koho 80 62,072 (Cl. C07D233/62), 10 May 1980, Appl. 78/135,389, 01 Nov 1978; 4 pp.

I

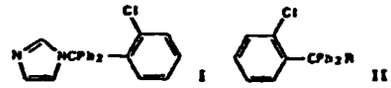
1-Tritylimidazole deriv. (I; R = Ph_3C, R^1, R^2, R^3 = H, alkyl, alkenyl, etc.) were prepd. by reaction of sulfamoyl deriv. (I; R = sulfamoyl deriv.) with Ph_3COH. Thus, 1.40 g I (R = Me_3Si, R^1 = R^2 = R^3 = H) was treated with 1.19 g $SOCl_2$ in $CHCl_3$ at 0–10° for 1 h, followed by 850 mg piperidine and 1.01 g Et_3N at 0–10° to give I (R = piperidinosulfonyl, R^1 = R^2 = R^3 = H), which was treated with 2.03 g Ph_3COH 1 h at room temp. and 2 h at reflux to give 95% I (R = Ph_3C, R^1 = R^2 = R^3 = H). Similarly prepd. was I [R = (*o*-ClC_6H_4)Ph_2C, R^1 = R^2 = R^3 = H].

A3.22. 94: 4011t 1-(o-Chlorophenyldiphenylmethyl)imidazole. Sumitomo Chemical Co., Ltd. Jpn. Kokai Tokkyo Koho 80 62,069 (Cl. C07D233/62), 10 May 1980, Appl. 78/134,965, 31 Oct 1978; 2 pp. The title compd. (I) was prepd. by reaction of



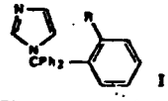
chloride II with 1*H*-imidazole over $AlCl_3$ in C_6H_6. Thus, 0.05 mol II was added to 0.055 mol $AlCl_3$ in C_6H_6 at 60° and refluxed 4 h, 0.2 mol 1*H*-imidazole added, and the mixt. refluxed 2 h to give I.

A3.23. 94: 4010s 1-(o-Chlorophenyldiphenylmethyl)imidazole. Sumitomo Chemical Co., Ltd. Jpn. Kokai Tokkyo Koho 80 62,070 (Cl. C07D233/62), 10 May 1980, Appl. 78/135,385, 01 Nov 1978; 3 pp. The title compd. (I) was prepd. by reaction of



chloride II (R = Cl) with C_6H_6 over $AlCl_3$ followed by treatment with H_2O, and subsequent reaction of the resultant alc. (II; R = OH) (III) with tri(1-imidazolyl)phosphine. Thus, a soln. of 0.6 mol II (R = Cl) in C_6H_6 was added to 0.66 mol $AlCl_3$ suspension in C_6H_6 at 60°, the mixt. refluxed 2 h, H_2O added, refluxed 4 h to give 172.6 g III, which was refluxed with a soln. of 1.8 mol each 1*H*-imidazole and Et_3N in $CHCl_3$, and 0.6 mol PCl_3 to give 77.1% I.

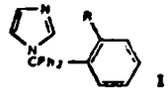
A3.24. 93: 71770g N-Substituted imidazoles. Agui, Hideo; Saji, Ikutaro; Nakashita, Mitsuo (Sumitomo Chemical Co., Ltd.) Jpn. Kokai Tokkyo Koho 80 02,044 (Cl. C07D233/62), 10 Jan 1980, Appl. 78/75,114, 20 Jun 1978; 3 pp. *N*-Substituted



imidazoles I (R = H, Cl) were prepd. by reaction of penta(1-imidazolyl)phosphorane with (2-RC_6H_4)Ph_2COH (II) in polar solvents. Thus, 6.8 g imidazole in $CHCl_3$ was added to 2.1 g PCl_3 in $CHCl_3$ with ice cooling, the mixt. stirred 1 h at room temp., 2.6 g II (R = H) added, the whole stripped of $CHCl_3$, DMF added, and the whole stirred 3 h at 130–40° to give 2.8 g I (R = H).

K. Sempuku

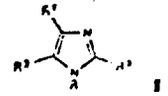
A3.25. 93: 71767m 1-Triphenylmethylimidazoles. Agui, Hideo; Saji, Ikutaro; Nakashita, Mitsuo (Sumitomo Chemical Co., Ltd.) Jpn. Kokai Tokkyo Koho 79,157,560 (Cl. C07D233/62), 12 Dec 1979, Appl. 78/66,339, 01 Jun 1978; 5 pp. Title



compds. I (R = H, Cl) were prepd. by reaction of 2-$RC_6H_4CPh_2O_2CR^1$ (R^1 = Me, CF_3) with imidazole (II). Thus, refluxing a mixt. of 1.52 g Ph_3COAc and 340 mg II in MeCN 2 h gave 82.6% I (R = H).

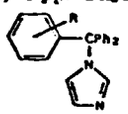
K. Sempuku

A3.26. 93: 8177d N-Tritylimidazole derivatives. Sumitomo Chemical Co., Ltd. Neth. Appl. 79 04,329 (Cl. C07D233/62), 04 Dec 1979, Japan. Appl. 78/66,341, 01 Jun 1978; 11 pp. Imidazoles



I (R = optionally substituted trityl; R^1–R^3 = H, alkyl, Ph) were prepd. Thus, Friedel-Crafts reaction of C_6H_6 with 2-ClC_6H_4... followed by hydrolysis, gave ... Ph_2OH which was ... tris(1-imidazolyl)ph... imidazole and PCl_3 ... = $CPh_2C_6H_4Cl$-2, R^1–R^3 = H) ... 75% yield.

A3.27. 93: 8174a Imidazoles. Yasukui, Hideo; Saji, Ikutaro; Nakashita, Mitsuo (Sumitomo Chemical Co., Ltd.) Jpn. Kokai Tokkyo Koho 79,151,970 (Cl. C07D233/62), 29 Nov 1979, Appl. 78/61,465, 22 May 1978; 4 pp. Ph_3CCl (0.01 mol) and 0.01 mol

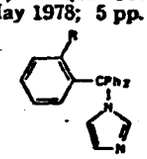


I

imidazole in MeCN were refluxed with 0.02 mol CsF for 3 h to give 77.7% I (R = H). I (R = *o*- and *p*-Cl) were similarly prepd.

S. Okuda

A3.28. 92: 215443g Imidazoles. Yasukui, Hideo; Saji, Ikutaro; Nakashita, Mitsuo (Sumitomo Chemical Co., Ltd.) Jpn. Kokai Tokkyo Koho 79,151,971 (Cl. C07D233/62), 29 Nov 1979, Appl. 78/61,466, 22 May 1978; 5 pp. A mixt. of Ph_3COH 0.01,

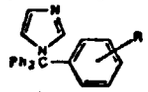


I

imidazole 0.03, and AcCl 0.03 mol in MeCN was refluxed 5 h to give 85.5% I (R = H) via Ph_3CCl; other chlorides, e.g., $MeSO_2Cl$, BzCl, *p*-$MeC_6H_4SO_2Cl$, and $PhCH_2COCl$ were also used. I (R = Cl) was similarly prepd. I had bactericidal activity (no data).

S. Okuda

A3.29. 85: 192737v N-Tritylimidazoles. Buechel, Karl H.; Regel, Erik; Grewe, Ferdinand; Scheinpflug, Hans; Kaspers, Helmut (Bayer A.-G.) Ger. 1,670,976 (Cl. C07D233/62), 22 Jul 1976, Appl. 29 Jan 1968; 7 pp. Fungicidal tritylimidazoles (I; R =



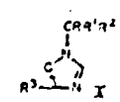
I

2-Cl, 2-MeO, 4-MeO, 3-F_3C, 4-F_3C) are prepd. by reaction of imidazole (II) with appropriate trityl halides in inert polar solvents at 0–100° in presence of hydrogen halide acceptors. Thus, reaction of II with (2-ClC_6H_4)Ph_2CCl in MeCN 4 hr at 50° in presence of Et_3N gives 74% I (R = 2-Cl).

A3.30. 77926m N-(o-Chlorophenyldiphenylmethyl)imidazole. Toth, Istvan; Toldy, Lajos (Gyogyszerkutato Intezet) Hung. Teljes 8037 (Cl. C 07*d*), 27 Apr 1974, Appl. GO-1179, 22 Dec 1971; 9 pp. *o*-$ClC_6H_4CPh_2Cl$ and imidazole (1:2 molar ratio) heated 1 hr at 100–10° and 2 hr at 110–18° gave 81% title compd.

T. Mohacsi

A3.31. 59632e N-(1,1,1-Trisubstituted) methylazole. Draber, Wilfried; Regel, Erik (Farbenfabriken Bayer A.-G.) Ger. Offen. 2,036,020 (Cl. C 07*d*, A 01*n*). 18 Nov 1971, Appl. 26 Feb 1970; 27 pp. The 143 title compds. I (R and R^1 = Ph or substituted



I

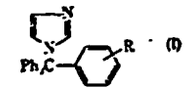
phenyl; R^2 = Ph, substituted phenyl, pyridyl, or alkyl, or R[illegible] = dibenzocycloheptenyl, xanthenyl, or thioxanthenyl; R^3 = H, Me, or Ph; Q = N, CH, or CMe) were prepd. from thienyl-bisazolides and carbinols and had good antimycotic and plant growth regulatory properties. Thus, 0.4 mole imidazole in MeCN was treated dropwise with 0.1 mole $SOCl_2$, imidazole hydrochloride filtered off, and the filtrate treated with α-(*N*-methylimidazol-2-yl)-α-(2-methylphenyl)phenyl alc., until SO_2 was released, to give I (R = Ph, R^1 = 2-methylphenyl, R^2 = methylimidazol-2-yl, R^3 = H, Q = CH).

A3.32. 125698t Fungicidal N-tritylimidazoles and -triazoles. Buechel, Karl H.; Draber, Wilfried (Farbenfabriken Bayer A.-G.) Ger. Offen. 1,940,628 (Cl. C 07d, A 61k, A 01n), 11 Feb 1971, Appl. 09 Aug 1969; 9 pp. Fungicidal title compds. Ph$_2$(R^{1}C$_6$H$_4$)(R^{2}C$_6$H$_4$)CR (I) (R = 1-imidazolyl, 1-triazolyl) were prepd. from RSiMe$_3$ and Ph(R^{1}C$_6$H$_4$)(R^{2}C$_6$H$_4$)CCl at −20 to +20°. Thus, Ph$_2$CCl in C$_6$H$_6$ was added at 0° within 30 min to RSiMe$_3$ (R = 1-imidazolyl) in C$_6$H$_6$ and the mixt. stirred 3 hr at 0° and 10 hr at room temp. to give 87% I (R = 1-imidazolyl, R^1 = R^2 = H). Among ~30 compds. similarly prepd. were I (R, R^1, and R^2 given): 1-imidazolyl, *m*-O$_2$N, H; 1-imidazolyl, *p*-F, *p*-Me$_2$N; 1,2,3-triazol-1-yl, 2,4-Cl$_2$, H. KHPG

A3.33. 125697s Fungicidal N-tritylimidazoles and -triazoles. Draber, Wilfried; Buechel, Karl H. (Farbenfabriken Bayer A.-G.) Ger. Offen. 1,940,627 (Cl. C 07d, A 61k, A 01n), 11 Feb 1971, Appl. 09 Aug 1969; 10 pp. Fungicidal title compds. Ph$_2$(R^{1}C$_6$H$_4$)(R^{2}C$_6$H$_4$)CR (I) (R = 1-imidazolyl, 1-triazolyl) were prepd. by reaction of RMgBr and Ph(R^{1}C$_6$H$_4$)(R^{2}C$_6$H$_4$)CCl at 20–50°. Thus, RMgBr (R = 1-imidazolyl), prepd. from PhMgBr and imidazole in DMF, and Ph$_3$CCl were heated 1 hr at 50° to give 100% I (R = 1-imidazolyl, R^1 = R^2 = H). Among ~32 compds. similarly prepd. were I (R, R^1, and R^2 given): 1-imidazolyl, *m*-O$_2$N, H; 1-imidazolyl, *p*-F, *p*-Me$_2$N; 1,2,4-triazol-1-yl, *o*-Cl, H; 1,2,3-triazol-1-yl, 2,4-Cl$_2$, H. KHPG

A3.34. 112048f Fungicidal N-tritylimidazoles and -triazoles. Jaeger, Gerhard; Buechel, Karl H. (Farbenfabriken Bayer A.-G.) Ger. Offen. 1,940,626 (Cl. C 07d, A 61k, A 01n), 11 Feb 1971, Appl. 09 Aug 1969; 11 pp. Fungicidal title compds. Ph(RC$_6$H$_4$)(R^{1}C$_6$H$_4$)CY (I) (Y = 1-imidazolyl or 1-triazolyl) were prepd. by reaction of RH with trityl salts at −20 to +90°. Thus, 33 g Ph$_3$C$^+$ BF$_4^-$ in 130 ml MeCN was added within 3 min to a soln. of 13.7 g imidazole in 50 ml MeCN to give 85% I (R = R^1 = H, Y = 1-imidazolyl). Among 32 compds. prepd. were I (R, R^1, and Y given): *m*-O$_2$N, H, 1-imidazolyl; *o*-Cl, H, 1,2,4-triazol-1-yl; *o*-Cl, *p*-Cl, 1,2,3-triazol-1-yl. KHPG

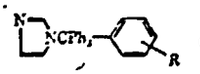
A3.35. 56939f Fungicidal 1-(substituted-phenyldiphenylmethyl)-imidazoles. Buechel, Karl H.; Regel, Erik; Grewe, Ferdinand; Scheinpflug, Hans; Kaspers, Helmut (Farbenfabriken Bayer A.-G.) S. African 69 00,039, 18 Jul 1969, Ger. Appl. 29 Jan 1968; 25 pp. 1-Tritylimidazoles (I), exhibit low toxicity to



(I)

warm-blooded animals and strong fungicidal activity. Thus, to 0.5 mole 4-ClC$_6$H$_4$CPh$_2$Cl and 0.5 mole imidazole in 500 ml MeCN, was added 0.5 mole NEt$_3$ and the mixt. kept 3 hr at 50° to yield 167 g 115 g I (R = *p*-Cl), m. 140° (C$_6$H$_6$-ligroine). The following I were similarly prepd. (R and m.p. given): *p*-F, 148°; *m*-Cl, 101°; *o*-Cl, 140°; *m*-CF$_3$, 156°; *o*-OMe, 130°; *p*-Br, 152°; *p*-SMe, 142°; *p*-Me 130°; *o*-F, 185°; *m*-F 174°; *p*-NO$_2$, 160–70°; *p*-CN, 164°. Sally Ann Sutton

A3.36. 91473m N-Tritylimidazoles as antimycotics. Buechel, Karl H.; Regel, Erich; Plempel, Manfred (Farbenfabriken Bayer A.-G.) S. African 68 05,392 24 Jan 1969, Ger. Appl. 15 Sep 1967; 19 pp. Title compds. (I) and their therapeutic uses are described. Thus, a mixt. of 1 mole Ph$_2$C(OH)C$_6$H$_4$Cl-*p* and 2 moles imidazole was heated 5 hrs. at 180° and the product ppte.



(I)

successively with xylene and benzene to give I (R = *p*-Cl) (II), m. 140–3°. Powd. imidazole Ag salt was added to an equimolar amt. Ph$_2$(*p*-ClC$_6$H$_4$)CCl in dry benzene, and the mixt. refluxed 2 hrs. with exclusion of light, filtered, and concd. to give II. The following salts of I (R = H) were prepd.: lactate, m. 170–80°; HCl, m. 155°; maleate, m. 106–7°; tartrate, m. 175–80°; citrate, m. 128–45°; acetate, m. 231°; salicylate, m. 145–60°; sorbate, m. 148–60°; succinate, m. 188–90°; fumarate, m. 20[illegible]–6°. Also prepd. were II.HCl, m. 128–30°; II lactate, m. [illegible]; II salicylate; I.HCl (R = *m*-Cl), m. 153°; I.HCl (R = *o*-Cl, m. [illegible]°; I.HCl (R = *p*-F) 119°; (lactate m. 95°; sal[illegible] m. [illegible]); I(R = *o*-F) lactate, m. 110°; and I (R = *m*-F) [illegible] m. [illegible]°. D.

CLOTRIMAZOLE

Use

A3.37. 99: 158423u 1-[(2-Chlorophenyl)diphenylmethyl]-1H-imidazole. Lazarescu, Marcela Niculina; Stoica, Constantina; Pescaru, Viorel; Cornilescu, Eugen; Cosofret, Vasile (Intreprinderea de Medicamente, Bucuresti) Rom. RO 74,907 (Cl. C07D233/62), 30 Sep 1980, Appl. 94,781, 26 Jul 1978; 2 pp. The title compd. (clotrimazole), useful as a pharmaceutical fungicide (no data), was obtained from (clotrimazole)$_2$-$ZnCl_2$ and NH_3 at 20–5°.

A3.38. 84: 175149s N-trityl imidazoles as plant fungicides. Buchel, Karl Heinz; Regel, Erik; Grewe, Ferdinand; Scheinpflug, Hans; Kaspers, Helmut (Bayer A.-G.) U.S. 3,934,022 (Cl. 424-273; A01H), 20 Jan 1976, Ger. Appl. 16 70,976, 29 Jan 1968; 10 pp.

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07712/24 75

A4

DIAZEPAM

PATENTS

1967-1985

APPENDIX P4

ANALYSIS OF THE ABSTRACTS OF PATENTS

78 patents concerning processes for production of diazepam reflect the 3 standard processes very well:

Standard Process A (reaction of ACB with ethyl glycinate chlorohydrate) is described in a modified form in patents A4.21. and A4.29., in which methylation (second step) is carried out with methyl toluene-sulfonate. In patent A4.49. methylation is carried out using trimethyl-sulfonium iodide / n-butyl lithium in DMSO/THF or trimethylsulfonium iodide / sodium hydride in DMSO. In patent A4.29. a yield of 80% and a purity of 95% is achieved which is increased to 100% by further purification steps. (The claim of the patent refers to high purity diazepam.)

In standard process B methylation is carried out prior to reaction with ethyl glycinate chlorohydrate. This last step is carried out with glycinate/zinc chloride in A4.58., glycinate chlorohydrate in pyridine in A4.66. In the patent A4.27. gycine reacts in the presence of phosphoroxychloride or phosphoroxychloride/phosphorpentoxide resp..

The synthesis claimed in patent A4.33. seems to be of particular interest because it avoids the synthesis of chloroaminobenzophenone.

In standard process C cyclisation occurs after nucleophilic replacement of halogen for amine. The use of hexamethylentetramine in this step

is described in patents A4.16.,A4.20.,A4.32.,A4.34. and A4.43. In A4.10. a process is described in which the cyclisation proceeds at temperatures ranging from 40-80°C using titanium, aluminum or zinc complexes with amine.

Two patents concern the purification of diazepam: In A4.79. purification is effected via a complex with zinc chloride, in A4.80. via the chlorohydrate.

Formula II in A4.32. is wrong, it is also cited wrong in the original patent as I in the description part, it is however cited correctly as I in the claims. Also the dihydro formula in A4.23. cannot be correct according to the production process.

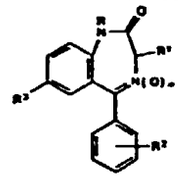
ABSTRACTS OF PATENTS

A4

DIAZEPAM

Preparation

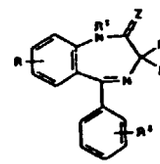
A4.1. 99: 175318u N-Alkyl derivatives of 1,4-benzodiazepine. Krawczynska, Bogumila; Morawski, Bogdan; Jaszkowska-Makosza, Anna; Chojnacka, Romualda; Kalis, Jadwiga (Tarchominskie Zaklady Farmaceutyczne "Polfa") Pol. PL 120,033 (Cl. C07D243/26), 25 Jul 1983, Appl. 210,425, 20 Oct 1978; 3 pp. I (R = C_{1-4} alkyl) were



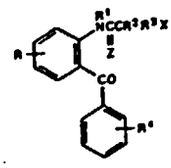
I

prepd. by two-phase alkylation of I (R = H). Thus, 9.4 mL MeI were added over 3 h at room temp. to 27.0 g I (R = R^1 = R^2 = H, R^3 = Cl, n = 0), 2.3 g $PhCH_2NEtCl$, 250 mL $ClCH_2CH_2Cl$, and 200 mL 10% NaOH to give 90% I (R^1 = Me, R^1 = R^2 = H, R^3 = Cl, n = 0). Also prepd. were I (R, R^1, R^2, R^3, n, and % yield = Et, H, H, Cl, 1, 92; Me, OH, H, Cl, 0, 98; Me, H, H, NO_2, 0, 89.3).

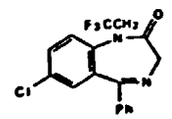
A4.2. 95: 43189x 1,4-Benzodiazepines. Schlesinger, Walter (Scherico Ltd.) Swiss 622,253 (Cl. C07D243/16), 31 Mar 1981, Appl. 76/11,575, 08 Sep 1975; 5 pp. The benzodiazepines I [R, R^4 independently = H, halo, CF_3, NO_2, allyl, OH, alkoxy; R^1 = H, (fluoro)alkyl; R^2, R^3 independently = H, alkyl; Z = O, H_2] were prepd. by the cyclization of benzophenones II (X = halo) with hexamethylenetetramine. Refluxing 5,2-Cl[$BrCH_2CON(CH_2CF_3$=)]C_6H_3COPh, hexamethylenetetramine, and NH_4Br in 85:15 Me_2CHOH-H_2O 2 h gave III.



I

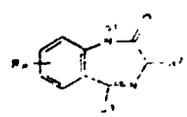


II

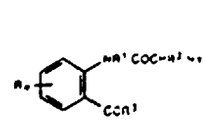


III

A4.3. 93: 46731n 1,4-Benzodiazepine derivatives. Tamura, Tsukamitsu; Ikeda, Masazumi; Ono, Kazunori (Japan Kokai Tokkyo Koho 79,157,595 (Cl. C07D243/24), 12 Dec 1979, Appl. 78/65,560, 30 May 1978; 9 pp. Sixty-six title derivs. I (R



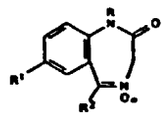
I



II

= H, NO_2, CF_3, halo, alkyl, alkoxy; R^1 = H, alkoxyl, alkenyl, (un)substituted alkyl; R^2 = H, alkyl; R^3 = pyridyl, (sub)substituted Ph; n = 1-2] were prepd. by reaction of II with Ph_3P. I had sedative, muscle-relaxing, and hypnotic activities (no data). Thus, 200 mg II (R = Cl, R^1 = R^2 = H, R^3 = Ph) was treated with 137 mg Ph_3P in [illegible] at room temp. to give 95% [illegible] (R^2 = H, R^3 = [illegible]

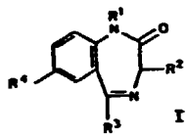
A4.4. 92: 6568n **Benzodiazepine derivatives.** Hoffmann-La Roche, F., und Co. A.-G. Austrian 351,545 (Cl. C07D243/28), 25 Jul 1979, Swiss Appl. 74/4,149, 25 Mar 1974; 6 pp. Benzodiazepines



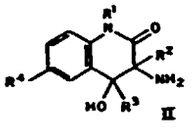
I

I (R = H, alkyl; R^1 = H, halogen, CF_3; R^2 = Ph, halophenyl, pyridyl; n = 0,1) were prepd. Thus, $O_2NCH_2CO_2H$ was converted into the chloride and treated with 5,2-Cl(H_2N)C_6H_3Bz to give $O_2NCH_2CONHC_6H_3$(Bz)Cl-2,4, which was reduced to the hydroxylamine and cyclized with acid to I (R = H, R^1 = Cl, R^2 = Ph, n = 1). Treatment of O_2NCH_2COCl with 5,2-Cl(MeNH)C_6H_3Bz and redn. of $O_2NCH_2CONMeC_6H_3$(Bz)Cl-2,4 gave I (R = Me, R^1 = Cl, R^2 = Ph, n = 0).

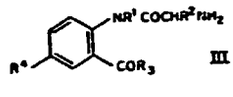
A4.5. 34598f **1,4-Benzodiazepin-2-one derivatives.** Hellerbach, Joseph; Szente, Andre; Walser, Armin (Hoffmann-La Roche Inc.) U.S. 3,657,223 (Cl. 260-239.3; C 07d), 18 Apr 1972, Appl. 1843, 09 Jan 1970; 8 pp. Twelve benzodiazepin-2-ones (I,



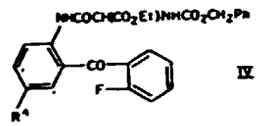
I



II



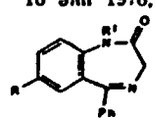
III



IV

R^1 = H, Me, $(CH_2)_2NEt_2$; R^2 = CO_2Me, CO_2Et; R^3 = 2-pyridyl, Ph, o-FC_6H_4; R^4 = H, Cl, Br, NO_2), useful as sedatives, tranquilizers, anticonvulsants, and muscle relaxants, were prepd. by acid-catalyzed ring expansion of quinolines (II), or by cyclization of malonanilates (III) in acid. E.g., 2,4-BzCl-$C_6H_3NHCOCH(NO_2)CO_2Et$ was reduced with Zn-HOAc, then refluxed in HOAc to give I (R^1 = H, R^2 = CO_2Et, R^3 = Ph, R^4 = Cl). Treating IV (R^4 = Cl, NO_2) with 30% HBr gave II (R^1 = H; R^2 = CO_2Et; R^3 = o-FB_6H_4; R^4 = Cl, NO_2). Decarboxylation of I, and prepn. of II and III were also described.

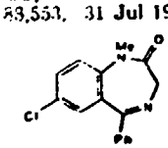
A4.6. 85: 177506a **Benzodiazepin-2-ones.** Hebron, S. A. Span. 414,741 (Cl. C07D), 16 Jan 1976, 14 May 1973; 8 pp.



I

Benzodiazepinones I (R = Cl, CF_3, R^1 = Me) were prepd. by condensing 2,4 Bz(R)$C_6H_3NH_2$ with $EtO_2CCH_2NH_2$.HCl and methylating I (R^1 = H).

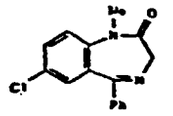
A4.7. 85: 108680r **Dihydrobenzodiazepin-2-ones.** Ishibashi, Kikuo; Mori, Kazuo; [illegible]aba, Shigeho; Yamamoto, Hisao (Sumitomo Chemical Co., Ltd.) Japan. Kokai 76 16,683 (Cl. C07D), 10 Feb 1976, Appl. 74 83,553, 31 Jul 1974; 6 pp. 7-Chloro-4-[illegible]



II

formyl-1-methyl-5-phenyl-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one (I) was oxidized to give II. II is a sedative, anticonvulsant, hypnotic and central depressant agent. Thus, 5 g 7-chloro-4-formyl-1-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine in dioxane was oxidized with $KMnO_4$ 6 hr at [illegible] to give 4.3 g I, which was [illegible] CrO_3-AcOH 24 hr at [illegible] to give II.

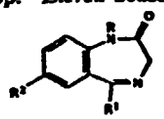
A4.8. 85: 33097v 7-Chloro-1-methyl-5-phenyl-1,3-dihydro-2H-=1,4-benzodiazepin-2-one. Hesoun, Dusan; Vondracek, Bohumir; Rajsner, Miroslav Czech. 160,857 (Cl. C07D53/06), 15 Oct 1975, Appl. 72/5,128, 19 Jul 1972; 2 pp. 2-(*N*-Methyl-2-chlo=



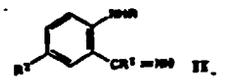
I

roacetamido)-5-chlorobenzophenone was refluxed 10 hr with alc. NH_4OH and aq. HCHO or paraformaldehyde to give 75-9% title compd. (I) which has sedative, myorelaxant, and anticonvulsive effects. L. J. Urbanek

A4.9. 84: 121913t 2-Oxo-5-phenyl-1,3-dihydro-1,4-benzodiazepine derivatives. Moriyama, Hiroaki; Yamamoto, Hisao; Nagata, Hideo; Inaba, Shigeho (Sumitomo Chemical Co., Ltd.) Japan. 75 26,555 (Cl. C07D), 01 Sep 1975, Appl. 66 33,131, 23 May 1966; 4 pp. Eleven benzodiazepinones (I, R = H, Me; R^1 =



I

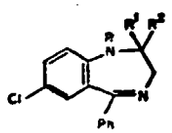


II

o-FC_6H_4, o-, *p*-MeC_6H_4, H; R^2 = Cl, O_2N, Me, F_3C, MeO, AcNH) or their hydrochlorides, useful as tranquilizers, hypnotics, and muscle relaxants (no data), were prepd. by treating the appropriate (iminomethyl)anilines II with a glycine ester. Thus, II (R = Me, R^1 = Ph, R^2 = Cl) was refluxed with $H_2NCH_2CO_2Et.HCl$ in pyridine to give 75% of I (R = Me, R^1 = Ph, R^2 = Cl).

A4.10. 84: 59592g Benzodiazepine derivatives. Hata, Tadayo Japan. Kokai 75,101,374 (Cl. C07D), 11 Aug 1975, Appl. 74 8903, 19 Jan 1974; 5 pp. 7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-ben=zodiazepin-2-one (I) and 7-chloro-1,3-dihydro-1-methyl-5-=phenyl-2*H*-1,4-benzodiazepin-2-one were prepd. by heating 2-chloroacetamido-5-chlorobenzophenone (II) and 2-chloro-*N*-=methylacetamido-5-chlorobenzophenone, resp., with ammine complexes of Ti, Al, or Zn (metal salts liberating NH_3 at low temps.) at 40-80° in solvents hardly dissolving NH_3. $(NH_4)_2CO_3$, $(NH_4)HCO_3$, or $NH_2CO_2NH_4$ may be used in place of the above complexes. Thus, a mixt. of 1 g II and 1 g NH_4HCO_3 in 10 ml PhMe was stirred 5 hr at 70° to give 15% I. K. Sempuku

A4.11. 84: 44190a 7-Chloro-1,2-dihydro-5-phenyl-1,4-benzodi=azepin-2-ones. Boehringer, C. H., Sohn Austrian 324,343 (Cl. C07D), 25 Aug 1975, Appl. 521/73, 22 Jan 1973; 4 pp.

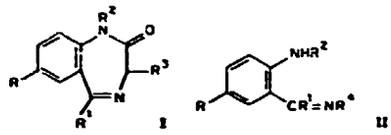


I

Benzodiazepinones I (R = H, Me; R^1R^2 = O) were prepd. by oxidn. of I (R = H, Me; R^1 = H, R^2 = Me, Et), resp.

A4.12. 84: 44186d Benzodiazepine derivatives. Specta International B. V. Ger. Offen. 2,501,937 (Cl. C07D), 14 Aug 1975, Neth. Appl. 74 01,801, 08 Feb 1974; 13 pp. Diazepam and nitrazepam were obtained in 86.7 and 90.6% yield resp. by cyclizing 2,4-Bz(Cl)C_6H_3NMeCOCH_2Br or 2,4-Bz$(O_2N)C_6H_3$NHCOCH_2Cl with PPh_3.

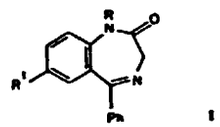
A4.13. 5012z 1,4-Benzodiazepines. CM Industries Neth. Appl. 75 00,364 (Cl. C07D, A61K), 29 Apr 1975, Fr. Appl. 978,360, 15 Jan 1964; 11 pp. Division of Neth. 65 07,637. Benzodiazepinones



I II

I (R = Cl, R^1 = Ph, R^2 = H, R^3 = H, Me, CH_2CHMe_2, CH_2CH_2SMe; R = Cl, R^1 = Ph, R^2 = Me, R^3 = H; R = Me, R^1 = Ph, R^2 = R^3 = H; R = Cl, R^1 = cyclohexyl, R^2 = R^3 = H) were prepd. in improved yields by treating imines II (R^4 = H) with $H_2NCHR^3CO_2Et$ and cyclizing II (R^4 = CHR^3CO_2Et) with HOAc.

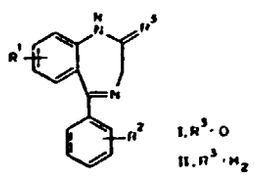
A4.14. 206341j 5-Phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one derivatives. Ishizumi, Kikuo; Mori, Kazuo; Inaba, Shigeho; Yamamoto, Hisao (Sumitomo Chemical Co., Ltd.) Ger. Offen. 2,508,332 (Cl. C07D), 04 Sep 1975, Japan. Appl. 74 24,622, 27 Feb 1974; 15 pp. Benzodiazepines I (R = Me, R^1 = Cl, NO_2; R



I

= CH_2CF_3, R^1 = Cl) were prepd. by condensing 2,4-Bz(R^1)C_6H_3NHR with $ClCOCH_2NCO$ and cyclizing with heat in a solvent.

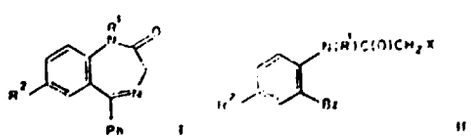
A4.15. 193408j 1,4-Benzodiazepin-2-one derivatives. Mori, Satoshi; Kitagawa, Yoshikazu; Komatsu, Shigeo (Kobayashi Pharmaceutical Co., Ltd.) Japan. Kokai 75 46,684 (Cl. C07D), 25 Apr 1975, Appl. 73 84,464, 26 Jul 1973; 3 pp. 1,4-Benzodia=



I, R^3 = O
II, R^3 = H_2

zepin-2-ones I (R = H, alkyl; R^1 = H, halo, NO_2, CF_3; R^2 = H, halo) and their acid salts were prepd. by cyclization of $R^1C_6H_4N$=$R^1CH_2CH_2N$:$C(NH_2)C_6H_4R^2$ or their acid salts followed by oxidn. of the resulting II with dichromates. I are psychotropics (no data). Thus, reflux of 6.5 g *N*-[2 (*N* methyl *p* chloroanilino)ethyl]benzamidine·HCl with 31 g $POCl_3$ 15 hr under N gave 4.35 g II·HCl (R = Me, R^1 = 7 Cl, R^2 = H) (III). Stirring 2.7 g III in 50% H_2SO_4 with 2 g $Na_2Cr_2O_7$ 2 hr at room temp. gave 91% I (R = Me, R^1 = 7-Cl, R^2 = H). K. Sempuku

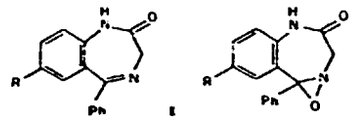
A4.16. 134253z 1,3-Dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one derivatives. Morawski, Bogdan; Krzeminski, Henryk (Farmaceutyczne "Polfa") Pol. 72,984 (Cl. C07d), 20 Dec 1974, Appl. 150,404, 24 Dec 1971; 3 pp.



I II

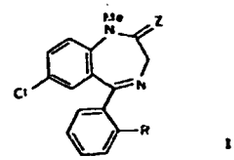
The title derivs. (I) (R^1 = H, lower alkyl contg. 1-4 C atoms; R = halogen) were obtained in the reaction of 2-(haloacetamido)benzophenone (II X = Cl, Br) with hexamethylenetetramine (1:1). For example, 0.01 mole I (R^1 = Me, R^2 = Cl) and 0.17 mole III in 200 ml [illegible] were refluxed 2 hr (I, R^1 = Me, R^2 = Cl). A. [illegible]

A4.17. 114504m Benzodiazepines. Ning, Robert Y. F.; Sternbach, Leo H. (Hoffmann-La Roche, F., und Co., A.-G.) Swiss 562,219 (Cl. C07D), 30 May 1975, US Appl. 131,770, 06 Apr 1971; 6 pp. Approx. 5 benzodiazepinones I were prepd. by



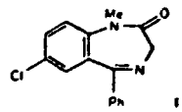
irradn. of I 4-oxides to give epoxy benzodiazepinones II which were deepoxidized to give I. Thus, I (R = Cl) 4-oxide was irradiated to give II (R = Cl) which, was deepoxidized to give I (R = Cl). I (R = Br, NO_2) were similarly prepd. Also prepd. was 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one and 7-chloro-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine.

A4.18. 58894z 1-Alkyl-1,4-benzodiazepin-2-ones. Sternbach, Leo H.; Ning, Robert Y. (Hoffmann-La Roche, Inc.) U.S. 3,873,525 (Cl. 260-239.3D; C07d), 25 Mar 1975, Appl. 392,598, 29 Aug 1973; 4 pp. Benzodiazepines (I, R = H, Z = CN, H; R =



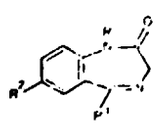
F, Z = CN, H; R = H, Z = O; R = H, Z = $CONH_2$, H; R = H, Z = CO_2H,H; R = H, Z = CO_2Me,H), useful as sedatives, anticonvulsants, and muscle relaxants (no data) were prepd. by the usual procedures from I (Z = H,OH) (II). E.g., 2.5 g II was heated on a steam bath with 16 ml $Me_2C(OH)CN$ for 20 min to give 1.6 g I (R = H, Z = CN,H), which (2.00 g) was hydrolyzed (HCl) to give I (R = H, Z = CO_2H,H).

A4.19. 133496q 7-Chloro-1-methyl-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one. Hromas, Josef; Novacek, Alois Czech. 150,806 (Cl. C 07*d*), 15 Oct 1973, Appl. 4094-70, 11 Jun 1970; 3 pp. 7-Chloro-5-phenyl-3*H*-1,4-benzodiazepin-2(1*H*)-one 4-oxide was methylated with Me_2SO_4 in dil. NaOH to give 95% 7-chloro-1-methyl-5-phenyl-3*H*-1,4-benzodiazepin-2(1*H*)-one 4-oxide. This was refluxed with powd. Fe in AcOH or in a mixt. of aq. EtOH



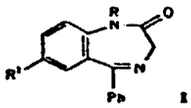
and dil. HCl to yield 70-8% title compd. (I). L. J. Urbanek

A4.20. 133493j 5-Aryl-1,3-dihydro-2H-1,4-benzodiazepin-2-ones. Chase, George O. (Hoffmann-La Roche, F., und Co., A.-G.) Ger. Offen. 2,340,159 (Cl. C 07*d*), 07 Mar 1974, US Appl. 282,217, 21 Aug 1972; 29 pp. Title benzodiazepinones I (R = H or Me; R^1 = Ph, 2-FC_6H_4, 2-ClC_6H_4, or 2-pyridyl; R^2 = H, CF_3, or Cl) were prepd. by reaction of 4,2-$R^2(R^1CO)C_6H_3$-



$NH(CH_2)_2NH_2$·2HCl with hexamethylenetetramine, followed by cyclization with NH$_4$(+) or addn. of a NH$_4$(+)-releasing agent prior to oxidation.

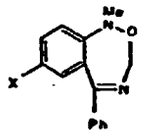
A4.21. 83078g 1,4-Benzodiazepin-2-one 1-N-methylates. Cotschoumian, Agaton; Neubauer, Georgeta (Fabrica de Medicamente si Produse Chimice, "Terapia") Rom. 55,580 (Cl. C 07d), 22 Jun 1973, Appl. 59,635, 01 Apr 1969; 2 pp. I (R = Me; R¹ =



I

H, Cl, NO_2) are prepd. by *N*-methylation of I (R = H) with MeO_3SPh in MeOH. C. T. Papadopol Calimah

A4.22. 37190q Sedative and tranquilizing 1,4-benzodiazepin-2-ones. Milkowski, Wolfgang; Funke, Siegfried; Hoffmeister, Rolf; Liepmann, Hans G.; Stuehmer, Werner; Zeugner, Horst (Kali-Chemie A.-G.) Ger. Offen. 2,221,536 (Cl. C 07d), 22 Nov 1973, Appl. P 22 21 536.7, 03 May 1972; 9 pp. The benzodiazepin-

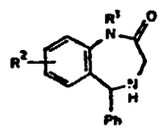


I, O·CO

II, O·CHR

ones (I, X = Cl, F), useful as sedatives and tranquilizers, were prepd. by oxidn. of II (R = Cl, OH, OMe, piperidino) with $KMnO_4$ or chromate.

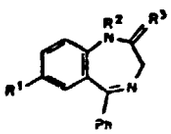
A4.23. 14973h Benzodiazepine derivatives. Sakakida, Taiji Japan. Kokai 73 61,492 (Cl. 16 E552), 28 Aug 1973, Appl. 71 96,740, 02 Dec 1971; 2 pp. The title compds. I (R^1 = H or alkyl, R^2 =



I

H, halo, or NO_2) were prepd. by reaction of *o*-$Bz(NHR^1)C_6H_2R^2$ (II) with $H_2NCH(CO_2H)_2$ ester or salt in the presence of a base, followed by hydrolysis. Thus, 2.45 g II (R^1 = Me, R^2 = 5-Cl) and 3.5 g $H_2NCH(CO_2Et)_2$ in 50 ml pyridine was refluxed 3 hr at 100°, then stirred 2 hr at 60° with addn. of 100 ml of 0.1 *N* HCl to give 2.0 g I (R^1 = Me, R^2 = 5-Cl). Y. Tsuji

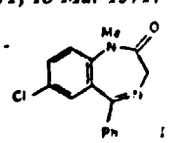
A4.24. 146569v Diazepam. Sakakida, Taiji Japan. Kokai 73 54,095 (Cl. 16 E552), 30 Jul 1973, Appl. 71 91,527, 17 Nov 1971; 2 pp. Benzodiazepines I (R^1 = halo, NO_2; R^2 = H,



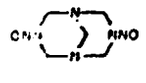
I

Me; R^3 = H_2, O; when R^1 = Cl, R^2 = Me, R^3 = O, H_2; when R^1 = NO_2, R^2 = H, R^3 = O) were prepd. by heating the corresponding benzophenone isocyanates in the presence of Lewis acids. Thus, 2-(2-bromo-*N*-methylacetamido)-5-chlorobenzophenone was heated with KNCO in $CHCl_3$ and the 2-isocyanatoacetamido deriv. was cyclized to diazepam by heating with $AlCl_3$ in DMF at 110° for 5 hr. Ikuo Matsumoto

A4.25. 115047q 7-Chloro-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one. Oklobdzija, Milan; Japelj, Miha; Ostroverhnik, Srecko; Jerman, Peter (KRKA Tovarna Zdravil) Ger. Offen. 2,211,647 (Cl. C 07d), 09 Aug 1973, Yugoslav Appl. P 634-71, 15 Mar 1971; 8 pp. The title compd. (I), use-



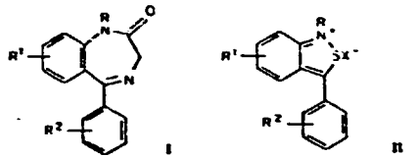
I



II

ful as sedative, muscle relaxant, analgetic, and prophylactic in the withdrawal phase in the treatment of alcoholics, was prepd. by reducing 4,2-$ClBzC_6H_3$(NO)CH$_2$NMe and dinitrosopentamethylenetetramine (II) in DMF

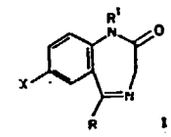
A4.26. 165306p 1,4-Benzodiazepine derivativ[illegible]i, Osami; Nakagawa, Yasushi; Shirakawa, Kenzo; [illegible]moto, Masaki (Takeda Chemical Industries, Ltd.) Jap. 73 21,114 (Cl. C 07d, B 61j), 26 Jun 1973, Appl. 70 93,010, 21 Oct 1970; 5 pp.



I II

1,4-Benzodiazepines (I, R = C_{1-4} alkyl, alkylamino, cyclic amino, alkoxyl; R^1, R^2 = H, halo, alkyl, alkoxyl, etc.), tranquilizers, were prepd. by heating the corresponding 2,1-benzisothiazolium salts II (R, R^1, R^2 = same as above, X^- = halide, BF_4, $SbCl_4$, $FeCl_4$, $PhSO_3$) with glycine or its esters in the presence of azoles (pyrazoles, imidazoles). Thus, II (R = Me, R^1 = 5-Cl, R^2 = H, X = BF_4^-), $H_2NCH_2CO_2Et$, and 2-methylimidazole were heated 30 min at 160° to give I (R = Me, R^1 = 5-Cl, R^2 = H). Similarly prepd were I (R, R^1, and R^2 given): Me, 5-Cl, 4-Cl; Et, 5-Cl, H. S. Morita

A4.27. 42575c 1,3-Dihydro-2H-1,4-benzodiazepin-2-ones. Boemches, Helmut; Meyer, Hans (Hoffmann-La Roche, F., und Co., A.-G.) Ger. Offen. 2,252,378 (Cl. C 07d), 24 May 1973, Swiss Appl. 15,774/71, 18 Nov 1971; 12 pp. Five benzodiazepinones

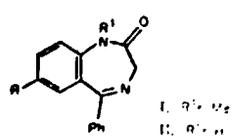


I

(I; R = Ph, 2-pyridyl; R^1 = H, Me; X = H, Cl, Br, NO_2), useful as sedatives, muscle relaxants, and anticonvulsants, were prepd. by condensation of 5,2-X(R^1NH)C_6H_3COR with $H_2NCH_2CO_2H$ in the presence of $P(O)Cl_3$ or $P(O)Cl_3$–P_2O_5. I (X = NO_2) was prepd. by nitration of I (X = H).

A4.28. 42572z Benzodiazepine derivatives. Shinto, Minoru; Shinozaki, Teizo; Moro, Kanji (Chugai Pharmaceutical Co., Ltd.) Japan. 73 08,119 (Cl. C 07d, B 01j), 12 Mar 1973, Appl. 70 99,462, 13 Nov 1970; 2 pp. The prepn. of 7-chloro-1-methyl-5-phenyl-1,3(2*H*)-dihydrobenzo[1,4]diazepin-2-one (I), a psychotherapeutic, by halogenation of *N*-aminoacetyl-5-chloro-*N*-methylanthranilic acid (II) and treatment of its product with C_6H_6 in the presence of a Friedel-Krafts catalyst is described. In an example, dry HCl gas is introduced into a suspension of II in dry benzene, PCl_5 is added with stirring, finely powd. $AlCl_3$ is added, and the mixt. is refluxed to yield I. Dorothy U. Mizoguchi

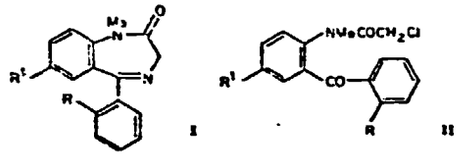
A4.29. 111388n 1,3-Dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-ones of high purity. Neubauer, Georgeta; Cotschoumian, Agaton; Arizan, Sofia; Pirneci, Veronica (Fabrica de Medicamente "Terapica") Ger. Offen. 2,227,977 (Cl. C 07d), 08 Feb 1973, Rom. Appl. 67,632, 12 Jul 1971; 10 pp. Three title



I, R' = Me
II, R' = H

compds. (I, R = H, Cl, or O_2N) were prepd. in 70.7–81% yield and 99–100% purity by reaction of II with $PhSO_2Me$ (III) in NaOH–MeOH and subsequent purifn. of the crude product by selective recrystn. from Me_2CHOH or by ppt'n. from AcOBu and washing with Et$_2$oine. Thus, III was added to II (R = Cl) in 8% NaOH–MeOH and the mixt. heated 1.5 hr at 40–5° to give 80% I (R = Cl) (IV) of 95% purity. This IV was refluxed 1 hr in Me_2CHOH–charcoal, the mixt. filtered, cooled to −5°, and the ppt. purified once more by the same procedure to give IV of 99.5% purity. This IV was recrystd. from Me_2CHOH to give 98% [illegible] of 100% purity.

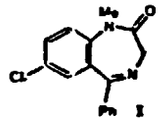
A4.30. 111335j 1-Methyl-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-ones. Hindley, Nathan Chadwick; McClyment, Thomas M. (Hoffmann-La Roche, F., und Co., A.-G.) Ger. Offen. 2,233,482 (Cl. C 07D). 25 Jan 1973, Brit. Appl. 32,107/71, 03 Jul 1971; 10 pp. Four title compds. (I; R = H, F; R^1 = H, Cl,



I II

iodo, NO_2), useful as sedative, muscle relaxant, or anticonvulsive agents, were prepd. by reaction of II with hexamethylenetetramine in the presence of HCl.

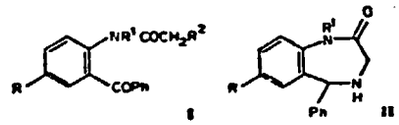
A4.31. 111384h 7-Chloro-1-methyl-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one. KRKA Tovarna Zdravil Fr. Demande 2,130,148 (Cl. A 61k, C 07d), 08 Dec 1972, Yugoslavia Appl. P 634/71, 15 Mar 1971; 6 pp. The title compd. (I) (2.1 g) was



I

prepd. by treating 5 g 4,2-Cl(PhCO)C_6H_3NMeCOCH$_2$Br with 5 g 3,7-dinitroso-1,3,5,7-tetraazabicyclo[3.3.1]nonane for 9 hr.

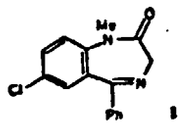
A4.32. 97727p 1,4-Benzodiazepines. CRC Compagnia di Ricerche Chimiche S. A. Fr. Demande 2,123,218 (Cl. A 61K, C 07d), 13 Oct 1972, Appl. 71 03,131, 29 Jan 1971; 7 pp. Benzophenones



I II

(I, R = Cl, NO_2; R^1 = H, Me; R^2 = Cl, Br) refluxed with hexamethylenetetramine gave benzodiazepinones II (R, R^1 given): Cl, Me; Cl, H; NO_2, H.

A4.33. 58480h 7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one. Shindo, Minoru; Moro, Kanji (Chugai Pharmaceutical Co., Ltd.) Japan. 72 44,753 (Cl. C 07d, B 01j), 11 Nov 1972, Appl. 70 70,408, 13 Aug 1970; 3 pp. The

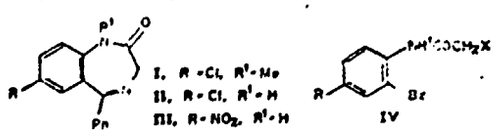


I

title compd. (I) was prepd. by heating *N*-(haloacetyl)-*p*-chloro-*N*-methylaniline with PhCN in the presence of $TiCl_4$. Thus, $TiCl_4$ was added to stirred and ice-cooled PhCN, the solid mixt. heated 5 hr at 180–5°, and cooled. To this was added *N*-(chloroacetyl)-*p*-chloro-*N*-methylaniline and stirred 1.5 hr at 185–8° to give I.

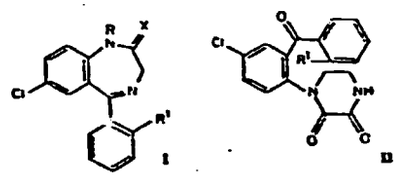
K. Sempuku

A4.34. 126712s 1,4-Benzodiazepines. Kajfez, Franjo; Blazevic, Nicola (CRC Compagnia di Ricerche Chimiche S.A.) S. African 71 01,563, 03 Nov 1971, Appl. 71/1563, 10 Mar 1971; 10 pp. 2*H*-1,4-Benzodiazepin-2-ones (I, II, and III) were prepd.



by refluxing the corresponding acetamidobenzophenones (IV, X = Br, Cl) with hexamethylenetetramine in EtOH. In I prepn. of I an intermediate was isolated which was cyclized by refluxing with [illegible] HCl to give I of high purity.

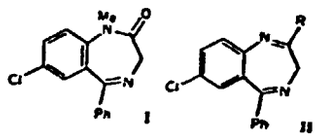
A4.35. 126709w 1-Alkyl-5-aryl-7-chloro-2,3-dihydro-1H-1,4-benzodiazepines and -1,3-dihydro-2H-1,4-benzodiazepin-2-ones. Okamoto, Tadashi; Akase, Takeshi; Izumi, Takahiro; Akasu, Mitsuhiro; Kume, Yoshiharu; Inaba, Shigeho; Yamamoto, Hisao (Sumitomo Chemical Co., Ltd.) Ger. Offen. 2,151,540 (Cl. C 07d), 03 Aug 1972, Japan. Appl. 70 91,354, 17 Oct 1970; 25 pp. Fifteen title compds. (I, X = H_2, O; R = H, Me,



I II

CH_2CH_2OMe, $CH_2CH_2NEt_2$, cyclopropylmethyl, 2-phthalimidoethyl; R^1 = H, Cl, F) or their di-HCl, useful as anticonvulsants, sedatives, muscle relaxants, and hypnotics, were prepd. by successive reaction of I (X = H_2, O, R = H) with PhLi and RI, RCl, or RBr. I (X = H_2, R = H) were prepd. by hydrolysis of 2-(2,3-dioxo-1-piperazinyl)-5-chlorobenzophenones (II) in aq. NaOH and EtOH.

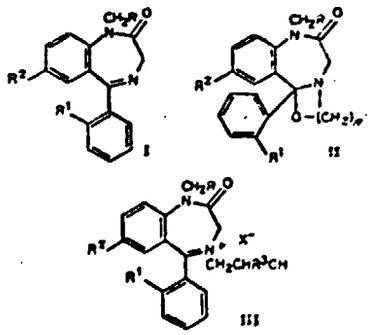
A4.36. 126706t 1-Alkyl-1,4-benzodiazepin-2-ones. Earley, James Valentine; Fryer, Rodney Ian; Ning, Robert Y. F.; Sternbach, Leo Henryk (Hoffmann-La Roche Inc.) U.S. 3,681,341 (Cl.



I II

260/239.3D; C 07d), 01 Aug 1972, Appl. 101,188, 23 Dec 1970; 5 pp. The benzodiazepinone (I) was prepd. by heating neat II (R = MeO) in a sealed tube for 30 min at 240–60°. The latter was prepd. by refluxing II (R = MeS) in NaOMe-MeOH to give II (R = MeO).

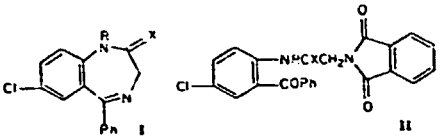
A4.37. 126704r 1-Alkyl-5-aryl-1,2-dihydro-3H-1,4-benzodiazepin-2-ones. Tachikawa, Ryuji; Miyadera, Tetsuo; Terada, Atsusuke; Yabe, Yuichiro; Tanaka, Tetsuya (Sankyo Co., Ltd.) Ger. Offen. 2,164,154 (Cl. C 07d), 20 Jul 1972, Japan. Appl. 70 116,301, 21 Dec 1970; 16 pp. Six title compds. (I, R = H, Et_2-



I II III

NCH_2; R^1 = H, F, Cl; R^2 = Cl, NO_2, Br), useful as depressants for the central nervous system, were prepd. by heating II (n = 2, 3) or III (R^3 = Me, H) with Ac_2O–NaOAc (or AcOH) optionally in the presence of BF_3–Et_2O.

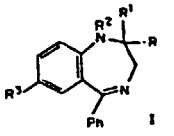
A4.38. 114340p 7-Chloro-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepines and -1,3-dihydro-2H-1,4-benzodiazepin-2-ones. Laboratoires Pharmedical S. A. Ger. Offen. 2,159,920 (Cl. C 07d), 29 Jun 1972, Argentina Appl. 253,690, 21 Dec 1970; 11 pp. Three



I II

title compds. (I, R = H, Me, X = O, H_2) were prepd. by treatment of benzophenones (II) with $N_2H_4.H_2O$. Thus, phthaloylglycine was refluxed with $SOCl_2$ to give phthaloylglycyl chloride, which was refluxed with 5,2-Cl(H_2N)C_6H_3COPh in $CHCl_3$ to give II (R = H, X = O) (III). III was treated with $N_2H_4.H_2O$ in MeOH to give 84% I (R = H, X = O).

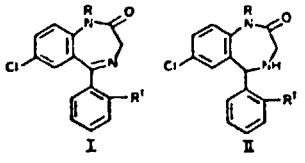
A4.39. 101691w Benzodiazepine derivatives. Takeda Chemical Industries, Ltd. Brit. 1,276,168 (Cl. C 07d, A 61k), 01 Jun 1972, Japan. Appl. 68 63,323, 03 Sep 1968; 5 pp. Title compds.



I

I (R = OH, R^1 = R^2 = H, R^3 = Cl; R = OH, R^1 = R^2 = H, R^3 = NO_2) were prepd. by cyclization of a 5-substituted 2-amino-α-phenylbenzylideneaminoacetaldehyde diethyl acetal in EtOH contg. 10% HCl at 50°, 10 min. I (RR^1 = O, R^2 = H, R^3 = Cl; RR^1 = O, R^2 = H, R^3 = NO_2; RR^1 = O, R^2 = Me, R^3 = Cl) were prepd. by treatment of I (R = OH, R^1 = H) with chromium trioxide.

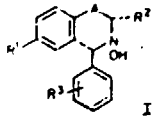
A4.40. 3914f 1,3-Dihydro-2H-1,4-benzodiazepin-2-ones. Inaba, Shigeho; Okamoto, Tadashi; Hirohashi, Toshiyuki; Ishizumi, Kikuo; Yamamoto, Michihiro; Maruyama, Isamu; Mori, Kazuo; Kobayashi, Tsuyoshi; Yamamoto, Hisao (Sumitomo Chemical Co., Ltd.) Ger. Offen. 2,113,122 (Cl. C 07d), 30 Sep 1971, Japan. Appl. 19 Mar 1970; 8 pp. Title compds. (I), useful



I II

as analgesic, hypnotic, spasmolytic, and muscle relaxant agents and as intermediates, were prepd. by irradn. of the corresponding tetrahydro derivs. (II). Thus, 1 g II (R = Me, R^1 = H) in Me_2SO was exposed to Hg light 20 hr to give 0.62 g I (R = Me, R^1 = H). Similarly prepd. were I (R = cyclopropylmethyl, R^1 = H and F).

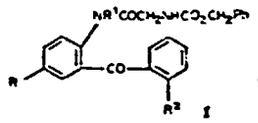
A4.41. 118349x 5-Phenyl-1,4-benzodiazepines and their derivatives. Sternbach, Leo H.; Metlesics, Werner (Hoffmann-La Roche, F., und Co., A.-G.) Swiss 507,965 (Cl. C 07d), 15 Jul 1971, US Appl. 01 Dec 1966; 4 pp. Benzodiazepines (I) are prepd.



I

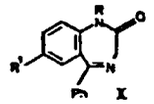
Thus, 5,2-Cl(O_2N)C_6H_3CH:NOH reduced catalytically in abs. over PtO_2 and the corresponding 2-amino compd. condensed with $ClCH_2COCl$ in 1,4-O to give 5,2-Cl($ClCH_2CONH$)C_6H_3CH:NOH, cyclized by refluxing 7 hr in C_6H_6 with $BF_3.Et_2O$ to 6-chloro-2-chloromethylquinazoline 3-oxide. This stirred with $MeNH_2$ in MeOH gave 7-chloro-2-(methylamino)-3*H*-1,4-benzodiazepine 4-oxide. This in THF treated with PhLi in 7:3 C_6H_6-Et_2O and the product isolated gave I [A = N:C(NHMe) R^1 = Cl, R^2 = R^3 = H], oxidized with HgO in 10:1 Me_2CO-H_2O at 20° to 7-chloro-2-(methylamino)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide. Similarly, 7-chloro-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one 4-oxide treated with PhLi in aq. Me_2SO gave I [A = N:CO R^1 = Cl, R^2 = R^3 = H], hydrogenated with 5% Pd/C in refluxing $CHCl_3$ to 7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one, methylated by treatment of the Na deriv. with MeI, to give 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (II).

A4.42. 63844r 2-[N-(Benzyloxycarbonyl)glycylamido]benzophenones. Yamamoto, Hisao; Inaba, Shigeho; Okamoto, Tadashi; Hirohashi, Toshiyuki; Ishizumi, Kikuo; Yamamoto, Michiitiro; Maruyama, Isamu; Mori, Kazuo; Kobayashi, Tsuyosi; Izumi, Takahiro (Sumitomo Chemical Co., Ltd.) Ger. Offen. 1,817,794 (Cl. C 07c), 24 Jun 1971, Japan. Appl. 25 Dec 1967; 16 pp. Division of Ger. Offen. 1,816,046 (*CA* 73: 120690d). Title



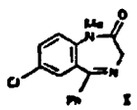
compds. (I) were prepd. by oxidn. of indole derivs. and used for the prepn. of II. Thus, reaction of 2-(benzyloxycarbonylaminomethyl)-5-chloro-3-phenylindole with CrO_3 in aq. HOAc 15 hr gave 93% I (R = Cl, R^1 = R^2 = H). Similarly prepd. I were (R, R^1, and R^2 given): Cl, Me, H (III); H, Me, H; H, H, H; CF_3, H, H; MeO, H, H; and Cl, H, Cl. III (1.4 g) was refluxed 8 hr with 2.6 g HBr and 20 ml HOAc to give 1.07 g II (R = Cl). Similarly prepd. was II (R = NO_2).

A4.43. 36155s Psychotropic 5-phenyl-1,4-benzodiazepin-2-ones. Kajfez, Franjo; Blazevic, Nikola (C.R.C Compagnie di Ricerca Chimica S.A.) Ger. Offen. 2,016,084 (Cl. C 07d), 29 Apr 1971, Swiss Appl. 16 Oct 1969; 8 pp. Title compds. (I, R = Me, or



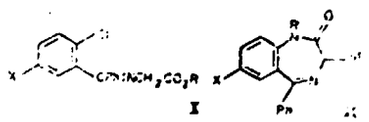
H, R^1 = Cl or NO_2), useful as tranquilizers, sedatives, and hypnotics, were prepd. in 70–90% yield by refluxing 2-(2-haloacetamido)benzophenones and hexamethylenetetramine (II) in EtOH. Thus, 1 g 4,2-$ClBzC_6H_3NMeCOCH_2Br$ and 1 g II were refluxed 10 hr in 15 ml EtOH to give 85–90% I (R = Me, R^1 = Cl).

A4.44. 141897n 7-Chloro-5-phenyl-1-methyl-2,3-dihydro-1H-1,4-benzodiazepin-2-one. Lenkowski, Przemyslaw; Kycia, Henryk; Lasocka-Tatar, Barbara; Roszkowska-Chimelewska, Danuta; Surgiewicz, Janusz; Bartkiewicz, Boguslaw; Sobolew, Marek; Rolak, Hanna (Tarchominskie Zaklady Farmaceutyczne "Polfa") Ger. Offen. 2,028,448 (Cl. C 07d), 25 Mar 1971, Pol. Appl. 11 Jun 1969; 10 pp. The title compd. (I), useful as seda-



tive, spasmolytic, and hypnotic, was prepd. Thus, $2,5-H_2NClC_6H_3CPh:N(O)CH_2CO_2H$ was added to a soln. of NaOH in MeOH, the mixt. cooled to 10°, $(MeO)_2SO_2$ added, and the mixt. heated 16 hr to give the *N*-oxide of I, which was reduced by addn. of $HCHO.Na_2SO_2$ to give I. KHPG

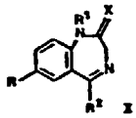
A4.45. 141895k 1,4-Benzodiazepine derivatives, useful as sedatives. Roemer, Ulysses (C.R.C. Compagnia di Ricerca Chimica S.A.) Swiss 473,123 (Cl. C 07d), 15 Dec 1970, Appl. 21 Nov 1966; 2 pp. I were condensed with NH_3 or primary aliphatic



amines under pressure to give II. II possess sedative properties. I were prepd. from 2,5-dichlorobenzophenone (III) and amino acid esters. For example, 20 g III and 21 g [illegible]·HCl in 50 ml pyridine were refluxed 5 hr to give [illegible] X = Cl) (Ia), b$_{0.6}$ [illegible]. Ia was heated 6 hr at 50° with [illegible]·HCl, and 100 g [illegible] autoclave with shaking [illegible] Cl, R = Me, [illegible] m. 125.6°. [illegible] (X = [illegible] H), m. 120° [illegible] prepd.

A4.46. 112062f Anticonvulsant, muscle relaxant, and sedative compounds obtained by oxidation of benzodiazepines with ruthenium tetroxide. Felix, Arthur M.; Fryer, Rodney I.; Sternbach, Leo H. (Hoffmann-La Roche Inc.) U.S. 3,546,212 (Cl. 260–239.3; C 07*d*), 08 Dec 1970, Appl. 12 Jun 1968; 4 pp. To 7-chloro-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepine was added a $CHCl_3$ soln. of RuO_4 at −10° in 30 min. Stirring 30 min gave 7-chloro-2,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one, m. 215–17° (CCl_4-hexane). Similarly, 9 addnl. diazepinones were prepd. K. Sempuku

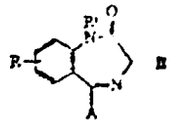
A4.47. 100116p Pharmaceutical 2-oxo-1,2-dihydro-3H-1,4-benzodiazepines. Von Brachel, Hanswilli; Graewinger, Otto (Cassella Farbwerke Mainkur A.-G.) Ger. Offen. 1,942,743 (Cl. C 07*d*), 25 Feb 1971, Appl. 22 Aug 1969; 22 pp. The title



compds. (I, X = O), used as pharmaceuticals, were prepd. by hydrolysis of I (X = NH), which were obtained by cyclization of 5,2-R(R^1NH)$C_6H_3CR^2$:NCH_2CN. Thus, Cl was passed into 5,2-Cl(MeNH)C_6H_3CPh:NCH_2CN in PhMe to give I [R = Cl, R^1 = Me, R^2 = Ph, X = NH (II)]. NH_3 was passed into II in PhMe to give the corresponding I (X = O). Among ~30 I (X = O) prepd. were (R-R^2 given): Br, Me, *o*-FC_6H_4; Cl, iso-Pr, *o*-ClC_6H_4; Cl, CH_2:$CHCH_2$, Ph; Cl, $PhCH_2$, Ph; F, Me, 2,4-$Cl_2C_6H_3$; CF_3, Me, 2-pyridyl. KBPG

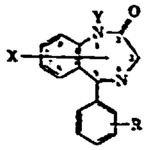
A4.48. 88082q Derivatives of benzodiazepine. Morawski, Bogdan; Janasik, Justyna (Tarchominskie Zaklady Farmaceutyczne "Polfa") Pol. 60,627 (Cl. C 07*d*), 05 Aug 1970, Appl. 12 Jul 1967; 2 pp. The title compds. were obtained in an economic way by redn. of derivs. of 1,4-benzodiazepine 4-oxide with Fe in nic. or aq.-alc. solns. of NH_4Cl. Thus, of 7-chloro-5-phenyl-3*H*-1,4-benzodiazepin-2(1*H*)-one 4-oxide suspended in MeOH was treated with KOH in MeOH, MeI added dropwise at 16–18°, the mixt. heated at 36–8° 2 hr, and when the reaction was complete H_2O added to give 88% 7-chloro-1-methyl-5-phenyl-3*H*-1,4-benzodiazepin-2(1*H*)-one 4-oxide (I), m. 179–81°. Iron filings were added to a mixt. contg. I, MeOH, NH_4Cl, and H_2O and the mixt. was heated 17 hr at 67–8° and neutralized with Na_2CO_3 to give 87% 7-chloro-1-methyl-5-phenyl-3*H*-1,4-benzodiazepin-2-(1*H*)-one, m. 130–2°. 7-Chloro-1-ethyl-5-phenyl-3*H*-1,4-benzodiazepin-2(1*H*)-one, m. 127–32°, was obtained similarly from its 4-oxide in 84% yield. Cf. Pol. 47,084. Karol Butkiewicz

A4.49. 53870t Methylation of 1,4-benzodiazepines. Deriag, Michael E.; Fryer, Rodney I.; Sternbach, Leo H. (Hoffmann-La Roche Inc.) U.S. 3,534,021 (Cl. 260–239.3; C 07*d*), 13 Oct 1970, Appl. 20 May 1968; 2 pp. Me_2S:CH_2 and $Me_2S(O)$:CH_2



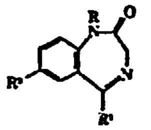
were used as methylating agents in situ for prepn. of the 1-Me derivs. (I) of 1,4-benzodiazepines (II, R^1 = H; R = H, alkyl, halogen, CF_3, NO_2; A = Ph, substituted phenyl, pyridyl). Thus, BuLi in pentane was added to trimethylsulfonium iodide in Me_2SO-THF at −10° under N, the $Me_2S^+C^-H_2$ ylide soln. stirred 1 hr at −10° with addn. of 7-chloro-5-phenyl-3*H*-1,4-benzodiazepin-2(1*H*)-one (III), and the mixt. stirred 18 hr at 20° to give II (R = 7-Cl, R^1 = Me, A = Ph) (IV), m. 130–2°. Similarly, trimethoxysulfonium iodide and NaH in Me_2SO stirred under N until evolution of H ceased (to give dimethoxysulfonium methylide) and the mixt. treated with III in THF 3 hr at 60° to give IV. Useful as tranquilizers, muscle relaxants, anticonvulsants, and hypnotics. C. R. A. [illegible]

A4.50. 53564u 1,4-Benzodiazepine series compounds. Hasegawa, Hitoshi (Japan Synthetic Chemical Industry Co., Ltd.) Japan. 70 31,303 (Cl. C 07d, A 51$\bar{c}$), 09 Oct 1970, Appl. 26 Jun 1957; 3 pp. I, useful as psychotherapeutics, are manufd. 4-ClC_6H_4-


I

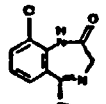
$N(Me)COCH_2N:C(Ph)Cl$ (10 g) in 2 vols. $AlCl_3$ is heated 4 hr at 230° in an autoclave, poured on ice, the mixt. treated with 4% NaOH and extd. with CH_2Cl_2 to give I (X = 7-Cl, Y = Me, R = H), m. 124-5° (Me_2CO-petroleum ether). Similarly prepd. are 12 addnl. I. Hiroshi Kataoka

A4.51. 22904c Pharmaceutical 1,3-dihydro-2H-1,4-benzodiazepin-2-ones. Yamamoto, Hisao; Inaba, Shigeho; Kume, Yoshiharu; Izumi, Takahiro; Hirohashi, Tosiyuki; Yamamoto, Michihiro; Ishizumi, Kikuo; Maruyama, Isamu; Akatsu, Mitsuhiro; Mori, Kazuo (Sumitomo Chemical Co., Ltd.) Ger. Offen. 2,017,060 (Cl. C 07d), 29 Oct 1970, Japan. Appl. 18 Apr 1969-03 Jul 1969; 46 pp. The title compds. (I) were prepd. by condensa-


I

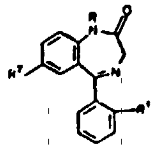
tion of 5,2-$R^2(RNH)C_6H_3COR^1$ with 2,5-oxazolidinedione (II). Thus, HCl in Et_2O was added to 5,2-$Cl(MeNH)C_6H_3Bz$ in CH_2Cl_2 and II to give 90% I (R = Me, R^1 = Ph, R^2 = Cl). Among about 130 I prepd. were (R, R^1, and R^2 given): Me, o-FC_6H_4, NO_2; H, Ph, Cl; H, Ph, NO_2; H, o-MeC_6H_4, Cl; H, Me, Cl; cyclopropylmethyl, Ph, Cl; $Et_2NCH_2CH_2$, o-FC_6H_4, Cl; $NCCH_2$, Ph, Cl. KBPG

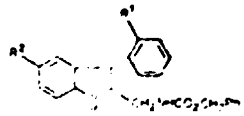
A4.52. 13186t Benzodiazepine derivatives having anticonvulsant, tranquilizing, and muscle relaxant activity. Moriyama, Hiroaki; Yamamoto, Hisao; Inaba, Shigeho; Nagata, Hideo; Tamaki, Toshio; Hiroshashi, Toshiyuki (Sumitomo Chemical Co., Ltd.) U.S. 3,524,848 (Cl. 260-239.3; C 07d), 18 Aug 1970, Japan. Appl. 02 Nov 1966-08 Sep 1967; 5 pp. Tosyloxyacetic acid (10


I

g) and 12.5 ml $SOCl_2$ was refluxed to give tosyloxyacetyl chloride. To this product was added 65 ml. $CHCl_3$ and 8.8 g 2-amino-5-chlorobenzophenone and the mixt. refluxed for 32 hr to form 5-chloro-2-(tosyloxyacetamido)benzophenone, m. 148-9°. This compd. (4.4 g) and 10% alc. NH_3 was stirred for 3 days at 25° to give 5-phenyl-7-chloro-1,3-dihydro-2H-1,4-benzodiazepin-2-one (I), m. 214-15°. Similarly prepd. were 5-chloro-2-(N-methyltosyloxyacetamido)benzophenone; 7-chloro-1-methyl-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one, m. 127.5-30°, and the 3H-isomer, m. 125.5-28°; 5-nitro-2-(tosyloxyacetamido)benzophenone, m. 156-7°; and 5-phenyl-7-nitro-1,3-dihydro-2H-1,4-benzodiazepine, m. 223-4°. Judith A. Douville

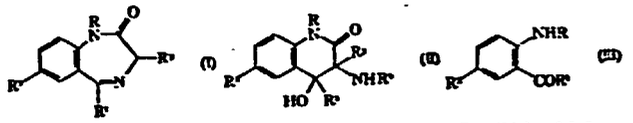
A4.53. 120690d Benzodiazepines synthesis. Yamamoto, Hisao; Inaba, Shigeho; Yamamoto, Michihiro; [illegible]i, Takahiro; Okamoto, Tadashi; Hirohashi, Toshiyuki; Mori, Kazuo; Ishizumi, Kikuo; Maruyama, Isamu; Ko[illegible]yashi, Tsuyoshi (Sumitomo Chemical Co., Ltd.) Ger. Offen. 1,816,046 (Cl. C 07d), 03 Sep 1970, Japan. Appl. 25 Dec 1967-09 Apr 1968; 16 pp. I prepd. were (R-R^2 given): Me, H, [illegible]; H, H, Cl; H, H, H; H, H, MeO; H, Cl, Cl; H, H, CF_3; Me, H, NO_2. I were


(I)


(II)

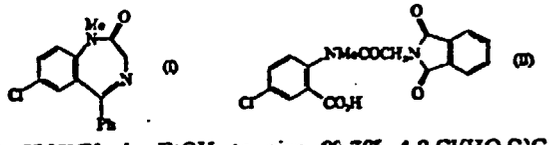
[illegible] by cyclization of 4,2-[illegible]NRCOC[illegible] [illegible]Ph (II) with HBr-[illegible]. [illegible] prepd. by oxid[illegible] [illegible] of the corresponding [illegible] (or O_3). D[illegible]

A4.54. 87947t Benzodiazepinones and benzodiazepinecarboxylates. Hellerbach, Joseph; Szente, Andre; Walser, Armin (Hoffmann-La Roche, F., und Co., A.-G.) Ger. Offen. 2,001,276 (Cl. C 07d), 20 Aug 1970, Swiss Appl. 17 Jan 1969-22 Apr 1969; 34 pp. The title compds. (I) (R^3 = H, CO_2Me, CO_2Et) were prepd. by treatment of the corresponding II (R^3 = CO_2Me, CO_2Et) with HOAc. II were prepd.: *a*) by reaction of III with $ClCOCH(CO_2R^3)NHCO_2CH_2Ph$, cyclization with a base and removal of the 3-*N*-protecting group with HBr or *b*) by reaction of III with $ClCOCH_2CO_2R^3$, nitration, redn., and cyclization. Thus, $PhCH_2O_2CNHCH(COCl)CO_2Me$ was treated with III (R = Me, R^1 = Ph, R^2 = Cl) to give 2'-benzoyl-2-(benzyloxycarbonylamino)-2-carbomethoxy-4'-chloro-*N*-methylacetanilide (IV). IV was treated with Et_3N 18 hr at room temp. to give II (R = Me,



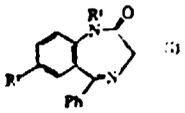
R^1 = Ph, R^2 = Cl, R^3 = CO_2Me, R^5 = CO_2CH_2Ph) which on treatment with 30% HBr in HOAc gave II (R = Me, R^1 = Ph, R^2 = Cl, R^3 = CO_2Me, R^5 = H) (IIa). IIa in C_6H_6 was refluxed 3 hr with HOAc to give I (R = Me, R^1 = Ph, R^2 = Cl, R^3 = CO_2Me). Reflux of IIa in 80% HOAc 20 hr gave I (R = Me, R^1 = Ph, R^2 = Cl, R^3 = H). Among 10 compds. prepd. were the I (R^3 = H) (R, R^1, and R^2 given): Me, Ph, Cl; H, Ph, NO_2; $CH_2CH_2NEt_2$, *o*-FC_6H_4, Cl. KSPG

A4.55. 56141w 7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one. Shindo, Minoru; Moro, Kanji; Shinozaki, Teizo (Chugai Pharmaceutical Co., Ltd.) Ger. Offen. 1,957,420 (Cl. C 07cd), 18 Jun 1970, Japan. Appl. 15 Nov 1968-24 Apr 1969; 11 pp. The title compd. (I) was prepd. and could be used as a drug against neuropsychosis. II, prepd. from 5,2-Cl(MeNH)$C_6H_3CO_2H$ and phthalimidoacetyl chloride, reacted



with H_2NNH_2 in EtOH to give 89.7% 4,2-Cl$(HO_2C)C_6H_3$-$NMeCOCH_2NH_2$ (III). I was prepd. in 70% yield from III by reaction with PCl_5 and subsequently with C_6H_6 and $AlCl_3$. III had some antipyretic, analgetic, antiphlogistic and antiviral activities. KBPG

A4.56. 121597v Benzodiazepines. Moriyama, Hiroaki; Yamamoto, Hisao; Nagata, Hideo; Inabe, Shigeiio (Sumitomo Chemical Co., Ltd.) Japan. 70 06,029 (Cl. 16 E 552), 28 Feb 1970, Appl. 28 May 1966; 3 pp. I, a tranquilizer, hypnotic, and muscle-relaxant, is prepd. Thus, 4.2 g $BrCH_2CO_2Et$ in 10 vols pyridine is gradually added to 5.3 g *o*-(2-aminophenyl)-*α*-phenylmethyleneimine in 10 vols pyridine under N and the



mixt. refluxed and evapd. to give I (R^1 = R^2 = H), m. 178–9° (EtOH). Similarly prepd. are I (R^1, R^2, and m.p. given): Me, H, 180–2°; Me, Cl, 130–2°; H, NO_2, 221.5°.

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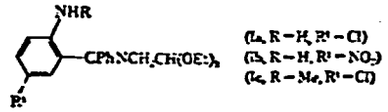
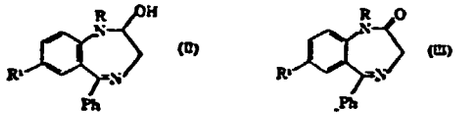
A4.57. 100775m 1,2-Dihydro-3H-1,4-benzodiazepin-2-ols and 3H-1,4-benzodiazepin-3-ones. Meguro, Kanji; Masuda, Toru; Kuwada, Yutaka; Tawada, Hiroyuki (Takeda Chemical Industries, Ltd.) Ger. Offen. 1,944,404 (Cl. C 07d), 12 Mar 1970, Japan. Appl. 03 Sep 1968; 14 pp. The title compds. were prepd. Thus, 5,2-Cl(H$_2$N)C$_6$H$_3$CPh:NCH$_2$CH$_2$OH, H$_2$NCH$_2$-CH(OEt)$_2$, 2-methylimidazole·HCl, and EtOH were refluxed 4 hr to give Ia, m. 103–4°. Similarly prepd. were Ib, m. 161–



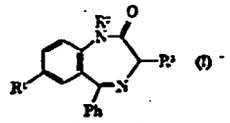
(Ia, R = H, R^1 = Cl)
(Ib, R = H, R^1 = NO$_2$)
(Ic, R = Me, R^1 = Cl)

4°, and Ic, m. 62–3.5°. Ring closure of Ia by treatment with ethanolic HCl 10 min at 50° yielded II·HCl (R = H, R^1 = Cl)



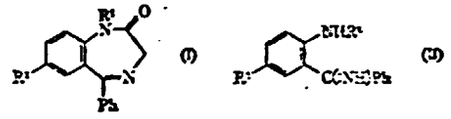
(IIa), m. 125° (decompn.) Similarly prepd. were II·HCl (R, R^1, and m.p. given): H, NO$_2$, 178° (decompn.); Me, Cl, 108–10° (decompn.). Oxidn. of IIa with CrO$_3$-pyridine gave III (R = H, R^1 = Cl), m. 212–13°. Similarly prepd. were III (R = H, R^1 = NO$_2$), m. 223–4°, and III (R = Me, R^1 = Cl), m. 130–2°. II are tranquilizers, anticonvulsants and muscle relaxants. KCPG

A4.58. 43752a Benzodiazepine derivatives. Kawai, Masamichi (Takeda Chemical Industries, Ltd.) Japan. 69 26,302 (Cl. 16 E 552), 05 Nov 1969, Appl. 18 Apr 1956; 5 pp. The prepn. of I, useful as analgesics, sedatives, antispasmodics, and muscle relaxants, is described. Thus, a mixt. of 2.3 g 5-chloro-2-amino-benzophenone, 2.9 g Me ester of L-isoleucine·HCl, and 1 g ZnCl$_2$ is heated at 150°, heated 2 hr with 2 g ZnCl$_2$, and the mixt. heated 2 hr at 150° with 2 g ZnCl$_2$ to give I (R^1 = Cl, R^2 = H,



R^3 = *sec*-Bu), m. 205–7° (EtOH). Similarly prepd. are the following I (R^1, R^2, R^3, and m.p. given): Cl, H, PhCH$_2$, 160–1°; Cl, H, iso-Bu, 213–16°; Cl, H, H, 213–14°; Cl, Me, H, 127–9°; H, H, H, 177–8°; NO$_2$, H, H, 220–1°; H, H, PhCH$_2$, 192.5–3°; H, H, iso-Bu, 196–7°. Hiroshi Kataoka

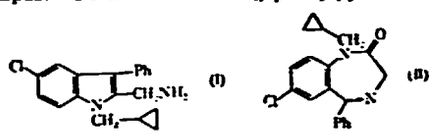
A4.59. 12779k 2-Oxo-5-phenyl-1,3-dihydro-1,4-benzodiazepines. Moriyama, Hiroaki; Yamamoto, Hisao; Nagata, Hideo; Inaba, Shigeho (Sumitomo Chemical Co., Ltd.) Japan. 69 17,138 (Cl. 16 E 552), 29 Jul 1969, Appl. 23 May 1966; 6 pp. Manuf. of I, useful as a tranquilizer, hypnotic, and muscle-relaxant, from II is described. In an example, a soln. of 14.1 g PhBr in 30 ml Et$_2$O is dropped into 50 ml ethereal soln. of 2.2 g Mg, 130 ml ethereal soln. of 9.2 g *o*-aminobenzonitrile dropped in during 1 hr, and the mixt. refluxed 4 hr to give 90% II (R^1 = R^2 = H), b$_5$ 175–5.5°. Similarly prepd. are the following II (R^1 and R^2



given; all being yellow oil): Me, H; Me, Cl; H, NO$_2$. I (R^1 = R^2 = H) (4.8 g) and 5.4 g glycine Et ester hydrochloride are refluxed in 45 ml pyridine under anhyd. condition to give 3.2 g I (R^1 = R^2 = H), m. 181–3° (C$_6$H$_6$-petr ether). Similarly prepd. are the following I (R^1, R^2, and m.p. given): Me, H, 180–2°; Me, Cl, 130–2°; H, NO$_2$, 221–8°. Hiroshi Kataoka

A4.60. 87863c 2H-1,4-Benzodiazepin-2-ones. [illegible], Lajos; Rohrich, Julianna; Low, Miklos (Richter, Gedeon, Vegyeszeti Gyar R.T.) Hung. 155,373 (Cl. C 07d), 22 Nov 19[illegible], Appl. 28 Dec 1966; 6 pp. A soln. of 0.01 mole 1-methyl-3,4,5-tetrahydro-5-phenyl-7-chloro-2*H*-benzodiazepin-2-one in [illegible] ml. CHCl$_3$ is treated with Br in CHCl$_3$ at room temp. 15 min, and worked up to yield 81% 1-methyl-1,3-dihydro-5-phenyl-7-chloro-2*H*-benzodiazepin-2-one, m. 129–31° (70% EtOH). 1,3-Dihydro-5-phenyl-7-nitro-2*H*-benzodiazepin-2-one, m. [illegible] (70% EtOH), was obtained similarly in 73.5% yield. [illegible]

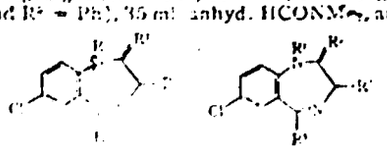
A4.61. 124519n Tranquilizer benzodiazepine derivatives. Yamamoto, Hisao; Inaba, Shigeho; Okamoto, Tadashi; Hirohashi, Toshiyuki; Ishizumi, Kikuo; Yamamoto, Michimiro; Maruyama, Isamu; Mori, Kazuo; Kobayashi, Tsuyoshi (Sumitomo Chemical Co., Ltd.) S. African 68 03,041 28 Jan 1969, Japan. Appl. 22 Sep 1967; 106 pp. Benzodiazepine derivs. were prepd. by the reaction of a 2-aminomethylindole derivative or its salt with an oxidizing agent. Chromic acid is a preferred oxidizing agent. When HOAc is used as a solvent, 2–3 times the stoichiometric amt. of chromic acid is preferable. Thus, to a soln. of 0.69 g. 1-cyclopropylmethyl-2-aminomethyl-3-phenyl-5-chloroindole (I) in 10 ml. HOAc was added 1 ml. aq. soln. of 1.0 g. CrO_3 under cooling, and the mixt. stirred 15 hrs. at room temp. and worked up to yield 1-cyclopropylmethyl-5-phenyl-7-chloro-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (II), m. 143–5°. The 2-aminomethylindole derivs. used as starting materials are also novel compds. To a soln. of 22.5 g phenylpyruvic acid in 500



ml. EtOH was added 20 g. *p*-$ClC_6H_4NHNH_2$, and the mixt. heated 30 min. and evapd. to give oily *p*-chlorophenylhydrazone of phenylpyruvic acid. Anhyd. HCl was passed into a soln. of 27.1 g. Et phenylpyruvate *p*-chlorophenylhydrazone in 30 ml. EtOH 2 hrs. and the mixt. worked up to give 19.8 g. Et 3-phenyl-5-chloroindole-2-carboxylate, m. 172–2.5°. $SOCl_2$ (1.6 g.) was added to a suspension of 1.5 g. 1-cyclopropylmethyl-3-phenyl-5-chloroindole-2-carboxylic acid in 30 cc. C_6H_6, and the mixt. refluxed 8 hrs. and evapd. in vacuo to leave 1.6 g. oily residue, which was then dissolved in 30 cc. anhyd. Et_2O, and gaseous NH_3 introduced 20 min. to ppt. 1-cyclopropylmethyl-3-phenyl-5-chloroindole-2-carboxamide, m. 187–8°. To a suspension of 1.6 g. $LiAlH_4$ in 300 ml. Et_2O was added 3.0 g. 1-methyl-3-phenyl-5-chloroindole-2-carboxamide, and the mixt. refluxed 4 hrs. and worked up to give 2.9 g. 1-methyl-2-aminomethyl-3-phenyl-5-chloroindole-HCl hydrochloride, m. 256.5° (decompn.); free base m. 63–7°. Several alternate methods and prepns. are given. The benzodiazepines prepd. are tranquilizers, muscle relaxants, anticonvulsants, and hypnotics. Other compds. prepd. were Et α-benzyl-α-(*p*-chlorophenylazo)acetoacetate (m. 61–2.5°), Et phenylpyruvate *p*-chlorophenylhydrazone (m. 87–93°), Et 5-chloro-3-phenylindole-2-carboxylate (m. 178–80°), Et 1-cyclopropylmethyl-3-phenyl-5-chloroindole-2-carboxylate (m. 113–16°), Et 3-phenyl-5-chloroindole-2-carboxylate (m. 172–2.5°), 3-phenyl-5-chloroindole-2-carboxylic acid (m. 231°), *p*-chlorophenylhydrazone of Et phenylpyruvate, Et 1-methyl-3-phenyl-5-chloroindole-2-carboxylate (m. 88–9°), 5-chloro-3-phenylindole-2-carboxylic acid (m. 231°), 1-methyl-3-phenyl-5-chloroindole-2-carboxylic acid (m. 211–13°), 1-cyclopropylmethyl-3-phenyl-5-chloroindole-2-carboxylic acid (m. 197–8°), 3-phenyl-5-chloroindole-2-carboxamide (m. 217–19°), 1-methyl-3-phenyl-5-chloroindole-2-carboxamide (m. 191–2°), 3-phenyl-5-chloroindole-2-carbonyl chloride, 1-cyclopropylmethyl-3-phenyl-5-chloroindole-2-carboxamide (m. 187–7.5°), 5-chloro-1-cyclopropylmethyl-3-phenylindole-2-carboxamide (m. 187–9°), 2-aminomethyl-3-phenyl-5-chloroindole-HCl [m. 231–3° (decompn.)], 1-methyl-2-aminomethyl-3-phenyl-5-chloroindole sulfate [m. 243–5° (decompn.)], 1-cyclopropylmethyl-2-aminomethyl-3-phenyl-5-chloroindole-HCl (m. 218–19.5°), 5-chloro-3-phenylindole-2-carbonitrile (m. 200–2.5°), 2-aminomethyl-3-phenyl-5-chloroindole-HCl [m. 231–2° (decompn.)], 1-methyl-2-aminomethyl-3-phenyl-5-chloroindole-HCl [m. 256° (decompn.)], 1-methyl-3-phenyl-5-chloroindole-2-carbonitrile [illegible -30.5°), 5-phenyl-7-chloro-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (m. 212–15°) (HCl salt m. 230–50°), and 1-methyl-5-phenyl-7-chloro-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one [illegible]

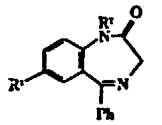
Peter Selver

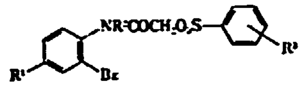
A4.62. 78827f Benzodiazepines. Fryer, Rodney [illegible]ch, Leo H. (Hoffmann-La Roche, F., and Co. A.G.) [illegible]rican 68 00,799 09 Aug 1968, US Appl. 06 Feb 1967, [illegible] A mix contg. 3 g. I (R¹ = Me, R² = H, R³ = H, R⁴ = *p*-$MeC_6H_4SO_2$, and R⁵ = Ph), 35 ml. anhyd. HCONMe₂, and 0.8 g. [illegible] NaH in



mineral oil is stirred at room temp. to give II.HCl (R^1 = Me, R^2 = H, R^3 = H_2, R^4 = Ph), m. 240–50°. A mixt. contg. 14 g. I (R^1 = Me, R^2 = H, R^3 = H_2, R^4 = H, R^5 = Ph) and 11.7 g. p-$MeC_6H_4SO_2Cl$ is refluxed in pyridine 1.5 hrs. to give I (R^1 = Me, R^2 = H, R^3 = H_2, R^4 = p-$MeC_6H_4SO_2$, R^5 = Ph), m. 127–30°. Similarly are prepd. the following compds. (R^1, R^2, R^3, R^4, R^5, and m.p. given): II, Me, H, O, Ph, —, 127–30°; I, H, H, O, p-$MeC_6H_4SO_2$, Ph, 246–52°; I, Me, H, O, p-$MeC_6H_4SO_2$, Ph, 260–2°; III, H, H, O, Ph, —, 202–10°; II, H, H, O, Ph, —, 215–21°; I, H, H, O, $MeSO_2$, Ph, 203–6°; II, H, H, O, 2-fluorophenyl, 196–202°; I, H, H, O, p-$MeC_6H_4SO_2$, 2-fluorophenyl, 242–3°; II.HCl, Me, H, H_2, Ph, —, 256–7°; I, Me, H, H_2, CHO, Ph, 121–2°; and I, Me, H, H_2, Ac, Ph, 106–8°. The compds. are useful pharmaceuticals, e.g. sedatives and anticonvulsants. Maurice Zweigle

A4.63. 68444y **1,4-Benzodiazepines.** Bahr, Fritz; Roehnert, Helmut; Carstens, Ernst Ger. (East) 61,268 (Cl. C 07*d*), 20 Apr 1968, Appl. 23 Feb 1967; 4 pp. Title compds. of the general formula I were prepd. by treating compds. of the general formula II with NH_3 in an inert org. solvent. Thus, 5 g. II (R^1 = Cl, R^2 = R^3 = H), m. 135–7°, was refluxed 2 hrs. in 50 ml. dioxane and 50 ml. concd. aq. NH_3, the mixt. evapd. in vacuo, the

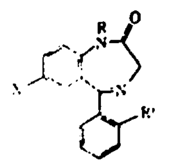

(I)


(II)

residue heated with 50 ml. Me_2CO 30 min., the hot soln. filtered to remove ammonium benzene sulfonate, and the filtrate evapd. in vacuo to 25 ml. to give 73% I (R^1 = Cl, R^2 = H), m. 215° (BuOH). Similarly prepd. were the following I (R^1, R^2, m.p., and % yield given): H, H, 181°, ~100; Me, H, 206–8° (Me_2CO), 81; Cl, Me, 125–7° (iso-PrOH), 62; and NO_2, H, 226° (EtOH or iso-PrOH), 55. As precursors the following II were used (R^1, R^2, R^3, m.p., and % yield given): Cl, H, Me, 150–2° (AcOH), 65; H, H, Me, 115–17° (alc.), 61; Me, H, Me, 123–5° (alc.), 85; Cl, Me, Me, 110–14°, 93; and NO_2, H, Me, 178–81°, 89. The products are sedatives and tranquilizers. A. Roders

A4.64. 57919f **1-Methyl-5-phenyl-7-chloro-1,3-dihydro-2H-1,4-benzodiazepin-2-one.** Yamamoto, Hisao; Inaba, Shigeho; Hirohashi, Toshiyuki; Ishizumi, Kikuo; Maruyama, Isamu; Mori, Kazuo (Sumitomo Chemical Co., Ltd.) S. African 68 00,805 17 Apr 1968, Appl. 07 Feb 1968; 5 pp. The title compd. (I), a tranquilizer, was prepd. by treating 1-methyl-2-aminomethyl-3-phenyl-5-chloroindole (II) with an oxidizing agent. II was prepd. by methylation, amidation, and redn. of 2-ethoxycarbonyl-3-phenyl-5-chloroindole, prepd. by treating a diazonium salt of p-chloroaniline with Et α-benzylacetoacetate. Thus, 3 g. CrO_3 and 3 ml. H_2O was added dropwise to a suspension of 3.38 g. II in 30 ml. HOAc at 20–30°. The soln. was stirred 12 hrs., and cooled to 0–10° while 160 ml. 10.5% aq. NH_3 soln. was added to give 2.21 g. I, m. 131–3° (iso-PrOH). FDPN

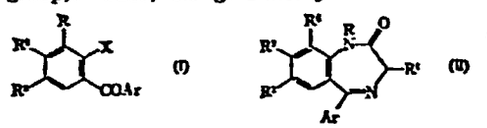
A4.65. 57916c **1-Substituted 1-alkyl-5-aryl-1,2-dihydro-3H-1,4-benzodiazephin-2-ones.** Sorrentino, Pasquale P. (Aktieselskabet Dumex (Dumex Ltd.)) S. African 67 [illegible] Apr 1968, Dan. Appl. [illegible] Nov 1966; 8 pp. N-[2-[illegible] haloacetamido[illegible]phthalimides are treated with [illegible] OEt to give I. [illegible] 5,2-Cl(MeNH)C_6H_3]CH[illegible]


(I)

verted to N-(2-methyl[illegible]o-5-chlorobenzhydryl[illegible] (m. 191.2–1.9°) and N-[2-[illegible]dichloroacetyl N-[illegible]-5-chlorobenzhydryl[illegible] (II) (m. 206–7°). A [illegible] g. II in 200 ml. [illegible] with a soln. of [illegible] in 100 ml. EtOH and the [illegible] refluxed 2.5 hrs. [illegible] pH 7–7.5 to give 2.8 [illegible] 7-chloro-1-methyl[illegible] hydro-3H-1,4-benzo[illegible]one, m. 1[illegible] prepd. are th[illegible] R, R[1], X, [illegible] Cl, 137.8°, [illegible]; Me, [illegible] Br, 151°; Me, [illegible], Me, Cl, Cl, [illegible] 164–1.5°.

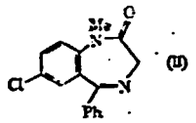
A4.66.

37850y 5-Aryl-3H-1,4-benzodiazepin-2(1H)-ones. Reeder, Earl; Sternbach, Leo H. (Hoffmann-La Roche Inc.) U.S. 3,402,171 (Cl. 260-239.3), 17 Sep 1968, Swiss Appl. 02 Dec 1960; 18 pp. Continuation-in-part of U.S. 3,051,701 and division of U.S. 3,136,815 (*CA* 57: 16641c and *CA* 61: 9515f). I (X = amino) are treated with amino acids to give benzodiazepinones (II), which are also prepd. by cyclization of I (X = $NHCOCH_2Y$)(Y = amino group). Thus, 6.5 g. 2-methylamino-5-chlorobenzophenone is heated with 10 g. Et glycinate-HCl in pyridine to give 7-chloro-1-methyl-5-phenyl-3*H*-1,4-benzodiazepin-2(1*H*)-one, m. 125–6°. Similarly prepd. are the following II (R, R^1, Ar, R^2, R^3, R^4, and m.p. given): H, H, Ph, H, Me, H, 255–6°; H, H, *o*-ClC_6H_4, Me, H, H, 223–4°; H, iso-Pr, Ph, Cl, H, H, 226–7°; H, iso-Bu, Ph, Cl, H, H, 213–14°; H, H, Ph, F, H, H, 197–8°; H, $MeOCH_2$, Ph, Cl, H, H, 166–7°; and H, H, *m*-tolyl, Cl, H, H, 198–9°. 2-Bromoacetamido-3-methylbenzophenone (18.2 g.) is treated with liq. NH_3 and the product heated in pyridine to give 9-methyl-5-phenyl-3*H*-1,4-benzodiazepin-2(1*H*)-one, m. 184–5°. Similarly prepd. are the following II (R, R^1, Ar, R^2, R^3, R^4, and m.p. given): H, H, *o*-FC_6H_4, H, H, H, 180–1°; H, H, *p*-FC_6H_4, Cl, H, H, 223–4°; H, H, *o*-ClC_6H_4, H, H, H, 212–13°; H, H, *o*-ClC_6H_4, Cl, H, H, 199–201°; H, H, Ph, Br, H, H, 219–20.5°; H, H, Ph, Me, H, H, 209–10°; H, H, Ph, F, H, H, 197–8°; H, H, *p*-ClC_6H_4, Cl, H, H, 247–8°; Me, H, Ph, Cl, H, H, 125–6°; and H, H, *o*-FC_6H_4, Br, H, H, 186–7°. Also prepd., according to known methods are the following I (Ar, X, R, R^1, R^2, and m.p. given): Ph, NH_2, Cl, H, H, 56.5–58°; *o*-ClC_6H_4, $BrCH_2CONH$, H, H, Cl, 136°; Ph, EtNH, H, H, Cl, 56–7°; *o*-tolyl, $BrCH_2CONH$, H, H, Cl, 137–8°; *o*-ClC_6H_4, *p*-$MeC_6H_4SO_2NH$, H, H, Cl, 136–8°; *o*-ClC_6H_4, *p*-$MeC_6H_4SO_2NMe$, H, H, Cl, 153–5°; *o*-ClC_6H_4, *p*-$MeC_6H_4SO_2NMe$, H, H, Cl, 153–5°; *o*-ClC_6H_4, MeNH, H, H, Cl, 88–90°; *o*-FC_6H_4, *p*-$MeC_6H_4SO_2NH$, H, H, Cl, 119–20°; *o*-FC_6H_4, *p*-$MeC_6H_4SO_2NMe$, H, H, Cl, 151–2°; *o*-FC_6H_4, MeNH, H, H, Cl, 119–20°; Ph, NH_2, Cl, H, Cl, 93–4°; Ph, NH_2, Me, H, Cl, —; Ph, NH_2, Me, H, H, 51–2°; Ph, $BrCH_2CONH$, Me, H, H, 117–18°; OH, N:CHNMe$_2$, H, Me, H, 196–8°; Ph, NH_2, H, Me, H, 68–70°; *o*-FC_6H_4, NH_2, H, H, Me, 68.5–5°; *o*-ClC_6H_4, NH_2, H, H, Me, 106–7°; *o*-FC_6H_4, *p*-$MeC_6H_4SO_2NH$, H, H, H, 129.5–30°; *o*-FC_6H_4, $BrCH_2CONH$, H, H, H, 117–18.5°; *p*-FC_6H_4, NH_2, H, H, Cl, 108–9°; *p*-FC_6H_4, *p*-$MeC_6H_4SO_2NH$, H, H, Br, 114–15°, *o*-FC_6H_4, *p*-$MeC_6H_4SO_2NMe$, H, H, Br, 154–5°; *o*-FC_6H_4, MeNH, H, H, Br, 112–13°; *o*-$O_2NC_6H_4$, Cl, H, H, H, 76–9°; *o*-ClC_6H_4, NH_2, H, H, H, 58–60°; *o*-ClC_6H_4, $BrCH_2CONH$, H, H, H, 119–21°; *o*-ClC_6H_4, H_2NCH_2CONH, H, H, H, 162–4°; *o*-FC_6H_4, *p*-$MeC_6H_4SO_2NH$, H, H, Cl, 132–3°; *o*-ClC_6H_4, $ClCH_2CONH$, H, H, Cl, 157–9°; Ph, $BrCH_2CONH$, H, H, Br, 117.5–18.5°; Ph, $BrCH_2CONH$, H, H, Me, 116–17°; *m*-tolyl, NH_2, H, H, Cl, 90–1°; Ph, $BrCH_2CONH$, H, H, F, 103–5°; *p*-ClC_6H_4, $BrCH_2CONH$, H, H, Cl, 127–8°; *p*-ClC_6H_4, H_2NCH_2CONH, H, H, Cl, 139–40°; Ph, $ClCH_2CONMe$, H, H, Cl, 123–4°; Ph, ICH_2CONMe, H, H, Cl, 95°; *o*-FC_6H_4, $BrCH_2CONH$, H, H, Br, 139–40°; *o*-FC_6H_4, H_2NCH_2CONH, H, H, Br, 110–11°; *o*-FC_6H_4, $ClCH_2CONH$, H, H, Cl, 141–2°; Ph, $BrCH_2CONH$, H, H, H, 94–5°; and Ph, $BrCH_2CONH$, Cl, H, Cl, 162–3°. Also prepd. were the following II (R, R^1, Ar, R^2, R^4, and m.p. given): H, H, Ph, Cl, H, H, 216–17°; Me, H, Ph, Cl, H, H, 125–6°; Me, H, *o*-FC_6H_4, H, H, H, 113–14°; iso-Pr, H, *o*-ClC_6H_4, Cl, H, H, 143–50°; allyl, H, *o*-ClC_6H_4, Cl, H, H, 128–30°; Me, H, Ph, F, H, H, 109–10°; Me, H, *p*-ClC_6H_4, Cl, H, H, 154–6°; and $NCCH_2CH_2$, H, Ph, Cl, H, H, 117–19°. Also prepd. were the following compds. (m.p. given): 7-chloro-2-(*N*-methylacetamido)-5-phenyl-3*H*-1,4-benzodiazepin 4-oxide, 186–7°; 7-chloro-5-phenyl-3*H*-1,4-benzodiazepin-2(1*H*)-one 4-oxide, 235–6°; and 7-bromo-1,3-dihydro-5-phenyl-3*H*-1,4-benzodiazepin-2(1*H*)-one, 161–2°. BDP



A4.67. 3561q 2-Aminobenzophenone imine derivatives. Fryer, Rodney I.; Sternbach, Leo H. (Hoffmann-La Roche, F., und Co., A.-G.) Fr. 1,503,346 (Cl. C 07c), 24 Nov 1967, US Appl. 09 Dec 1965; 3 pp. Title products, useful as intermediates in the prepn. of 1,4-benzodiazepines are prepd. as follows: A mixt. of 100 g. 2-amino-5-chlorobenzophenone, 200 cc. MeOH, 200 cc. aq. NH_3, and 2 g. $ZnCl_2$ is heated in a pressure vessel under 15 atm. N at 150° for 15 hrs., and then evapd. in vacuo to give 2-amino-5-chlorobenzophenonimine, m. 73–4°. A mixt. of 100 g. 2-amino-5-nitrobenzophenone, 200 cc. MeOH, 200 cc. aq. NH_3 and 2 g. $ZnCl_2$ is heated in a pressure vessel under 15 atm. N at 160° for 12 hrs.; after cooling, the ppt. is filtered and treated with 650 cc. *N* HCl and 300 g. ice, and neutralized with NH_3 to give 2-amino-5-nitrobenzophenonimine, m. 152–4° (petroleum ether). A mixt. of 97 g. 5-chloro-2-methylaminobenzophenone, 200 cc. aq. NH_3 200 cc. MeOH, and 0.20 g. $ZnCl_2$ is heated 24 hrs. at 145° to give 2-methylamino-5-chlorobenzophenonimine (I), m. 95–7° (MeOH). A soln. of 5 g. I in 50 cc. benzene is cooled and treated with 50 cc. 0.5*N* NaOH, then with a soln. of 4.6 g. $BrCH_2COBr$ in 10 cc. benzene, stirred 15 min., then treated with 23 cc. *N* NaOH and stirred 2 hrs. to give 7-chloro-2,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one, m. 128–30°; in a similar way 2-methylamino-5-nitrobenzophenonimine gives 2,3-dihydro-1-methyl-7-nitro-5-phenyl-2*H*-1,4-benzodiazepin-2-one. Juan Castaner Gargallo

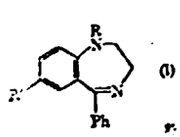
A4.68. 59299g 7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one. Fryer, Rodney I.; Sternbach, Leo H. (Hoffmann-La Roche Inc.) U.S. 3,376,290 (Cl. 260–239.3), 02 Apr 1968, Appl. 09 Dec 1965; 2 pp. A mixt. of 97 g. 5-chloro-2-methylaminobenzophenone (I), 200 ml. NH_4, 2 g. $ZnCl_2$, and 200 ml. MeOH is introduced into an autoclave, the autoclave charged with an overpressure of 15 atm. N, and the mixt. heated 24 hrs. at 145° and worked up to give I imine, m. 95–7°. A soln. of 5 g. I imine in 50 ml. C_6H_6 is cooled in ice and treated with 50



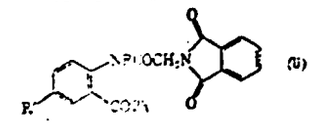
(II)

ml. 0.5*N* NaOH, a soln. of 4.6 g. $BrCH_2COBr$ in 10 ml. C_6H_6 added, the mixt. agitated 15 min., 23 ml. *N* NaOH added, and the mixt. agitated 2 hrs. and worked up to give I and the title compd. (II), m. 128–30°. BDPN

A4.69. 36192c 1,4-Benzodiazepines. Roehnert, Helmut; Bahr, Fritz; Carstens, Ernst Ger. (East) 57,126 (Cl. C 07d), 05 Aug 1967, Appl. 12 Sep 1966; 4 pp. I are prepd. by treating the corresponding 2-aminobenzophenone with phthaloylglycyl chloride and cyclizing the 2-(phthaloylglycylamino)benzophenone (II) so formed. Thus, 100 g. 5,2-Cl(NH_2)C_6H_3Bz in 600 ml. $CHCl_3$ was heated with 92.6 g. phthaloylglycyl chloride at 70° 6 hrs. to give 94% II (R = H, R′ = Cl) (III), m. 211–19°. III (8.4 g.) in 200 ml. MeOH and 7.2 ml. 18% aq. NH_2NH_2 was refluxed for



(I)

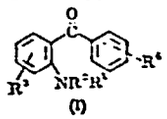


(II)

2 hrs. at 60° to form 37% I (R = H, R′ = Cl), m. 214–17°. The following I and II were similarly prepd. (R, R′, % yield II, m.p. II, % yield I, and m.p. I given): Me, Cl, 80, 124–6°, 81, 173–6°; H, NO_2, 50, 224–6°, 83, 196–200°; H, H, 82.5, 180–2°, 85, 152–4°. CVPG

A4.70. 9[illegible]f 2-N-Substituted amidobenzophenones. Earl Roeder and Leo H. Sternbach (to Hoffmann-La Roche Inc.) U.S. 3,344,183 (Cl. 260–558), Sept. 26, 1967; Swiss Appl. Dec. 2, 1960; 24 pp. Continuation-in-part of U.S. 3,051,701 (*C.A.* 57: 16431c); Division of U.S. 3,136,815 (*C.A.* 61: 9515f; U.S. 3,219,653 (*C.A.* 66: 28808f); U.S. 3,280,134 (*C.A.* 64: 19236g). The disclosure is the same but the claims are different. C2PG

A4.71. 2-(*N*-Substituted amino)halobenzophenones. Earl Reeder and Leo H. Sternbach. U.S. 3,239,564 (Cl. 260–570), March 8, 1966; Swiss Appl. Dec. 2, 1960; 11 pp. The title compds. (I)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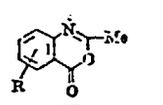
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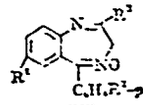
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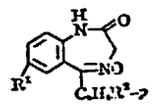
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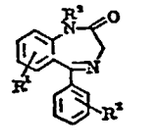
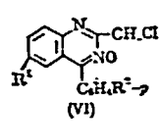

(V)


(VI)

were prepd. by published methods by condensing substituted benzoyl chlorides with anilines in the presence of $ZnCl_2$ or by reaction of II with Grignard reagents. I were used as intermediates for III, IV, V, and VI which are sedatives, muscle relaxants, and anticonvulsants. The I prepd. were tabulated. Further prepd.

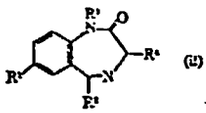
R^1	R^2	R^3	R^4	M.p.
H	H	5-Br	4-Me	105–6°
H	H	5-Cl	4-Cl	118–19°
H	Ac	3,5-Cl_2	H	143–4°
H	H	3,5-Cl_2	H	93–4°
H	H	H	4-Cl	98–9°
H	H	6-Cl	H	101–2.5°
H	Ac	3-Cl	H	129–31°
H	H	3-Cl	H	56.5–9°
H	H	4-Cl	H	84–5°
H	H	5-Cl	4-Cl	88–9°
H	H	5-Cl	2-Me	50–5°
H	H	5-Cl	2-F	94–5°
H	H	5-Cl	3-F	90–1°
H	H	5-Br	2-F	101–2°
Na	*p*-$MeC_6H_4SO_2$	5-Cl	H	298–9°
H	*p*-$MeC_6H_4SO_2$	5-Cl	H	120–1°
Me	*p*-$MeC_6H_4SO_2$	5-Cl	H	151–2°
H	Me	5-Cl	H	95–6°
H	CH_2:$CHCH_2$	5-Cl	H	76–7°
$PhCH_2$	*p*-$MeC_6H_4SO_2$	5-Cl	H	116–18°
H	$PhCH_2$	5-Cl	H	86–7°
Me	$BrCH_2C(O)$	5-Cl	H	95–6°
CH_2:$CHCH_2$	$BrCH_2C(O)$	5-Cl	H	85–6°
$PhCH_2$	$BrCH_2C(O)$	5-Cl	H	159–60°
H	Et	5-Cl	H	56–7°
H	$BrCH_2C(O)$	5-Cl	2-Me	137–8°
H	*p*-$MeC_6H_4SO_2$	5-Cl	2-Cl	136–7°
Me	*p*-$MeC_6H_4SO_2$	5-Cl	2-Cl	152–5° and 145°
Me	H	5-Cl	2-Cl	88–90° and 78–80°
H	*p*-$MeC_6H_4SO_2$	5-Cl	2-F	119–20°
Me	*p*-$MeC_6H_4SO_2$	5-Cl	2-F	151–2°
Me	H	5-Cl	2-F	119–20°
H	H	3,5-Cl_2	H	93–4°
H	H	Me	H	51–2°
H	$BrCH_2C(O)$	Me	H	117–18°
H	H	5-Me	F	68.5–9.5°
H	H	5-Me	2-Cl	106–7°
H	H	H	2-F	126–8°
H	*p*-$MeC_6H_4SO_2$	H	2-F	129.5–30°
H	H	5-Cl	4-F	108–9°
H	*p*-$MeC_6H_4SO_2$	5-Cl	4-F	126–8°
H	*p*-$MeC_6H_4SO_2$	5-Br	2-F	114–15°
Me	*p*-$MeC_6H_4SO_2$	5-Br	2-F	154–5°
Me	H	5-Br	2-F	112–13°
H	H	H	2-Cl	58–60°
H	$BrCH_2C(O)$	H	2-Cl	119–20°
H	$H_2NCH_2C(O)$	H	2-Cl	162–4°
H	*p*-$MeC_6H_4SO_2$	5-Cl	2-F	142–3°
H	H	5-Cl	Me	90–1°
Me	$ClCH_2C(O)$	5-Cl	H	123–4°
Me	$ICH_2C(O)$	5-Cl	H	95°

were II (R, m.p. given): 5-Cl, 143.5–46°; 8-Cl, 131.5–2.5°; 7-Cl, solid. 2,5-$R(NHR^1)C_6H_3C(NOH)C_6H_4R^2$-*p* (III) (α or β form, R, R^1, R^2, m.p. given): α, H, Br, Me, 204–5°; β, H, Br, Me, 115–16°; α, $ClCH_2CO$, Br, Me, 179–80°; α, H, Cl, Cl, 151–4°. Other compds. prepd. were listed in the 2nd table.

Structure	R	R^1	R^2	M.p.
III	Br	Me	MeNH	255–6°
III	Br	Me	$NH_2CH_2CH_2NH$	202–10°
III	Cl	Cl	MeNH	254–5°
III	Cl	Cl	$AcNHCH_2CH_2NH$	191–2°
IV	Br	Me		237–5°
IV	Cl	Cl		250–2°
V	7,9-Cl_2	H	H	207–8°
V	H	4-Cl	H	262–3°
V	7-Cl	H	Me	125–6°
V	7-Cl	H	CH_2:$CHCH_2$	105–6°
V	7-Cl	H	$PhCH_2$	173–4°
V	9-Me	H	H	(solid)
V	7-Me	2-Cl	H	223–4°
V	H	2-Cl	H	212–13°
V	7-Cl	3-Me	H	198–9°
V	7-Cl	H	Me	125–6°
VI	Br	Me		162–4°
VI	Cl	Cl		163–4°

Also prepd. was 2-Bromo-2'-methylamino-5-nitrobenzophenone, m. 76–9°, and 2-chloro-2'-formamido-benzanthrone. Th. Weil

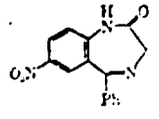
A4.72. 78324g Substituted o-aminoarylketimines and benzodiazepines. Etablissements Clin-Byla. Fr. M4205 (Cl. A 61k, C 07c,d), July 11, 1966, Appl. Sept. 14, 1964; 18 pp. 5,2-R^1-(NHR^2)$C_6H_3CR^3$:NCHR^4CO_2R^5 (I) and II are prepd. They



(II)

have sedative effects on the central nervous system. Thus, a soln. of PhMgBr from 109 g. Mg and 848 g. PhBr in 3600 ml. Et_2O was treated with 228.7 g. 5,2-Cl(H_2N)C_6H_3CN in 1800 ml. Et_2O and the mixt. refluxed 15 hrs. which was then poured into a soln. of 500 g. NH_4Cl in 2000 ml. H_2O and 3 kg. ice to give 309 g. 5,2-R^1(NHR^2)$C_6H_3CR^3$:NH (III, R^1 = Cl, R^2 = Ph, R^3 = H) (IV), m. 74°. Similarly prepd. were the following III (R^1, R^2, R^3, and m.p. given): Cl, Ph, Me; 97°; H, Ph, H, 48°; Cl, cyclohexyl, H, 65° (and 95°); Cl, Bu, H, 27–8° (decompn.). A mixt. of 27.6 g. IV and 20.7 g. $H_2NCH_2CO_2Et.HCl$ (V) in 150 ml. MeOH was stirred for 2.5 hrs. to give 32.4 g. I (R^1 = Cl, R^2 = Ph, R^3 = R^4 = H, R^5 = Et) (VI), m. 130–5° (mixt. of 2 stereoisomers) (recrystn. from Me_2CO gives chelated form, m. 148–50° and non-chelated m. 142–6°). The following I were similarly prepd. (R^5 = Et, R^1, R^2, R^3, R^4, and m.p. given): Cl, Ph, Me, H, 70–5°; Cl, Ph, H, CO_2Et, 106°; Cl, Ph, Me, CO_2Et, 88°; H, Ph, H, H, 106°; H, Ph, H, CO_2Et, 100°; Me, Ph, H, H, 131°; Cl, Bu, H, H, 96–7°. Proceeding from IV and V as above the intermediate VI was not isolated; but HOAc (150 ml.) was added, the mixt. refluxed for 30 min. to give 25.7 g. II (R^1 = Cl, R^2 = Ph, R^3 = R^4 = H), m. 214–16°, which was also prepd. from 0.409 g. [2-phenyl(2-amino-5-chlorophenyl)-1-azavinyl]malonic acid di-K salt in 4 ml. H_2O adjusted to pH 4 with HOAc and heated for 15 min. The following II were similarly prepd. (R^1 = Cl, R^2 = Ph, R^3, R^4, and m.p. given): Me, H, 132°; H, Me, 224°; H, iso-Bu, 213°; H, $(CH_2)_2SMe$, 184°; H, CO_2Et, 244°; H, CO_2Me (VII), 226°; Me, CO_2Et, 180°; H, $CONH_2$, 255–6°; H, CONHMe, 294°; H, $CONMe_2$, 297°; H, $CONH(CH_2)_2NEt_2$, 220°; and II (R^2 = H, R^1, R^3, R^4, and m.p. given): H, Ph, CO_2Et, 226°; Me, Ph, H, 208°; Me, Ph, CO_2Et, 260°; NO_2, Ph, CO_2Et, 271°; NH_2, Ph, CO_2Et, 305°(decompn.); Cl, cyclohexyl, H, 210°; Cl, cyclohexyl, CO_2Et, 208°. K (50 g.) was dissolved in 1350 ml. warm 96° (sic) EtOH and treated at 70° with 82 g. VII to give I (R^1 = Cl, R^2 = Ph, R^3 = H, R^4 = CO_2K, R^5 = K). Similarly prepd. were the following I (R^1 = Ph, R^4 = CO_2K, R^5 = K, R^1 and R^2 given): Cl, Me; H, H; Me, H; NO_2, H; NH_2, H; and I (R^1 = Cl, R^2 = Ph, R^3 = H, R^4 = CO_2NH_2, R^5 = K). A soln. of 1 g. I (R^1 = Cl, R^2 = Ph, R^3 = H, R^4 = CO_2K, R^5 = K) (VIII) in 15 ml. H_2O with 0.55 g. $CaCl_2.2H_2O$ in 5 ml. H_2O pptd. 0.75 g. the corresponding Ca salt of VIII (2.1 g.) and 0.68 g. KH_2PO_4 in 18 ml. H_2O gave 1.8 g. II (R^1 = Cl, R^2 = Ph, R^3 = H, R^4 = CO_2K) which decarboxylated readily on treating an aq. soln. Similarly prepd. were the following II (R^2 = Ph, R^3 = H, R^4 = CO_2K, R^1 given): H, Me, and NO_2. G. Smalley

A4.73. 69054s 1,4-Benzodiazepine derivatives. F. Hoffmann-La Roche & Co. (by Earl Reeder, Leo H. Sternbach, Oscar Keller, Norbert Steiger, and Arthur Stempel). Swiss 414,652 (Cl. C 07d). Dec. 30, 1966, U.S. Appl. Dec. 10, 1959, April 26, and June 27, 1960; 16 pp. Cf. Ger. 1,145,625 (*CA* 59: 10056d); Belg. 615,104 (*CA* 59: 12827c); Ger. 1,136,709 (*CA* 59: 12328g); Ger. 1,145,626 (*CA* 60: 12033h); Ger. 1,212,105 (*CA* 64: 17492h). In addn. to a description of the title compds. mentioned in the earlier patents (*loc. cit.*) the prepn. of some new ones and of the starting materials by conventional methods are given. 2-Chloroacetamido-5-chlorobenzophenone, m. 117–18° (C_6H_6–petroleum ether) is prepd. from 2-amino-5-chlorobenzophenone (I) and $ClCH_2COCl$; 2-(α-bromopropionamido)-5-chlorobenzophenone, m. 114–15°, from I and $MeCHBrCOBr$; 2-aminoacetamido-5-nitrobenzophenone (II), m. 186–7° ($CHCl_3$–Et_2O) (decompn.), from 2-bromoacetamido-5-nitrobenzophenone (III) and NH_3 in MeOH. II heated 5 min. at 190–5° gives 7-nitro-5-phenyl-3*H*-1,4-benzodiazepin-2(1*H*)-one (IV). 2-Amino-5-nitrobenzophenone and $BrCH_2COBr$ (V) give III, m. 155–6°.



(IV)

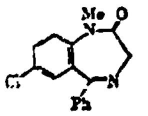
2-Amino-4-nitrobenzophenone and IV gives 2-bromoacetamido-4-nitrobenzophenone, m. 120–1°, which with NH_3–MeOH gives 8-nitro-5-phenyl-3*H*-1,4-benzodiazepin-2(1*H*)-one, m. 252° (decompn.) (EtOH). I and *p*-$MeC_6H_4SO_2Cl$ gives the Na salt (V) of 2-(*p*-toluenesulfonamido)-5-chlorobenzophenone, m. 293–9° ($HCONMe_2$–$CHCl_3$), which, refluxed 1.5 hrs. in MeCN with allyl bromide, gives 2-allylamino-5-chlorobenzophenone (VI), m. 76–7°; VI treated with IV gives 2-(α-bromo-*N*-allylacetamido)-5-chlorobenzophenone, m. 81–2° (C_8H_{14}); treated with NH_3–MeOH it gives 1-allyl-7-chloro-5-phenyl-3*H*-1,4-benzodiazepin-2(1*H*)-one, m. 105–6° (C_8H_{14}). 2-Methylamino-5-chlorobenzophenone and IV gives 2-(α-bromo-*N*-methylacetamido)-5-chlorobenzophenone, m. 95–6° (Et_2O–petroleum ether) which with NH_3–MeOH gives 7-chloro-1-methyl-5-phenyl-3*H*-1,4-benzodiazepin-2(1*H*)-one, m. 125–6° (Et_2O). V (61.2 g.), 30 ml. $PhCH_2Cl$, 0.5 g. NaI and 250 ml. MeCN refluxed 5 hrs. gives 2-(*N*-benzyl-*p*-toluenesulfonamido)-5-chlorobenzophenone, m. 116–18°, which treated at 145° with 70% H_2SO_4 gives 2-benzylamino-5-chlorobenzophenone, m. 86–7°; this treated with IV gives 2-(α-bromo-*N*-benzylacetamido)-5-chlorobenzophenone, m. 159–60°. 2-Aminoacetamido-2′,5-bis(trifluoromethyl)-benzophenone is heated 0.5 hr. at 210° to give 2′,5-bis(trifluoromethyl)-5-phenyl-3*H*-1,4-benzodiazepin-2(1*H*)-one, m. 226–7° (C_8H_6–C_8H_{14}). 2-Amino-6-chlorobenzophenone and IV gives 2-bromoacetamido-6-chlorobenzophenone, m. 97–8° (EtOAc–C_8H_{14}). 2-Bromoacetamido-3-chlorobenzophenone m. 129–30°. Condensation of aceto-*m*-anisidine with BzCl in CS_2 in the presence of $AlCl_3$ gives 2-acetamido-4-methoxybenzophenone, m. 118–19.5° (dil. EtOH), which, refluxed 3 hrs. with alc. HCl and then condensed with IV, gives 2-bromoacetamido-4-methoxybenzophenone, m. 105–7.5° (C_8H_6–C_8H_{14}). Bromination of 2-acetamido-4-methoxybenzophenone gives 2-acetamido-5-bromo-4-methoxybenzophenone, m. 144–6° (dil. EtOH), which when hydrolyzed with boiling alc. HCl gives 2-amino-5-bromo-4-methoxybenzophenone, m. 150–1.5° (C_8H_6–C_8H_{14}); it is condensed with IV to give 2-bromoacetamido-5-bromo-4-methoxybenzophenone, m. 144–5°. Addn. of a Grignard reagent from 10.3 g. *o*-bromoanisole and 1.3 g. Mg in 100 ml. Et_2O to 9.3 g. 6-chloro-2-methyl-3,1-4*H*-benzoxazin-4-one (VII) in 150 ml. ice-cold C_6H_6 and 50 ml. Et_2O gives 2-acetamido-5-chloro-2′-methoxybenzophenone, m. 124–6°, which sapond. and condensed with IV gives 2-bromoacetamido-5-chloro-2′-methoxybenzophenone, m. 129–30.5° (MeCN). Condensation of *m*-$MeOC_6H_4MgBr$ with VII gives 2-acetamido-5-chloro-3′-methoxybenzophenone, which sapond. and treated with IV gives 2-bromoacetamido-5-chloro-3′-methoxybenzophenone, 97–8.5° (C_8H_{14}). Sapon. of 2-acetamido-5-chloro-4′-methoxybenzophenone and condensation with IV give 2-bromoacetamido-5-chloro-4′-methoxybenzophenone, m. 116–18° (C_8H_6–C_8H_{14}). Condensation of 2-amino-3-nitrobenzophenone in $MeNO_2$ with IV gives 2-bromoacetamido-2-nitrobenzophenone, m. 120.5–1.5°. Treatment of 2-bromoacetamido-5-chloro-2′-fluorobenzophenone (VIII) with liquid NH_3 gives 2-aminoacetamido-5-chloro-2′-fluorobenzophenone, m. 115–15.5°, which, refluxed 17 hrs. in C_5H_5N, PhMe, or *p*-cymene gives up to 90% 7-chloro-5-(2-fluorophenyl)-3*H*-1,4-benzodiazin-2(1*H*)-one, m. 205–6° (MeOH–C_8H_{14}); it is also obtained when VIII is stirred overnight with alc. NH_3. Condensation of 175 g. *o*-FC_6H_4COCl and 64 g. *p*-$ClC_6H_4NH_2$ at 180° in the presence of $ZnCl_2$ gives 2-amino-5-chloro-2′-fluorobenzophenone, m. 94–5° (MeOH), which condensed with IV gives 2-bromoacetamido-5-chloro-2′-fluorobenzophenone (IX), m. 132.5–33°. IX and liquid NH_3 gives 2-aminoacetamido-5-bromo-2′-fluorobenzophenone, m. 110–11°. Condensation of *o*-FC_6H_4COCl with *p*-$BrC_6H_4NH_2$ in the presence of $ZnCl_2$ gives 2-amino-5-bromo-2′-fluorobenzophenone, m. 101–2°, which with IV gives 2-bromoacetamido-5-bromo-2′-fluorobenzophenone, m. 139–40°. 8-Trifluoromethylbenzophenone m. 184–6°. The following R-substituted-3*H*-1,4-benzodiazepin-2(1*H*)-one are prepd. (R and m.p. given): 1-methyl-7-chloro-5-(2-chlorophenyl), 135–8°; 7-chloro-5-(*p*-tolyl), 180–1°; 7,8-dimethyl-5-(2-chlorophenyl), 259–60°; 7-chloro-1-hydroxymethyl-5-phenyl, 201–2°; 7-chloro-1-ethyl-5-phenyl, 127–8°; 7-chloro-5-(2-methoxyphenyl)-1-methyl, 151–2°; 7-chloro-1-methyl-5-(2-fluorophenyl), oil.

F. E. Brauns

A4.74. 39663z Oxidation of 5-phenyl-1,4-benzodiazepines and 5-phenyl-1,4-benzodiazepin-2-ones. Rodney I. Fryer and Leo H. Sternbach (to Hoffmann-La Roche Inc.). U.S. 3,322,753 (Cl. 260-239.3), May 30, 1967, Appl. June 18, 1965; 5 pp. Continuation-in-part of U.S. 3,247,187 (see Neth. Appl. 6,407,-796, *CA* 63: 1808e). Oxidns. of various 5-phenyl-1,4-benzodiazepines are described. The products are known compds., useful as sedatives, tranquilizers, anticonvulsants, and muscle relaxants. E.g., 2.0 g. CrO_3 in 2 ml. H_2O was added to a soln. of 5.45 g. 7-chloro-1,3,4,5-tetrahydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (I) in 50 ml. AcOH. After 12 hrs. at room temp., the mixt. was dild. with ice water and make alk. with aq. NH_3 to ppt. 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one, m. 216-17° (Me_2CO). Similar oxidns. of the 5-(2-fluorophenyl), 5-(4-chlorophenyl) (m. 190-5°, prepd. by redn. of oxidn. product), 5-(3-nitrophenyl) (II) and 5-(4-nitrophenyl) (III) analogs of 5-phenyl-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one (IV) to dihydro analogs are described. II, m. 158-60°, and III, m. 222-8°, were prepd. by nitration of IV and sepd. by cryst. 7-Fluoro-1,3,4,5-tetrahydro-5-(4-chlorophenyl)-2*H*-1,4-benzodiazepin-2-one (V) was oxidized similarly to 7-fluoro-1,3-dihydro-5-(4-chlorophenyl)-2*H*-1,4-benzodiazepin-2-one. V, m. 178-9°, was prepd. from *p*-fluoroaniline and *p*-chlorobenzoyl chloride via 2-amino-4'-chloro-5-fluorobenzophenone, m. 97-8°, and 2-bromo-2'-(4-chlorobenzoyl)-4'-fluoroacetanilide, m. 144-5°. 2,3-Dihydro-7-nitro-5-phenyl-1*H*-1,4-benzodiazepine (VI) gave 1,3-dihydro-7-nitro-5-phenyl-2*H*-1,4-benzodiazepin-2-one, m. 224-6°; 7-chloro-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepine gave 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one, m. 216-17°; 2,3-dihydro-7-trifluoromethyl-5-phenyl-1*H*-1,4-benzodiazepine gave 1,3-dihydro-7-trifluoromethyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one, m. 233-5°; 7-chloro-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine gave 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one, m. 130-1°; and 7-chloro-1-methyl-5-phenyl-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepine gave 7-chloro-1-methyl-5-phenyl-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one, m. 144-5°. Although CrO_3 in AcOH is the preferred reagent, chromate in Me_2CO, CrO_3 in H_2SO_4 + AcOH, and $KMnO_4$ in Me_2CO were also used with VI, and SeO_2 and Ag_2O were also used with I. Frank R. Mayo

A4.75. 2928m 5-Aryl-3H-1,4-benzodiazepin-2(1H)-ones. Earl Reeder and Leo H. Sternbach (to Hoffmann-La Roche, Inc.). U.S. 3,311,612 (Cl. 260-239.3), March 28, 1967; Swiss Appl. Dec. 2, 1960; 7 pp. Continuation-in part of U.S. 3,051,701. Division of U.S. 3,136,815 (*CA* 61: 9515f); U.S. 3,270,053 (*CA* 66: 28808f); U.S. 3,239,564 (*CA* 64: 19498a). The disclosure is the same but the claims are different. CRPN

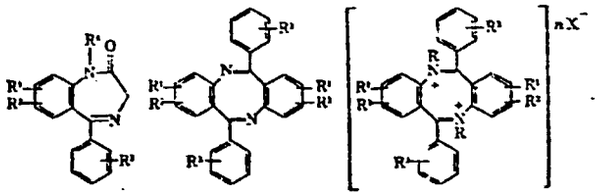
A4.76. 82225x 7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one. Rexolin Chemicals Aktiebolag. Neth. Appl. 6,613,087 (Cl. C 07d), March 20, 1967; Dan. Appl. Sept. 17, 1965; 7 pp. The title compd. (I) is prepd. from 2-(2-azido-*N*-methylacetamido)-5-chlorobenzophenone (II) by reductive ring closure. Thus, to a soln. of 12.28 g. 5-chloro-2-



(I)

methylaminobenzophenone in 25 ml. $CHCl_3$ was added at room temp. with stirring 7.17 g. azidoacetyl chloride (exothermic reaction) and the mixt. was kept 1 hr. at 40-50° to yield [illegible]% II, m. 112-13°. To a soln. of 6.44 g. 2-(2-chloro-*N*-methyl)acetamido)-5-chlorobenzophenone in 25 ml. $HCONMe_2$ was added with stirring 1.43 g. NaN_3 and the mixt. was kept [illegible] min. at 60° to yield 96% II. To a mixt. of 32.83 g. II, [illegible] g. 5% Pd/C, and 300 ml. EtOH was added with stirring at room temp. a soln. of 3.13 g. $N_2H_4.H_2O$ in 100 ml. EtOH, and the mixt. was kept with stirring 1 hr. at 40° to yield 80% pure I, m. 131.4-2.6° (details of purification are given). Similarly, I was prepd. from II with Pd/C and H (74% yield) or Pt/C and H ([illegible] yield).
[illegible]els

A4.77. 55531s 2-Oxobenzodiazepines. Joseph Hellerbach, Werner Metlesics, and Leo H. Sternbach (to Hoffmann-La Roche, Inc.). U.S. 3,297,685 (Cl. 260–239.3), Jan. 10, 1967, Appl. Aug. 9, 1965; 3 pp. The title compds. of structure I are prepd. by treat-



(I) (II) (IV, $n-1$) (V, $n-2$)

ing a substituted 6,12-diphenyldibenzo[*b*,*f*][1,5]diazocine (II) with a quaternizing agent (III) to give the mono- (IV) or diquaternary imonium salt (V) and splitting IV or V with an amino acid ester such as $H_2NCH_2CO_2Et$ (VI). Hydrolysis of V gives 2-$HRNR^1R^2C_6H_2COC_6H_4R^3$. II are prepd. by autocondensation of 2-$H_2NR^1R^2C_6H_2COC_6HR^3$ in the presence of a Friedel-Crafts catalyst. Thus, 23.2 g. 5,2-Cl(H_2N)C_6H_2Bz is added with stirring to a cooled suspension of 0.1 mole $AlCl_3$ in 300 ml. PhCl, the mixt. refluxed 3 hrs., cooled, poured onto ice, made basic with NaOH, and extd. with CH_2Cl_2, and the washed and dried ext. evapd. to give II ($R^1 = R^3 = H$, $R^2 = 2,8\text{-}Cl_2$) (VII), yellow prisms, m. 215–17° (CH_2Cl_2–EtOH). VII (86 g.) and 50 ml. Me_2SO_4 in 450 ml. C_6H_6 is refluxed 16 hrs. and the soln. cooled to give 2,8-dichloro-5-methyl-6,12-diphenyldibenzo[*b*,*f*]-[1.5]diazocine-Me_2SO_4 (VIII), tan, m. ~150–205° (decompn.). VIII (4.4 g.) and 13.3 g. VI.HCl in 30 ml. C_5H_5N is refluxed 40 hrs., the soln. concd. in vacuo, and the residue dissolved in CH_2Cl_2. The soln. is washed with aq. NaOH and the CH_2Cl_2 distd. on a steam bath to give 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (IX), m. 212–15° (MeOH). VII (43 g.) and 100 ml. Me_2SO_4 on 20 ml. C_6H_6 is refluxed 10 min. and the mixt. kept overnight to give 2,8-dichloro-5,11-dimethyl-6,12-diphenyldibenzo[*b*,*f*][1,5]diazocine-2$MeSO_4$ (X). X (6.8 g.) and 13.9 g. VI.HCl in 50 ml. MeOH is refluxed 6 hrs., the MeOH distd. in vacuo, the residue dissolved in 50 ml. C_5H_5N and refluxed 16 hrs., the C_5H_5N distd. in vacuo, the residue dissolved in Et_2O passed through 50 g. Al_2O_3 (basic, grade 1, Woelm) and the column washed with Et_2O and eluted with EtOAc to give 7-chloro-1-methyl-5-phenyl-3*H*-1,4-benzodiazepin-2(1*H*)-one (I, $R^1 = R^2 = H$, $R^3 = 7\text{-}Cl$, $R^4 = Me$). X (2.5 g.) is heated 1 hr. in 20 ml. MeOH and 20 ml. 20% HCl and the mixt. concd. in vacuo, poured into ice-H_2O, and made alk. with NH_4OH to give 2-methylamino-5-chlorobenzophenone, yellow, m. 95–7°. From the II listed above the corresponding IV, V, and 1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-ones are prepd. but no phys. data are given. I are pharmaceutically useful.

F. E. Brauns

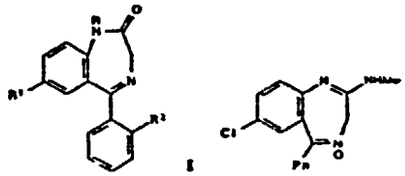
A4.73. 28808f 2-(α-Halo-lower alkanoylamino)benzophenones. Earl Reeder and Leo H. Sternbach (to Hoffmann-La Roche Inc.). U.S. 3,270,053 (Cl. 260–562), Aug. 30, 1966; Swiss Appl. Dec. 2, 1960; 26 pp. Continuation-in-part of U.S. 3,051,701 (CA 57, 16641*c*). The disclosures are the same as U.S. 3,133,815 (CA 61, 9515*f*), but the claims are different. Compds. described here but not previously abstracted are: *m*-[5,2-Cl(H_2NCH_2CO)-C_6H_3F, m. 90–1°; 5,2-Me(HO_2C)C_6H_3N:CHNMe[illegible], m. 196–8° (MeCN–Et_2O); and 7-chloro-3-isopropyl-5-[illegible]-1,4 benzodiazapin-2(1*H*)-one, m. 226–7° (Et_2O–petroleum ether).

D. E. Nar[illegible], Jr.

DIAZEPAM

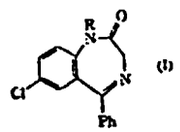
Purification

A4.79. 101: 191976j **Purification of 1,4-benzodiazepines.** Lewandowska, Maria Bozena; Morawski, Bogdan; Zarecka, Barbara; Parszewska, Halina; Tomaszewska, Irena (Tarchominskie Zaklady Farmaceutyczne "Polfa") Pol. PL 122,616 (Cl. C07D243/24), 05 Apr 1934, Appl. 221,252, 07 Jan 1980; 4 pp. Title compds. (I) (R = H, alkyl; R^1 = Cl, NO_2; R^2 = H, Cl) or II were purified by complexing them with $ZnCl_2$ in an org. solvent, then decompg. the complex with H_2O.



I II

A4.80. 67002g **Purification of 1-alkyl-2-oxo-5-phenyl-7-chloro-2,3-dihydro-1H-1,4-benzodiazepines.** Sumitomo Chemical Co., Ltd. Fr. Demande 2,002,315 (Cl. C 07c), 17 Oct 1969, Japan. Appl. 21 Feb 1968; 8 pp. The title compds. (I) are purified by soln. in 1–6*M* HCl, then partially neutralizing the soln. to ppt. impurities. 7-Cl (R = Me) (II), m. 130–2°, (5 g) prepd. by oxidn. of the sulfate of 1-methyl-2-(aminomethyl)-3-phenyl-5-chloroindole with CrO_3, was dissolved at room temp. in 50 ml 2*M*



(I)

HCl, 33.5 ml 2*M* NaOH added at 20°, and the mixt. worked up to yield 4.30 g II, m. 132–4° (iso-PrOH). Similarly prepd. was I (R = cyclopropylmethyl), m. 144.5–5.0°. Max Hubacher

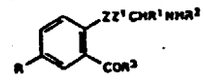
DIAZEPAM

Miscellaneous

A4.81. 94016t **Stable and palatable diazepam formulations.** Margaret R. Zentner (to Hoffman-La Roche Inc.). U.S. 3,337,422 (Cl. 167–55), Aug. 22, 1967, Appl. Sept. 3, 1963; 4 pp. Continuation-in-part of 3,136,686. The reaction product of diazepam [7-chloro-1-methyl-5-phenyl-3*H*-1,4-benzodiazepin-2(1*H*)-one] (I) and a *Mg* Al silicate is useful in the prepn. of stable and palatable pharmaceutical suspensions. For example, 1.0 g. I was dissolved at about 60° in a mixt. of 30 ml. iso-PrOH and 20 ml. H_2O, and this soln. added to neutral 60 g. Veegum and mixed to form a paste. The paste was dried and powd.

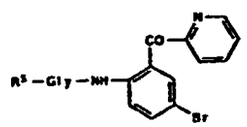
Robert F. Drenga

A4.82. 90: 138205k **Substituted-phenyl ketones containing a protected dipeptide residue.** Hassall, Cedric Herbert; Johnson, William Henry; Kroehn, Antonin; Smithen, Carey Ernest; Thomas, William Anthony (Roche Products Ltd.) Brit. 1,517,165 (Cl. C07D233/64), 12 Jul 1978, 20 Aug 1974; 16 pp. Division of 1,517,164. The title compds. I [R = halo, NO_2, CF_3;



I

II



III

R^1 = H, lower alkyl; R^2 = acyl group derived from a naturally occurring amino acid in which all NH_2 groups are protected; R^3 = Ph, halophenyl, 2-pyridyl; Z = N which may be substituted by Me, cyclopropylmethyl, di(C_{1-4} alkyl)aminoethyl, $MeOCH_2$, $HO(CH_2)_2$; Z' = CO; ZZ' = group II [R^4 = H, lower alkyl, $HOCH_2$; X = N, CR^5 (R^5 = H, lower alkyl, $HOCH_2$)]] were prepd. Thus, 7-bromo-1,3-dihydro-5-(2-pyridyl)-2*H*-1,4-benzodiazepin-2-one was cleaved by 2N HCl overnight at room temp. to give 99% glycinamide III (R^5 = H), which was coupled with Z-Phe-OSu (Z = $PhCH_2O_2C$, Su = succinimido) to give 64% III (R^5 = Z-Phe).

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A5

ETHAMBUTOL.HCL

PATENTS

1967-1985

APPENDIX P5

ANALYSIS OF THE ABSTRACTS OF PATENTS

In none of the patents for preparation the standard process is applied and none seems to be equally simple.

A process which however only in one case delivers the required optically active compound is claimed in 4 patents by PLIVA Tvornica Farmaceutskih i Kemijskih Proizvoda. The process results in an excellent yield and consists in reduction of 4,4'-diethyl-2,2'-bisoxazolidin with lithiumaluminumhydride (A5.2.), with lithiumaluminumhydride or sodiumborohydride (A5.3.) or catalytic reduction (A5.4. and A5.7.).

ABSTRACTS OF PATENTS

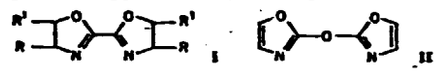
A5

ETHAMBUTOL.HCL

Preparation

A5.1. 85: 20601e (+)l-1,2-Bis-(2'-imino-1'-butanol)ethane. Kajfez, Franjo; Vitomir (CRC Compagnia di Ricerche Chimiche) Swiss 574,389 (Cl. C07C91/02), 15 Apr 1976, Appl. 73/3,026, 01 Mar 1973; 3 pp. The title compd., $HOCH_2CHEtNHCH_2C=NHCHEtCH_2OH$ (I), was prepd. by redn. of $RO_2CCHEtNHCH_2CH_2NHCHEtCO_2R$ (R = H, Et) with $NaAlEt_2H_2$ in MePh; the dihydrochloride of I was pptd. from abs. EtOH with HCl(g).

A5.2. 13101f N,N'-Bis-(α-hydroxyalkyl)ethylenediamines and homologs. PLIVA Tvornica Farmaceutskih i Kemijskih Proizvoda Fr. Demande 2,187,761 (Cl. C 07*cd*, A 61*k*), 22 Feb 1974, Yugoslavia Appl. P-1.544/72, 09 Jun 1972; 5 pp. The

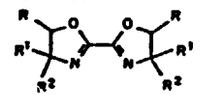


I II

$LiAlH_4$ redn. of bis(oxazolines) (I) and bis(oxazoles) (II) gave $R^1CH(OH)CHRNH(CH_2)_2NHCHRCH(OH)R^1$ (R and R^1 given): Et, H; H, Me; and $HO(CH_2)_2NHCH_2QCH_2NH(CH_2)_2OH$ [Q = *p*-phenylene, $(CH_2)_4$], useful as tuberculostatics.

A5.3. 13102g (+)-N,N'-Bis[1-(hydroxymethyl)propyl]ethylenediamine. PLIVA Tvornica Farmaceutskih i Kemijskih Proizvoda Fr. Demande 2,187,762 (Cl. C 07*c*, A 61*k*), 22 Feb 1974, Yugoslavia Appl. P 1545/72, 09 Jun 1972; 4 pp. 4,4'-Diethyl-2,2'-bisoxazolidine was reduced by $LiAlH_4$ or NaH–B to give (+)-$EtCH(CH_2OH)NHCH_2CH_2NHCH(CH_2OH)Et$ useful in the treatment of tuberculosis.

A5.4. 145968n Tuberculostatic N,N'-bis(hydroxyalkyl)ethylenediamines. PLIVA Tvornica Farmaceutskih i Kemijskih Proizvoda Brit. 1,327,315 (Cl. C 07*c*), 22 Aug 1973, Yugoslavia Appl. 17 Aug 1970; 3 pp. Six title diamines, [$RCH(OH)CR^1R^2NHCH_2$]$_2$ (I, R, R^1 = H, Me, R^2 = H, Me, Et), were prepd. by hydrogenation of bis(oxazolines) (II) over a Pt-Rh catalyst at 20–80° and 1–85 atm. Thus, 1.4 g 2,2'-bis(oxazoline) in the presence of 0.2 g Pt-Rh in EtOH at 20° and 50 atm for 4 hr gave 1.35 g (91%) diamine I (R = R^1 = R^2 = H).

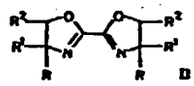


II

A5.5. 78371x Ethambutol. Bernardi, Luigi; Foglio, Maurizio; Temperilli, Aldemio (Societa Farmaceutici Italia). Ger. Offen. 2,263,715 (Cl. C 07*cd*), 05 Jul 1973, Ital. Appl. 33,117 A/71, 30 Dec 1971; 19 pp. (+)-$(HOCH_2CHEtNHCH_2)_2$ (I), useful as tuberculostatic, was prepd. from 1,2-epoxy-3-butene (II). Thus, II was treated with $COCl_2$ at −30° to give $CH_2:CHCHClCH_2O_2CCl$, which on reaction with $PhCH_2NH_2$ gave $CH_2:CHCHClCH_2O_2CNHCH_2Ph$ (III). III was treated with KOH or NaOH in EtOH to give $CH_2:CHCH(CH_2OH)NHCH_2Ph$ (IV), optionally via 3-benzyl-4-vinyloxazolidin-2-one. Resolution of IV with (+)-dibenzoyltartaric acid or (−)-mandelic acid gave (+)-IV, which reacted with $BrCH_2CH_2Br$ at 120–35° and with HCl to give (+)-$[CH_2:CHCH(CH_2OH)N(CH_2Ph)CH_2]_2$.HCl (V). V was hydrogenated in 90% MeOH over Pd/C to give I.

A5.6. 71409m (+)-2,2'-(Ethylenediimino)di-1-butanol. Yamada, Shunichi; Otsuka, Katsuyuki; Ishiyama, Nobuo (Kaken Chemical Co., Ltd.) Japan. Kokai 72 29,303 (Cl. 16 B 45), 05 Nov 1972, Appl. 71 66,470, 16 Feb 1971; 3 pp. Condensation of L-methioninol (13.4 g) with $ClCH_2CH_2Cl$ (4:1 moles) at 110–20° 2 hr gave 7.05 g (+)-2,2'-(ethylenediimino)bis[4-(methylthio)-1-butanol]-2HCl (I), m. 134–5°, $[\alpha]_D^{25}$ = +36.25° (c = 2, 0.5% HCl). A soln. of 5 g I in 75% MeOH was refluxed with 50 g Raney Ni 5 hr to give 2.06 g HCl salt of the title compd., m. 199–200°, useful as a tuberculosis remedy. Y. Tsuji

A5.7. 100759n N,N'-Bis(2-hydroxyalkyl)ethylenediamines. Butula, Ivan; Karlovic, Gordana (Pliva Tvornica Farmaceutskih i Kemijskih Proizvoda) Ger. Offen. 2,140,681 (Cl. C 07c, A 61k), 25 May 1972, Yugoslavia Appl. P 2077/70, 17 Aug 1970; 9 pp. Three $HOCHR^2CR^1RNHCH_2CH_2NHCRR^1CHR^2OH$ (I,



R — R² = H or Me), and *d*-, *meso*-, and *dl*-I (R = Et, R¹ = R² = H), useful as tuberculostatic agents, were prepd. by hydrogenolysis of the corresponding bioxazolines (II) over Pt-Rh catalysts in EtOH or MeOH.

A5.8. 19171t Ethambutol. Societa Farmaceutici Italia Brit. 1,271,470 (Cl. C 07c), 19 Apr 1972, Ital. Appl. 25,737, 13 Dec 1969; 5 pp. Ethambutol, (+)-$HOCH_2CHEtNHCH_2CH_2NHCHEtCH_2OH$ (I), having antitubercular activity, was prepd. Thus, a mixt. of $CH_2:CEtCO_2Et$, EtOH, and liq. NH_3 was heated 40 hr at 130°/80 atm, and the product resolved via (−)-dibenzoyltartaric acid to give (+)-β-aminovaleramide (II). $(CHO)_2$ and II in EtOH was heated 1 hr at 40°. Pd-C added, and the whole kept 16 hr at 10–20 atm H to give (+)-3,3'-(ethylenediimino-*N*,*N*'-diacetyl)bis[valeramide] (III). Hofmann degradation and acylation of III gave (+)-2,2'-(ethylenediimino)bis-[*N*,*N*,*N*',*N*'-tetrabenzoyl-1-butylamine] (IV). Nitrosation and hydrolysis of IV gave I.

A5.9. 63110e Antitubercular ethambutol preparation. Societa Farmaceutici Italia. Brit. 1,234,349 (Cl. C 07c), 03 Jun 1971; Ital. Appl. 21 Mar 1969; 2 pp. (+)-2,2'-(Ethylenediimino)di-1-butanol was prepd. from (+)-2,2,4-triethyloxazolidine and glyoxal hydrate by catalytic hydrogenation (Pd/C). A. Roders

A5.10. 19686y Ethambutol. Bernardi, Luigi; Goffredo, Onofrio (Societa Farmaceutici Italia) Fr. 2,030,903 (Cl. C 07c), 13 Nov 1970, Ital. Appl. 21 Mar 1969; 5 pp. (+)-2,2,4-Triethyloxazolidine (1 mole) and 1 mole glyoxal (39% in H_2O) with a few drops AcOH was hydrogenated over 10% Pd(C) at atm. pressure and at room temp. to give the title compd. F. J. Sprules

A5.11. 24897f (+)-2,2'-(Ethylenediimino)-di-1-butanol (ethambutol). Societa Farmaceutici Italia Brit. 1,184,854 (Cl. C 07c), 15 Apr 1970, Ital. Appl. 30 Oct 1967; 3 pp. The title compd. (Ethambutol) is prepd. (+)-EtCH(NH[illegible])CH[illegible]OH was condensed with Et_2CO in benzene to give (+)-2,2,4-triethyloxazolidine which was refluxed with $BrCH_2CH_2Br$ in benzene, followed by a mild hydrolysis to give the product desired. Similar results were obtained by using (+)-2-methyl-2-propyl-4-ethyloxazolidine, (+)-2,2-dimethyl-4-ethoxyoxazolidine, or 2,2-dipropyl-4-ethyloxazolidine. DSIR

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A6

INDOMETHACIN

PATENTS

1967-1985

APPENDIX P6

ANALYSIS OF THE ABSTRACTS OF PATENTS

72 Patents for preparation of indometacin were analyzed, 52 of which are held by MERCK & Co. and 9 by Sumitomo.

The standard process involving reaction of the N-p-chlorobenzoyl substituted 4-methoxyphenylhydrazine is described in patents A6.3., A6.4., A6.5., A6.8. and A6.72. In patent A6.55. high purity indometacin is synthesized from sodium-(p-methoxyphenyl)hydrazinesulfonate. The same starting material is described in A6.21. in which upon reaction with levulinic acid an intermediate is isolated which gives indometacin upon reaction with phosphoric acid.

A modification of this standard process using acetosuccinic acid instead of levulinic acid is described in patent A6.13.

The patents A6.2., A6.9 and A6.10. refer to the synthesis of the formylated p-methoxyphenylhydrazine, which in the standard process is benzoylated in the next step. Also patents A6.17. and A6.44. refer to this synthetic alternative. In A6.6. the introduction of the acetyl and propionyl rests instead of the formyl group is described.

Patent A6.87. claims the synthesis of N-(p-chlorobenzoyl)-N-(p-methoxyphenyl)hydrazine in 69% yield as intermediate for indometacin synthesis.

Another standard process involves Fischer-reaction with tert.butyl levulinate. A modification of this process is claimed in A6.76. with condensation and Fischer reaction carried out in one step.

An interesting alternative to the third standard process in which acylation is performed only after indole ring formation is described in A6.51.. In this process 2-oxopropylmalonicester is used instead of levulinic acid.

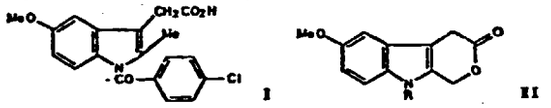
ABSTRACTS OF PATENTS

A6

INDOMETHACIN

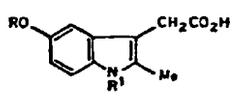
Preparation

A6.1. 85: 177249u 1-(p-Chlorobenzoyl)-5-methoxy-2-methyl= indole-3-acetic acid. Frantsits, Werner J. Ger. Offen. 2,528,590 (Cl. C07D209/26), 01 Jul 1976, Austrian Appl. 74/10,094, 18 Dec 1974; 10 pp. Indoleacetic acid I was prepd.



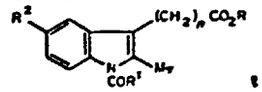
by refluxing 4-MeOC$_6$H$_4$NHNHSO$_3$Na and 4-oxo-Δ-valerolactone in THF with HCl several hr, stirring lactone II (R = H) 1 hr with NaH in DMF, then adding 4-ClC$_6$H$_4$COCl dropwise at 0°, and cleaving the lactone II (R = 4-ClC$_6$H$_4$CO) with H over Pd/BaSO$_4$.

A6.2. 84: 59187d Indolyl acetic acids. Pakula, Ryszard; Wojciechowski, Jan; Poslinska, Halina; Pichnej, Lidia; Ptaszynski, Leszek; Przepalkowski, Adam; Logwinieko, Roman (Lodzkie Zaklady Farmaceutyczne "Polfa") U.S. 3,919,247 (Cl. 260-295B; C07D), 11 Nov 1975, Appl. 764,923, 18 Sep 1968; 5 pp.



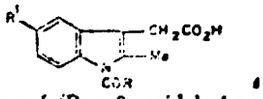
The title compds. I (R = Me, PhCH$_2$; R^1 = Bz, 4-ClC$_6$H$_4$CO, isonicotinoyl, nicotinoyl) were prepd. by acylation of 4-ROC$_6$H$_4$NHNHCHO with R^{1}Cl or R$^1_2$O to give 4-ROC$_6$H$_4$NR^{1}NHCHO, which cyclized with levulinic acid in the presence of HCl to give I.

A6.3. 125273r 1-Benzoyl-3-indoleacetates. Yamamoto, Hisao; Nakao, Masaru (Sumitomo Chemical Co., Ltd.) U.S. 3,770,752 (Cl. 260-295.5H; C 07cd), 06 Nov 1973, Japan. Appl. 35 24,928, 26 Apr 1965; 12 pp. Division of U.S. 3,629,284 (*CA* 76: 113060g). The indoles I (n = 1,3; R = H, Et; R^1 = Ph, p-ClC$_6$H$_4$, p-F$_3$CC$_6$H$_4$,



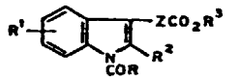
3-pyridyl, 4-pyridyl, etc; R^2 = H, MeO) were prepd. from acylhydrazines. Thus, p-MeOC$_6$H$_4$NHN:CMe$_2$ was treated with p-ClC$_6$H$_4$COCl and the product treated with HCl to give p-MeOC$_6$H$_4$N(NH$_2$)COC$_6$H$_4$Cl-p.HCl, which was cyclized with MeCO(CH$_2$)$_4$CO$_2$H to give I (n = 3, R = H, R^1 = p-ClC$_6$H$_4$, R^2 = MeO). The antiinflammatory ED$_{50}$ of I (n = 1, R = H, R^1 = 3-pyridyl, R^2 = MeO) is 105 mg/kg. I are antipyretic and analgesic.

A6.4. 125272q 3-Indolylaliphatic acid compounds. Yamamoto, Hisao; Nakao, Masaru (Sumitomo Chemical Co., Ltd.) U.S. 3,822,275 (Cl. 260-295B; C 07d), 02 Jul 1974, Japan. Appl. 65 24,963, 26 Apr 1965; 13 pp. Division of U.S. 3,629,284 (*CA* 76: 113060g).



Indomethacin analogs I (R = 3-pyridyl, 4-pyridyl, 2-thienyl, 2-furyl, 5-chloro-2-thienyl, Ph, 2-naphthyl; p-R^{2}C$_6$H$_4$; R^2 = Cl, Me, OMe, CF$_3$, SMe, Br, F; R^1 = H, OMe, Me, SMe, Cl, F, NO$_2$) some of their esters and some related indolealkanoic acids were prepd. Thus, I (R = 3-pyridyl, R^2 = OMe) (II) was obtained by acylating p-MeOC$_6$H$_4$NHN:CMe$_2$ with nicotinoyl chloride and treating with HCl(g) to give 3-pyridinecarbonyl-N-(p-methoxyphenyl)hydrazine, which (4.9 g) was condensed with 17.6 g levulinic acid to give 5.8 g II. On the carrageenin-induced edema test in rats II had an ED$_{50}$ of 80 mg/kg and a therapeutic ratio of >18.8.

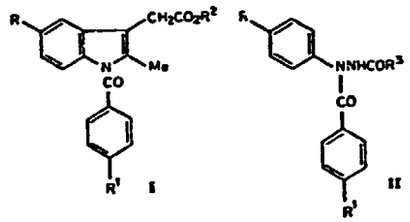
A6.5. 49563x N'-Heteroacylated phenylhydrazines. Yamamoto, Hisao; Nakao, Masaru (Sumitomo Chemical Co., Ltd.) U.S. 3,810,995 (Cl. 260–295H; C 07d), 14 May 1974, Appl. 541,967, 12 Apr 1966; 12 pp. Division of U.S. 3,629,284 (*CA* 76: 113060g). RCON(NH$_2$)C$_6$H$_3$R^1 (I, R = *p*-ClC$_6$H$_4$, *p*-MeC$_6$H$_4$, Ph, *p*-MeOC$_6$H$_4$, *p*-F$_3$CC$_6$H$_4$, *p*-BrC$_6$H$_4$, *p*-FC$_6$H$_4$, 3-pyridyl, 4-pyridyl, 2-thienyl, 5-chloro-2-thienyl, 2-furyl, *p*-MeSC$_6$H$_4$, 2-naphthyl; R^1 = H, *p*-Cl, *p*-Me, *p*-MeO, *p*-F, *m*-Me, *p*-MeS, *p*-NO$_2$, *p*-EtO) (25 compds.) were prepd. by acylating MeCH:NNHC$_6$H$_3$R^1 and treating the MeCH:NN(COR)C$_6$H$_3$R^1 with



II

HCl(g). I were cyclized with R^{2}COZCO$_2$R^3 (R^2 = H, Me; Z = CH$_2$, CHMe, (CH$_2$)$_2$, (CH$_2$)$_3$; R^3 = H, Me, Et, CMe$_3$, CH$_2$Ph) to give the indoles II (42 compds.). II (R = 3-pyridyl, 4-pyridyl, R^1 = 5-MeO, R^2 = Me, R^3 = H, Z = CH$_2$) had oral antiinflammatory ED$_{50}$ in the rat paw edema test of 80 and 105 mg/kg, resp., and therapeutic ratios >13.8 and >14.3, resp.

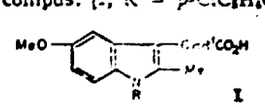
A6.6. 43269x 3-Indolylacetic acid derivatives. Kosa, Ildiko; Kovacs, Mrs. Gabor (Chinoin Gyogyszer es Vegyeszeti Termekek Gyara Rt.) Hung. Teljes 4889 (Cl. C 07d), 28 Aug 1972, Appl. CI-877, 03 Apr 1969; 17 pp. I (R = H, Me, Me$_2$N; R^1 = Cl,



I II

Me, MeO; R^2 = H, *tert*-Bu) were prepd. by acylation of *p*-RC$_6$H$_4$NHNHCOR^3 (R^3 = Ac, EtCO) with R^{1}C$_6$H$_4$COCl or the corresponding anhydride and treatment of the resultant II with levulinic acid (III) or *tert*-Bu levulinate. *p*-MeOC$_6$H$_4$NHNHAc was refluxed 6 hr with *p*-ClC$_6$H$_4$COCl and α-picoline–CHCl$_3$ to give 84.2% II (R = MeO, R^1 = Cl, R^2 = Me), which was suspended in III, treated with H$_2$SO$_4$ and heated ~4 hr to give 81.8% I (R = MeO, R^1 = Cl, R^2 = H). T. Mohacsi

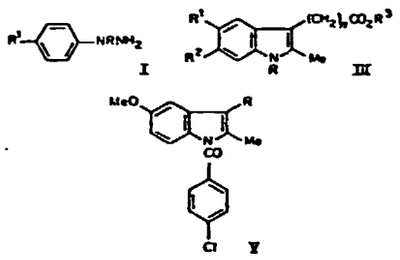
A6.7. 43229y 2-Methyl-5-methoxy-1-(*p*-chlorobenzoyl)-3-indolylacetic acids. Finotto, Martino Ger. Offen. 2,062,265 (Cl. C 07d), 18 May 1972, Ital. Appl. 31,817A/70, 16 Nov 1970; 14 pp. The title compds. [I, R = *p*-ClC$_6$H$_4$CO, R^1 = H (II),



I

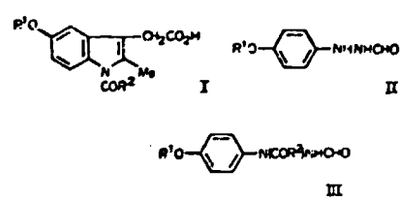
Me], analgesics and antiinflammatory agents, were prepd. from I (R = H). Thus, I (R = R^1 = H) was treated successively with Et$_3$N, ClCO$_2$Et, and NaH in C$_6$H$_6$ at 0–5°, and with *p*-ClC$_6$H$_4$COCl at 0–150° for 1 hr to give, after treatment with HCl, 86% II.

A6.8. 113060g Antiinflammatory 1-acylindole-3-aliphatic acid derivatives. Yamamoto, Hisao; Nakao, Masaru (Sumitomo Chemical Co., Ltd.) U.S. 3,629,284 (Cl. 260–326.13; C 07d), 21 Dec 1971, Japan. Appl. 65 23,078, 19 Apr 1965; 15 pp. The



hydrazine (I, R = nicotinoyl, R^1 = MeO) (II) was treated with $Ac(CH_2)_nCO_2H$ to give the indoleacetic acid (III, n = 1, R = nicotinoyl, R^1 = MeO, R^2 = R^3 = H) (IV). About 96 similar III (R = nicotinoyl, 2-thenoyl, 2-furoyl, isonicotinoyl, *p*-ClC_6H_4CO, *p*-$MeOC_6H_4CO$, Bz, *p*-MeC_6H_4CO, *p*-$MeSC_6H_4CO$, β-naphthoyl, *p*-BrC_6H_4CO, *p*-FC_6H_4CO; R^1 = H, MeO, Me, Cl, F, EtO; R^2 = H, Me; R^3 = H, *tert*-Bu, $PhCH_2$, Me, Et; n = 1, 2, 3) were prepd. V (R = $CH(CO_2Et)_2$, CH_2CONH_2) were similarly prepd. II was prepd. by treatment of *p*-$MeOC_6H_4NHN{:}CHMe$ with nicotinoyl chloride and treatment of the product with HCl. Several similar I (R^1 = Me, MeO, Cl, R = nicotinoyl, 2-thenoyl, 2-furoyl, *p*-MeC_6H_4CO, *p*-ClC_6H_4CO) were prepd. The ED_{50} of IV was 80 mg/kg for carrageenan-induced edema in rat paws. The LD_{50}/ED_{50} was >18.8 for IV (indomethacin was <6.5).

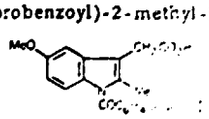
A6.9. 113058n N-Aroyl-2-methyl-5-alkoxy(or 5-aralkoxy)indole-3-acetic acids. Pakula, Ryszard; Wojciechowski, Jan; Poslinska, Halina; Pichnej, Lidia; Ptaszynski, Leszek; Przepalkowski, Adam; Logwinienko, Roman (Lodzkie Zaklady Farmaceutyzne "Polfa") Pol. 62,464 (Cl. C 07d), 30 Apr 1971, Appl. 27 Dec 1967; 4 pp. The title compds. (I, R^1 =



lower alkyl or benzyl, R^2 = Ph or halophenyl) are obtained from 1-(*p*-alkoxyphenyl)-2-formylhydrazines (II) by acylation with R^2COCl or $(R^2CO)_2O$ and condensation and cyclization of the product (III) with levulinic acid and HCl, H_2SO_4, or H_3PO_4, at <80°.

Wanda Pasiuk

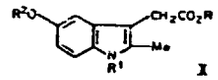
A6.10. 83694w 1-(*p*-Chlorobenzoyl)-2-methyl-5-methoxyindole-3-



acetic acid. Glassebaum, Heinz; Dierbach, Kurt; Hilger, Herbert (Ger. (East)) 77,974 (Cl. C 07d), 05 Dec 1970, Appl. 27 Mar 1969; 3 pp. *p*-$MeOC_6H_4NHNH_2$ and, e.g., 50% HCO_2H gave *p*-$MeOC_6H_4NHNHCHO$, which with *p*-ClC_6H_4COCl in C_5H_5N C_6H_6 gave *p*-$MeOC_6H_4N(NHCHO)COC_6H_4Cl$-*p*. This, levulinic acid, and HOAc-HCl heated 2 hr at 80° with frequent shaking, gave the title compd. (I).

A6.11.

5695p Cyclization of 3-(hydroxyphenyl)-4-aminovalerates to indole-3-acetates. Sletzinger, Meyer; Gal, George (Merck and Co., Inc.) U.S. 3,551,476 (Cl. 260–471; C 07c), 29 Dec 1970, Appl. 11 Apr 1968; 4 pp. The title valerates were cy-

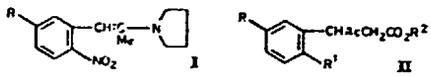


I

clized with $K_3Fe(CN)_6$ or $ON(SO_3M)_2$ (M = Na or K) to give 5-hydroxyindole-3-acetates. Thus, 2-$HOC_6H_4CH(CHMeNH_2)$-CH_2CO_2Me (sic) reacted with $ON(SO_3K)_2$ in aq. HOAc to give I (R = Me, R^1 = R^2 = H), which with $Me_2NCH(OMe)_2$ gave I (R = R^2 = Me, R^1 = H) (II). II in DMF was treated with NaH and *p*-ClC_6H_4COCl to give I (R = R^2 = Me, R^1 = *p*-Cl-C_6H_4CO), which with LiI in 2,6-lutidine gave I (R = H, R^1 = *p*-ClC_6H_4CO, R^2 = Me) (indomethacin). Similarly prepd. were I (R = *tert*-Bu or $PhCH_2$, R^1 = *p*-ClC_6H_4CO, R^2 = Me). Indomethacin esters were antiinflammatory. C. R. Addinall

A6.12.

141284k 3-(o-Aroylaminophenyl)levulinic acids. Chemerda, John M.; Sletzinger, Meyer (Merck and Co., Inc.) U.S. 3,542,862 (Cl. 260-519; C 07c), 24 Nov 1970, Appl. 19 Feb 1968; 4 pp.

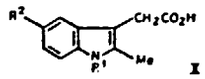


I II

Intermediates in the prepn. of 1-aroyl-3-indoleacetic acid are prepd. by nitration of phenylacetones to the corresponding *o*-nitrophenylacetones which, upon reaction with excess acid and pyrrolidine, yield 1-(*o*-nitrophenyl)-2-pyrrolidinopropenes. Reaction of the products with alkyl haloacetate followed by hydrolysis gives 3-(*o*-nitrophenyl)levulinic acids. Selective redn. of the NO_2 group followed by aroylation gives 1-aroyl-3-indoleacetic acid. Thus, *m*-methoxyphenylacetone was nitrated to give 2-nitro-5-methoxyphenylacetone with which pyrrolidine reacted to give 1-(2-nitro-5-methoxyphenyl)-2-pyrrolidinylpropene (I) (R = MeO). I in dioxane was treated with $ClCH_2CO_2Et$ to yield Et 3-(2-nitro-5-methoxyphenyl)levulinate (III) (II, R = MeO, R^1 = NO_2, R^2 = Et). A 5% ammoniacal soln. of III was treated with $FeSO_4$ to give 3-(2-amino-5-methoxyphenyl)levulinic acid (IV) (II, R = MeO, R^1 = NH_2, R^2 = H). Treatment of IV with *p*-chlorobenzoyl chloride gave 3-[2-(*p*-chlorobenzamido)-5-methoxyphenyl]levulinic acid (V) (II, R = MeO, R^1 = *p*-ClC_6H_4CONH, R^2 = H). V dissolved in Me_2CO was refluxed with trace 10% HCl in *N* to yield 1-*p*-chlorobenzoyl-2-methyl-5-methoxy-3-indoleacetic acid. Similarly prepd. were II derivs. with R = Me_2N. F. B. Wells

A6.13.

125421x 1-Acylindole derivatives. Yamamoto, Hisao; Nakao, Masaru (Sumitomo Chemical Co., Ltd.) Japan. 70 37,528 (Cl. C 07d, A 61k), 28 Nov 1970, Appl. 12 May 1967; 3 pp.

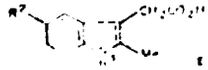


I

I, useful as an antiinflammatory, analgesic, and antipyretic, is prepd. In an example, *N*^{1}-(*p*-chlorobenzoyl)-*N*^{2}-(*p*-methoxyphenyl)hydrazine·HCl and acetosuccinic acid in AcOH are warmed 4 hr at 85–90° to give I (R^1 = *p*-ClC_6H_4CO, R^2 = MeO), m. 160–1° (aq. Me_2CO). Similarly prepd. are 9 addnl. I. Hiroshi Kataoka

A6.14.

87822u 1-Acyl-3-indoleacetic acid derivatives. Yamamoto, Hisao; Nakamura, Yasushi; Nakao, Masaru; Nakimura, Atsushi (Sumitomo Chemical Co., Ltd.) Japan. 70 37,522 (Cl. C 07d, A 61k), 28 Nov 1970, Appl. 20 Jun [illegible]; [illegible] I, useful

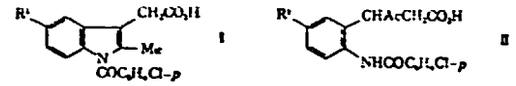


I

as antiinflammatories, analgesics, and antipyretics, are manufd. γ-[1-(*p*-Chlorobenzoyl)-2-methyl-5-methoxy-[illegible]-tolyl]butyric acid (150 mg) in 50 ml EtOH is cultured with [illegible] flakes of rabbits in a Kitta-Ringer phosphate buffer (pH [illegible]) 4 hr at 37°, boiled, concentrated, adjusted to pH 5, and extd. with CaH_4 to give 80 mg I (R^1 = *p*-ClC_6H_4CO, R^2 = [illegible], m. 156.5°; glucuronide, m. 142–4° (hexane-Et_2O). Similarly prepd. are I (R, [illegible] given): *p*-$ClC_6H_4(CO)$, [illegible]; *p*-Me-$C_6H_4(CO)$, [illegible]; $PhCH_2(CO)$, [illegible]; 2,4-hexadienoyl, [illegible]; *p*-$ClC_6H_4(CO)$, [illegible] crotonoyl, [illegible]. [illegible]

A6.15.

53514e Indole-3-acetic acids. Chemerda, John M.; Sletzinger, Meyer (Merck and Co., Inc.) Ger. Offen. 2,009,715 (Cl. C 07*d*c), 17 Sep 1970, US Appl. 03 Mar 1969; 18 pp. The

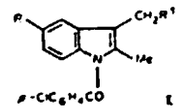


previously described indole-3-acetic acids (I, R^1 = MeO, NMe) are prepd. by ring closure of the levulinic acids (II) obtained from the known nitrobenzene derivs. 4,2-$R^1R^2C_6H_3NO_2$ (III, R = MeO, R^1 = MeO, Cl; R^1 = R^2 = NMe_2). III are esterified to the acetoacetic esters 5,2-$R^1(O_2N)C_6H_3CHAcCO_2R^3$ (IV) and converted in turn by heating with lower alkyl haloacetates and alkali metal alkoxides to the corresponding diesters 5,2-$R^1(O_2N)$-$C_6H_3CAc(CO_2R^4)CH_2CO_2R^3$ (V). Hydrolytic decarboxylation in the presence of an acidic reagent gave the levulinic acid compds. 5,2-$R^1(O_2N)C_6H_3CHAcCH_2CO_2H$ (VI) acylated in the presence of a reducing agent to II. Thus 3.25 g $AcCH_2CO_2Et$ and 3.4 g alc.-free NaOEt in 10.0 ml anhyd. PhMe thoroughly mixed with 4.65 g 3,4-$Cl(O_2N)C_6H_3OMe$ in 25 ml anhyd. PhMe and heated 4 hr at 100–10° with stirring and the cooled mixt. worked up gave IV (R^1 = MeO, R^2 = Et) (VII), also similarly prepd. from 3,4-$MeO(O_2N)C_6H_3OMe$. VII (14 g) and 6.8 g alc.-free NaOEt slurried in 50 ml anhyd. diglyme 15 min and heated 6 hr at 80–90° with 8.5 g $BrCH_2CO_2Et$ and the cooled mixt. poured into 200 ml 3% ice-cold HCl pptd. V (R^1 = MeO, R^3 = R^4 = Et) (VIII). VIII in 50 ml 75% AcOH contg. 0.2 g *p*-$MeC_6H_4SO_3H$ refluxed 3 hr with complete evolution of CO_2 and the cooled mixt. shaken with 100 ml H_2O yielded VI (R = MeO) (IX). IX (2.5 g) and 3.5 g (*p*-$ClC_6H_4CO)_2O$ in 100 ml diglyme hydrogenated at 20°/50 psi over 1 g 10% Pd-C gave II (R^1 = MeO) (X). X (1 g) in 10 ml MeOH contg. 1.0–1.5 g dry HCl refluxed 5 hr (N atm.) gave I (R^1 = MeO) Me ester, sapond. by refluxing in 90% HCO_2H contg. $MeSO_2H$ to give I (R = MeO). Similarly III (R^1 = R^2 = NMe_2) was esterified to IV (R^1 = NMe_2, R^2 = Et), converted to the diester V (R^1 = NMe_2, R^3 = R^4 = Et), decarboxylated to the levulinic acid VI (R^1 = NMe_2), acylated to II (R^1 = NMe_2), and finally cyclized to I (R^1 = NMe_2).

C. R. Addinall

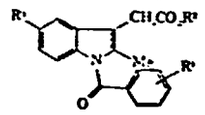
A6.16.

22695k 1-p-Chlorobenzoyl-2-methylindole-3-acetic acid derivatives. Chemerda, John M.; Sletzinger, Meyer (Merck and Co., Inc.) U.S. 3,535,337 (Cl. 260–326.16; C 07*d*), 20 Oct 1970, Appl. 26 Jul 1967; 4 pp. The title compds. (I, R = MeO,

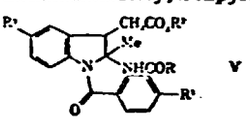


NMe_2; R^1 = alkali metal) (II) and related compds. I (R^1 = MgX, X) (III, IV) and I (R^1 = H) (V) were prepd. More particularly I (R^1 = CO_2H) (VI) was obtained by treating II or IV with solid CO_2. III may be obtained by refluxing I (R^1 = Cl) (VII) in Et_2O several hr with EtCl and PrMgBr or by treating IV with Mg in Et_2O or tetrahydrofuran. Anhyd. $HCONMe_2$ treated dropwise at −5 to 0° with $POCl_3$ and the mixt. treated portionwise with 2-methyl-5-methoxyindole at 20–5° and [illegible] at 50° with $CaCO_3$ gave 2-methyl-5-methoxyindole-3-carbaldehyde (VIII). VIII in $HCONMe_2$ stirred at 10° with [illegible] of NaH in $HCONMe_2$ and treated dropwise at 0–30° with *p*-ClC_6H_4COCl gave 1-*p*-chlorobenzoyl-2-methyl-5-methoxyindole-3-carbaldehyde (IX). IX [illegible] treated dropwise with [illegible] NaOH and the mixt. [illegible] cooled, and diluted with [illegible] MeO) (X). X [illegible] was treated with [illegible] in Et_2O to give [illegible] MeO, R^1 = MgBr) [illegible] with powd. dry [illegible] to give VI (R = MeO) [illegible] prepd. via I (R = MeO, R^1 = K and Li) [illegible] was VI (R = NMe_2) [illegible] have three routes. [illegible] small

A6.17. 22693h Pharmaceutical 1-benzoyl-2-methylindole-3-acetic acid derivatives. Kosa, Ildiko; Kovacs, Vera (Chinoin Gyogyszer es Vegyeszeti Termekek Gyara Rt.) Ger. Offen. 2,009,474 (Cl. C 07dc, A 61k), 05 Nov 1970, Hung. Appl. 03 Apr 1969; 19 pp. The title compds. (I) with antiinflammatory, antipyretic,



I

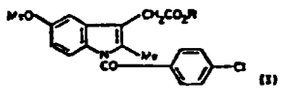


V

and analgesic effects were prepd. by acylating *p*-$R^2C_6H_4NHNH$-COR (II) to give *p*-$R^2C_6H_4(R^1C_6H_4CO)NNHCOR$ (III), reaction of III with $MeCOCH_2CH_2CO_2R^2$ (IV) to give V and elimination of H_2NCOR and (or) sapon. Thus, 3.04 g III (R = H, R^1 = *p*-Cl, R^2 = MeO) was dissolved in 30 ml $CHCl_3$ and 4 ml levulinic acid and HCl was passed 5 hr at room temp. and 2 hr at 80° into the soln. The product was kept 16 hr and filtered to give I (R^1 = *p*-Cl, R^2 = H, R^3 = MeO). Also prepd. were I (R^1–R^3 given): Cl, Bu, MeO; MeO, H, MeO; Me, H, MeO; H, H, H.

KHPG

A6.18. 3504f 1-Benzoylindole derivatives. Murakami, Masuo; Imai, Kazuo; Horiguchi, Hiroshi (Yamamouchi Pharmaceutical Co., Ltd.) Japan. 70 27,965 (Cl. 16 E 332), 12 Sep 1970, Appl. 28 Apr 1967; 3 pp. Antiinflammatory and antipyretic I are



(I)

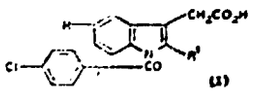
prepd. from the corresponding 1-benzimidoylindole compd. Thus, 1-(*N*-methyl-*p*-chlorobenzimidoyl)-2-methyl-5-methoxyindole-3-acetic acid is refluxed 1 hr in 70% aq. EtOH contg. H_2SO_4 to give I (R = H). Similarly prepd. is I (R = *tert*-Bu), m. 105–7° (aq. MeOH).

Hiroshi Kataoka

A6.19. 130381f 1-p-Chlorobenzoyl-2-methyl-5-methoxy-3-indoleacetic acid. Chemerda, John M.; Sletzinger, Meyer (Merck and Co., Inc.) U.S. 3,518,280 (Cl. 260–325.13; C 07d), 30 Jun 1970, Appl. 26 Jul 1967-27 Jun 1968; 2 pp. Di-*tert*-butyl 1-(*p*-chloro)benzoyl-2-methyl-5-methoxy-3-indolylmalonate (I) was hydrolyzed with *p*-toluenesulfonic acid to remove one CO_2Bu-*tert* group and saponifying the other without removing the Cl at 0–10° to form 1-(*p*-chlorobenzoyl)-2-methyl-5-methoxy-3-indolylacetic acid (II). Thus, *p*-methoxyphenylhydrazine·HCl and 2-acetoxymalonic acid was refluxed in *tert*-BuOH to give di-*tert*-butyl 2-methyl-5-methoxy-3-indolylmalonate (III). A soln. of III in DMF was added to NaH DMF soln., the mixt. stirred at 0–5° until H evolution ceased, and *p*-ClC_6H_4COCl added to give I. I was hydrolyzed to II. Dibenzyl 1-(*p*-chlorobenzoyl)-2-methyl-5-methoxy-3-indolylmalonate in AcOH contg. 1 molar equiv. HCl was hydrogenolyzed with Pd–C and H to give II.

O. L. Brauer

A6.20. 120498x 1-(p-Chlorobenzoyl)-2-methylindole-3-acetic acid derivatives and intermediates. Chemerda, John M.; Sletzinger, Meyer (Merck and Co., Inc.) U.S. 3,522,272 (Cl. 260–326.12; C 07d), 28 Jul 1970, Appl. 09 Aug 1967; 7 pp. The title compds. (I, R = MeO or Me_2N, R^1 = Me) are prepd. by reducing a 2-substituted indole-3-acetic acid. Thus, 1-(*p*-chloro-

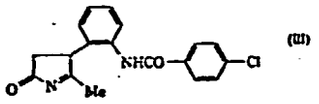


(II)

benzoyl)-2-(tosyloxymethyl)-5-methoxyindole-3-acetic acid and $NaHCO_3$ in Me_2SO was stirred under N at 100° for 5 min to give I (R = OMe and R^1 = CHO) (II). II in EtOH was added to amalgamated Zn covered by HCl and the mixt. stirred and refluxed 24 hr to give I (R = OMe and R^1 = Me). Also prepd. were 32 other I.

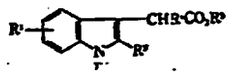
S. J. Johnson

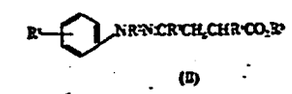
A6.21. 103677j 1-(p-Chlorobenzoyl)-2-methyl-5-methoxy-3-indoleacetic acid. Firestone, Raymond A.; Sletzinger, Meyer (Merck and Co., Inc.) Ger. Offen. 2,039,724 (Cl. C 07d, A 61k), 17 Sep 1970, US Appl. 03 Mar 1969; 14 pp. The antiinflammatory title compd. (I) was prepd. Thus, heating Na (p-methoxyphenyl)hydrazinesulfonate and p-ClC$_6$H$_4$COCl in H$_2$O-BuOH at 75–80°, addn. of hot PhMe, and treatment with aq. NaOH yielded p-MeOC$_6$H$_4$(p-ClC$_6$H$_4$CO)NNH$_2$ (II). Refluxing II and


(III)

levulinic acid in PhMe in the presence of 100% H$_3$PO$_4$ gave III. Refluxing III and 100% H$_3$PO$_4$ in PhMe gave I. KCPG

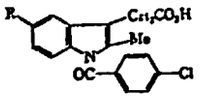
A6.22. 98797v Antiinflammatory and antipyretic 1-acyl-3-indolealkanoic acid derivatives. Sumitomo Chemical Co., Inc. Fr. 1,593,552 (Cl. C 07d, A 61k), 14 Nov 1969, Japan. Appl. 11 Apr 1967-14 Dec 1967; 49 pp. Antipyretic and antiinflammatory compds. I, their salts and esters are prepd. from II. Thus, Et levulinate p-methoxyphenylhydrazone and pyridine in Et$_2$O was treated with BzCl at 0–5° to give II (R^1 = p-OMe, R^2 = Bz,

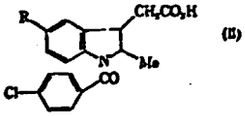

(I)


(II)

R^3 = Me, R^4 = H, R^5 = Et), oil. Similarly prepd. were II (R^1 = p-OMe or p-OEt, R^2 = nicotinoyl, isonicotinoyl, or cinnamoyl, R^3 = Me, R^4 = H, R^5 = Me or Et). To II (R^1 = p-OMe, R^2 = H, R^3 = Me, R^4 = H, R^5 = *tert*-Bu), pyridine, and dioxane was added p-ClC$_6$H$_4$COCl and the mixt. heated to 80° to give I (R^1 = 5-OMe, R^2 = p-ClC$_6$H$_4$CO, R^3 = Me, R^4 = H, R^5 = *tert*-Bu) (III), m. 103–4°. Heating III with ceramic powder at 200–215° gave I (R^1 = 5-OMe, R^2 = p-ClC$_6$H$_4$CO, R^3 = Me, R^4 = R^5 = H) (IV), m. 152–5°. II (R^1 = OMe, R^2 = cinnamoyl, R^3 = R^5 = Me, R^4 = H), HCl and AcOH was heated 2 hr to 90° to give Me 1-cinnamoyl-2-methyl-5-methoxy-3-indoleacetate m. 87–7.5° (MeOH). IV was heated with aq. NaHCO$_3$ to give the Na salt. By similar methods ~15 I analogs were prepd. I. Scriabine

A6.23. 98791p α-[1-(p-Chlorobenzoyl)-2-methyl-5-nitro-3-indolyl]-acetic acid. Chemerda, John M.; Sletzinger, Meyer (Merck and Co., Inc.) U.S. 3,509,172 (Cl. 260–326.11; C 07d), 28 Apr 1970, Appl. 26 Jul 1967; 2 pp. The title compds. (I) were prepd. by the catalytic dehydrogenation of II. Thus, 2-methyl-3-

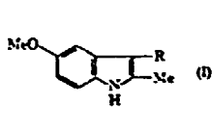

(I)


(II)

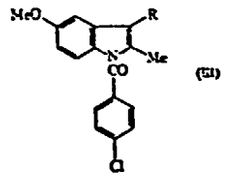
indolylacetic acid in MeOH was hydrogenated at 50–60° over Raney Ni to give 2-methyl-3-indolinylacetic acid (III). A soln. of III in C$_5$H$_5$N was treated with 4-ClC$_6$H$_4$COCl at 15–20° to give II (R = H). A mixt. of HNO$_3$–H$_2$SO$_4$ and II (R = H) kept 12 hr at 5–10° gave II (R = NO$_2$). II (R = NO$_2$) in EtOH was hydrogenated over 10% Pd/C at room temp./3 atm to give II (R = NH$_2$) (IV). IV·HCl and MeNO$_2$ in MeOH was heated 1 hr at 90–100° to give II (R = MeO). II (R = MeO), 10% Pd/C, and mesitylene was refluxed 3 hr to give I (R = MeO). IV and Me orthocarbonate was refluxed to give II (R = Me$_2$N), dehydrogenation of which gave I (R = Me$_2$N). Kay O. Loettler

A6.24. 66418f 5-Substituted-1-benzoyl-2-methylindole-3-acetic acids. Hinkley, David F.; Chemerda, John M. (Merck and Co., Inc.) Fr. Demande 2,003,168 (Cl. C 07d), 16 Jan 1970, Can. Appl. 09 May 1968; 15 pp. The key intermediates are α-carboxymethyl-β-methyl-β-nitro-5-substituted-styrene which are reductively ring-closed with triethyl phosphite. For example, a mixt. of 0.1 mole Et β-oxovalerate and 0.1 mole Mg in 600 ml Et$_2$O was treated with 0.1 mole 3-chloro-4-nitroanisole to give α-carbethoxymethyl-β-methyl-2-nitro-5-methoxystyrene. The free acid was obtained by hydrolysis with H$_3$PO$_4$ and 0.1 mole was heated 15 hr at 175° with 0.5 mole (EtO)$_3$P. Low boilers were removed under vacuum to give 2-methyl-5-methoxyindolylacetic acid, m. 157°. Under similar conditions but with portionwise addn. of p-chlorobenzoic acid anhydride there was obtained 1-p-chlorobenzoyl-2-methyl-5-methoxy-3-indolylacetic acid, m. 176–7°. Ca[illegible]

A6.25. 55669k Antiinflammatory 1-benzoyl-2-methyl-3-indoleacetic acids. Chemerda, John M.; Sletzinger, Meyer (Merck and Co., Inc.) U.S. 3,517,023 (Cl. 260–326.16; C 07*d*), 23 Jun 1970, Appl. 26 Jul 1967; 3 pp. Title compds. are prepd. Thus, 2-methyl-5-methoxyindole is treated with $POCl_3$ in DMF to yield I (R = CHO) (II). The *N*-Na salt of II, prepd. from NaH, is treated with *p*-ClC_6H_4COCl to form III (R = CHO)



(I)

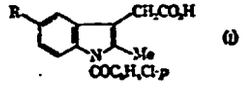


(III)

(IV). IV is reduced to III (R = CH_2OH) (V) with dimethylborane. V reacted with $SOBr_2$ to yield III (R = CH_2Br). Reaction of V with $Ni(CO)_4$, Ni chloride, and CO in HCl yields III (R = CH_2CO_2H). 5-Me_2N analogs of I and III were also prepd.

R. E. McClure

A6.26. 132512q Antiinflammatory 2-methyl-3-indoleacetic acids. Chemerda, John M.; Sletzinger, Meyer (Merck and Co., Inc.) U.S. 3,501,498 (Cl. 260–326.13; C 07*d*), 17 Mar 1970, Appl. 16 Jul 1967; 4 pp. The title compds. (I) were prepd. by the catalytic redn. of nitroindoleacetic acid to the corresponding amino analog; diazotization of the amino group to the diazonium salt; and redn. of the latter by chem. redn. Thus, 5 g benzyl 2-methyl-



(I)

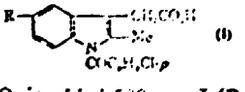
4-nitro-5-methoxyindole-3-acetate was treated with 20% molar excess 3-nitro-4-chlorobenzoyl chloride in a slurry of NaH in $(Me)_2NC(O)H$ to give benzyl 1-(3-nitro-4-chlorobenzoyl)-2-methyl-4-nitro-5-methoxyindole-3-acetate, which (3.0 g) with H gave 1-(3-amino-4-chlorobenzoyl)-2-methyl-4-amino-5-methoxyindole-3-acetic acid. This in AcOH was treated with $EtNO_2$ at 0°. The mixt was then added to 100 ml 30% hypophosphorous acid to give I (R = MeO). I are potent antiflammatory agents.

Harold M. Kaplan

A5.27. 111297h 5-Substituted derivatives of 1-benzoyl-2-methylindole-3-acetic acid. Gal, George (Merck and Co., Inc.) Fr. Demande 2,004,597 (Cl. C 07*dc*), 28 Nov 1969, Can. Appl. 23 Mar 1968; 9 pp. The title derivs. are prepd. by treating dihalopentenoic acids with acylated amines. Thus, 26.1 g *p*-$MeOC_6H_4NHCOC_6H_4Cl$-*p*, 18.0 g MeCH:CClCHClCO$_2$H (I), and 16.5 g Na_2HPO_4 in 100 ml diglyme heated 3 hr (N atm.) at 160–2° gave 1-(*p*-chlorobenzoyl)-2-methyl-5-methoxyindole-3-acetic acid, m. 159–60° (Me_2COH). Similarly from *p*-Me_2N-$C_6H_4NHCOC_6H_4Cl$-*p* (II) was obtained 1-(*p*-chlorobenzoyl)-2-methyl-5-(dimethylamino)indole-3-acetic acid, m. 176.7°. $PdCl_2$ (17.8 g) in 80 ml EtOH kept 15 min with 12.4 g $ClCH_2CCl$:CHMe, the mixt. concd. in vacuo, the residual 20 ml dild. with 60 ml C_6H_6 and filtered, and the complex (10 g) stirred 5 hr in 60 ml C_6H_6 (CO atm.) at 50°/200 atm gave I. Similarly were obtained MeCH:CBrCHBrCO$_2$H, MeCH:CBrCHClCO$_2$H, and MeCH:CClCHBrCO$_2$H. Anhyd. C_5H_5N (70 ml) contg. 13.6 g *p*-$Me_2NC_6H_4NH_2$ treated dropwise at 10–15° (external cooling) with 17.5 g *p*-ClC_6H_4COCl and the mixt. stirred 18 hr at 25° yielded II.

C. R. Addinall

A6.28. 150311x 5-Substituted-1-(*p*-chlorobenzoyl)-2-methyl-3-indoleacetic acid. Gal, George; Sletzinger, Meyer (Merck and Co., Inc.) Fr. Demande 2,002,611 (Cl. C 07*d*), 17 Oct 1969, Can. Appl. 22 Feb 1968; 24 pp. The title compds. (I) are prepd.

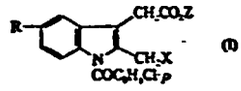


(I)

To 30 ml 85% H_3PO_4 is added 500 mg. I (R = OMe) Me ester and the mixt. heated to 100° in N_2 90 min to give I (R = OMe), m. 199–201°. Similarly prepd. is I (R = Me_2N), m. 176–7°.

R. K. Srivastava

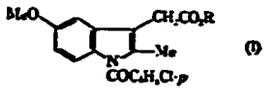
A6.29. 100502r 1-(p-Chlorobenzoyl)indole-3-acetic acids Grignard reagents. Chemerda, John M.; Sletzinger, Meyer (Merck and Co., Inc.) U.S. 3,497,526 (Cl. 260-326.13; C 07*d*, A 61*k*), 24 Feb 1970, Appl. 26 Jul 1967; 2 pp. 1-(*p*-Chlorobenzoyl)-2-methylindole-3-acetic acids (I), which have antiinflammatory, analgesic, and antipyretic characteristics, were prepd. Thus, 0.1 equiv. 1-(*p*-chlorobenzoyl)-2-(tosyloxymethyl)-5-methoxyindole-3-acetic acid in 100 ml Me_2CO contg. 0.1 equiv. LiCl was stirred 48 hr at 25° to give I (R = OMe, X = Cl, Z = H). Similarly prepd. I were (R, X, and Z given): NMe_2, Cl, H;



(I)

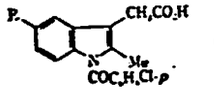
OMe, MgCl, Mg; NMe_2, MgCl, Mg; OMe, Me, H; NMe_2, Me, H. FPPN

A6.30. 90284j Indomethacin; antiinflammatory indole derivatives. Christensen, Svend A. (Merck and Co., Inc.) Brit. 1,132,441 (Cl. C 07*d*), 25 Feb 1970, Appl. 10 Nov 1966; 2 pp. I (R = H) was prepd. by alcoholysis of its trityl ester. Thus, 6.0 g I (R = CPh_3) in 50 cc MeOH, kept 24 hr at 30° and worked up, gave I (R = H), m. 156–9°. DGPN



(I)

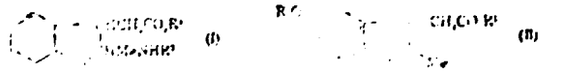
A6.31. 90278k 1-(p-Chlorobenzoyl)-2-methylindole-3-acetic acid derivatives. Chemerda, John M.; Sletzinger, Meyer (Merck and Co., Inc.) Fr. 1,555,374 (Cl. C 07*d*,*e*), 24 Jan 1969, Can. Appl. 08 Mar 1967; 9 pp. A process is given for the prepn. of title compds. I (R = MeO and Me_2N). Exptl. details are given but no phys. properties. A soln. of 500 ml 50% aq. MeOH contg. 5% NH_2 and 0.1 mole 2-(O_2N)-5-(MeO)C_6H_3CHO was added at 50° to 0.7 equiv. $FeSO_4$ in 2–3 parts H_2O, the mixt. treated portionwise with aq. NH_4OH to basic pH, stirred 1 hr, and filtered, the insol. solid washed with MeOH and the com-



(II)

bined filtrates evapd. to give 2-H_2N-5-$MeOC_6H_3CHO$ (II). Addg. 0.1 mole 4-ClC_6H_4COCl to a soln. of 0.1 mole II in 100 ml ml C_5H_5N and stirring at 20° 2 hr gave, after acidification, 2-(*p*-ClC_6H_4CONH)-5-$MeOC_6H_3CHO$ (III). To a mixt. of 0.1 mole III and 0.1 mole $EtNO_2$ was added 3 drops Et_3N and the mixt. kept several days to give 2-(*p*-ClC_6H_4CONH)-5-$MeOC_6H_3CH$:-$CMeNO_2$ (IV) (petroleum ether). A soln. of 0.1 mole $MeCH(CO_2Me)_2$ and 0.1 mole *tert*-BuOK in 50 ml *tert*-BuOH was stirred at 30° 1 hr and treated during 0.5 hr at 20–5° with 0.1 mole IV then kept at 25–30° overnight and dild. with 200 ml Et_2O to give 2-(*p*-ClC_6H_4CONH)-5-$MeOC_6H_3CH(CHMeNO_2)CX(CO_2Me)_2$ (V, X = Na) (VI). Treatment of 0.1 mole Na salt VI in 200 ml MeOH at −5 to 0° with Cl 1 hr, filtering, and evapg. gave V (X = Cl) (VII). A mixt. of 0.1 mole VII, 0.3 mole KOH and 250 ml aq. MeOH was heated at 50° 5 hr and acidified to pH 3 with AcOH. Solvent was removed and the residue extd. with Et_2O to give 2-(*p*-ClC_6H_4CONH)-5-$MeOC_6H_3C(:CMeNO_2)CH_2$-CO_2H (VIII). To a refluxing mixt. of 5 g Fe powder in 50 ml AcOH was added a warm soln. of 4.04 g VIII in 50 ml AcOH, the mixt. refluxed 1 hr, filtered hot, the filtrate concd. to low vol., 200 ml H_2O added, and the soln. cooled to give 2-(*p*-ClC_6H_4-$CONH$)-5-$MeOC_6H_3CHAcCH_2CO_2H$ (IX). Refluxing a mixt. of 1.4 g IX, 1.5 g 4-$MeC_6H_4SO_3H$, and 100 ml Me_2CO 5 hrs, cooling and addg. 100 ml H_2O gave I (R = MeO) (*tert*-BuOH). I (R = Me_2N) was prepd. by a similar sequence with analogous intermediates. P. Mamalis

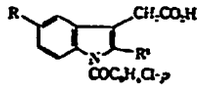
A6.32. 72s574w Substituted 2-methylindole-3-acetic acid esters. Sletzinger, Meyer; Cal, George (Merck and Co., Inc.) Fr. 1,566,937 (Cl. C 07*d*), 02 May 1969, Can. Appl. 27 May 1967; 12 pp. Cyclization of I with $NO(SO_3K)_2$ or $[Ni(CN)_4]$ gave the title compds. (II). Thus, to a stirred soln. of 0.1 mole I (R^1 = Me, R^2 = R^3 = H) in 300 ml 2*N* AcOH and 200 ml CH_2Cl_2 was added a soln. of 0.2 mole $NO(SO_3K)_2$ in 500 ml H_2O, and the mixt. stirred 5 min to give II (R^1 = Me, R^2 = R^3 = H). This



(I) (II)

(0.1 mole) in 50 ml CH_2Cl_2 was treated with $HC(OMe)_2NMe_2$ 2 days to give II ($R^1 = R^2 = Me$, $R^3 = H$). To a soln. of 0.1 mole of this in 50 ml $HCONMe_2$ was added a 10% excess of a 50% emulsion of NaH in 25 ml $HCONMe_2$ and then a 20% excess of *p*-ClC_6H_4COCl, and the mixt. kept 2 hr to give II ($R^1 = R^2 = Me$, $R^3 = p$-COC_6H_4Cl). Several other examples were described, but no phys. consts. were given. R. Haas

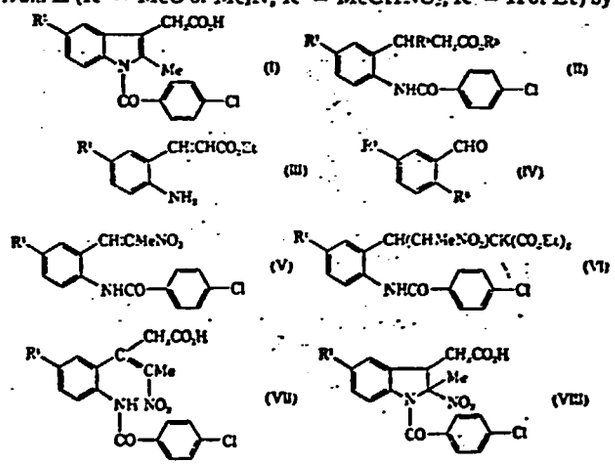
A6.33. 78871r 1-(p-Chlorobenzoyl)-2-formylindole-3-acetic acids. Chemerda, John M.; Sletzinger, Meyer (Merck and Co., Inc.) U.S. 3,489,765 (Cl. 260-326.13; C 07d), 13 Jan 1970, Appl. 26 Jul 1967; 3 pp. Compds. (I) were prepd. by treating II with N_2H_4 or $NH_2CONHNH_2$ and reducing the hydrazone or semi-



(I, R^1 = Me)
(II, R^1 = CHO)

carbazone. Thus 3.72 g II (R = MeO) and 0.64 g NH_2NH_2 gave 4.19 g hydrazone, which was reduced with Me_2COK–Me_2SO to give I (R = OMe). Similarly prepd. was I ($R = Me_2N$).
Harold M. Kaplan

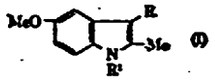
A6.34. 78868v Indoleacetic acids from nitrovaleric acids. Chemerda, John M.; Sletzinger, Meyer (Merck and Co., Inc.) Fr. 1,555,403 (Cl. C 07dc), 24 Jan 1969, Can. Appl. 09 Mar 1967; 14 pp. The title compds. (I) (R^1 = MeO or Me_2N) may be prepd. from II (R^1 = MeO or Me_2N, $R^2 = MeCHNO_2$, R^3 = H or Et) by



4 routes. Thus, 19.3 g III (R^1 = MeO), 15 cm³ C_5H_5N, and 18 g *p*-ClC_6H_4COCl 2–5 hr at 10–15° gave the anilide, 34.2 g of which with 7.5 g $EtNO_2$, dioxane 150, and 40% aq. Triton B 2 cm³ 5 hr at 70–100° gave II (R^1 = MeO, $R^2 = MeCHNO_2$, R^3 = Et). IV (R^1 = MeO, $R^4 = NO_2$) (0.1 equiv.) in 500 cm³ 5% NH_3 in aq. MeOH, and 0.7 equiv. aq. $FeSO_4.7H_2O$ at 50° gave the *o*-amino aldehyde which was acylated and treated with 1 equiv. $EtNO_2$ and 3 drops $EtNH_2$ several days at 20° to give V (R^1 = MeO) (from petroleum ether). V (R^1 = MeO) 0.1, $CH_2(CO_2Me)_2$ 0.1, *tert*-BuOK 0.1 equiv. and *tert*-BuOH 15 cm³ gave VI (R^1 = MeO), which with aq. KOH 2 hr at 50–60° gave II (R^1 = MeO, $R^2 = MeCHNO_2$, R^3 = H). II (R^1 = MeO, $R^2 = MeCHNO_2$, R^3 = Et) 0.1, NaOCl 0.1 equiv., and 250 cm³ H_2O 20 min, + 5% HCl to pH 5 gave II (R^1 = MeO, $R^2 = MeCOCHNO_2$, R^3 = H), 0.01 mole of which with 0.4 mole aq. NaOH [illegible] at 45–50°, then HCl at room temp. gave VII (R^1 = MeO). VII (R^1 = MeO) (4.34 g), 5 g. Fe powder, and 150 cm³ AcOH was refluxed 1 hr and the mixt. treated with 10 g Na_2CO_3 to give I (R^1 = MeO). II (R^1 = MeO, $R^2 = MeCOCHNO_2$, R^3 = H) 0.1, *tert*-BuOK 0.21 equiv. and 20 cm³ $HCONMe_2$ [illegible] and 4 hr at 100° and the mixt. treated with AcOH gave VIII (R^1 = MeO). VIII (R^1 = MeO) (0.1 equiv.) in 20 cm³ [illegible] kept at 10° and poured into H_2O and HCl added to [illegible] gave I (R^1 = MeO). II (R^1 = MeO, $R^2 = MeCHNO_2$, R^3 = H) (0.1 equiv.), 250 cm³ MeOH, 0.3 mole H, and 500 mg [illegible] gave II (R^1 = MeO, $R^2 = MeCHNH_2$, R^3 = H). [illegible] with 1.5 g *N*-chlorosuccinimide and 100 cm³ CH_2Cl_2 10 min gave II (R^1 = MeO, $R^2 = MeCHNHCl$, R^3 = H). This [illegible] with 1 g Na in 70 cm³ EtOH 30 min at reflux gave II ([illegible] $R^2 = MeCH$-NH_2, R^3 = [illegible] 2.5 g of which in 20 cm³ [illegible] mg. 100 mg *p*-$MeC_6H_4SO_2Cl$ [illegible] reflux (N) gave [illegible] (from 1:1 [illegible] = MeO, [illegible] R^2 = [illegible] 0 cm³ [illegible] g, and 15 cm³ [illegible] rise at 0° [illegible] gave II (R^1 = MeO, [illegible] H). This [illegible] mg *p*-$MeC_6H_4SO_2Cl$ [illegible] 20 5 hr at [illegible] = MeO). S[illegible] with R^1 =

A6.35. 75s05s Indole derivatives. Merck and Co., Inc. Brit. Amended 1,050,729 (Cl. C 07*d*), 07 Dec 1966, US Appl. 01 Feb 1963; 4 pp. Division of Brit. Amended 1,050,728 (See Neth. Appl. 64 00,813, *CA* 62: 4509a). Same disclosure with slight change in wording. M. D. Beach SNWV

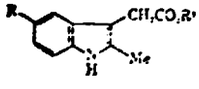
A6.36. **Indole derivatives. Merck & Co., Inc. Neth. Appl. 6,400,813 (Cl. C 07*d*), Aug. 3, 1964; U.S. Appl. Feb. 1, 1963; 82 pp. I, which had antiinflammatory and antipyretic activity, were prepd. Thus, to a stirred cooled (0°) mixt. of 2.25 g. 2,5-O_2N(MeO)C_6H_2Me and 2.24 g. *tert*-BuOK in 25 cc. Et_2O was added 2 cc. AcOEt in 10 cc. Et_2O over 6 hrs., the whole stirred 2 hrs. at room temp., the ppt. washed with Et_2O and suspended in 25 cc. Et_2O, 3.4 g. $BrCH_2CO_2Et$ in 10 cc. Et_2O added over 2 hrs., the whole stirred several hrs. and acidified with aq. AcOH at 0–5°, and the Et_2O layer washed with $NaHCO_3$ soln., dried, and concd. to give 2,5-O_2N(MeO)C_6H_3CHAcCH$_2CO_2$Et, which was stirred 8 hrs. with 100 cc. 1% NaOH at 0°, the soln. washed with Et_2O and acidified with HCl, the whole heated 10–15 min. on a steam bath, and the mixt. cooled to give a ppt., 10 g. of which was hydrogenated (Raney-Ni or Pd–C) in 100 cc. dioxane**



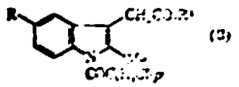
(I)

in the presence of 6.6 g. *p*-chlorobenzoic acid anhydride to give I (R = CH_2CO_2H, R^1 = COC_6H_4Cl-4) (II), m. 158–9°. A mixt. of 70 g. *tert*-BuOAc, 23.3 g. I (R = CH_2CO_2Me, R^1 = H), and 1.8 g. MeONa refluxed in a N atm. (the AcOMe formed distd.), and excess *tert*-BuOAc distd. *in vacuo* gave 80% I (R = CH_2CO_2 *tert*-Bu, R^1 = H), m. 110–11° (CH_2Cl_2-cyclohexane). Enzymic hydrolysis of I (R = CH_2CO_2Et, R^1 = COC_6H_4Cl-4) (III) gave II. To 0.03 mole I (R = CH_2CO_2Bu-*tert*, R^1 = COC_6H_4Cl-4) in 300 cc. C_6H_6 was added 1 g. 4-$MeC_6H_4SO_2H.H_2O$, the mixt. refluxed 40 min. in a N atm. (665 cc. isobutene evolved), the whole dild. with 200 cc. C_6H_6 at 55–60°, the soln. washed with H_2O at 60–5° to pH 4–5, and the C_6H_6 layer treated with C, and concd. to 70–5 cc. gave 9.7 g. II, m. 153–4° (*tert*-BuOH-cyclohexane). *N*-(*p*-Chlorobenzoyl)-*N*-(*p*-methoxyphenyl)-1-methyl-2-oxopropylamine (IV), $CO(OEt)_2$, and NaH gave the Et ester of *N*-(*p*-chlorobenzoyl)-*N*-(*p*-methoxyphenyl)-3-oxo-4-aminovaleric acid, which heated with $ZnCl_2$ gave III. *N*-(*p*-chlorobenzoyl)-*p*-anisidine, m. 208–9°, NaH, 2-bromobutanone, and $CO(OEt)_2$ gave IV. Many other prepns. were given but without phys. consts. for the products. A. Nederlof

A6.37. **66817q Antiinflammatory 1-(p-chlorobenzoyl)-2-methyl-5-methoxyindole-3-acetic acid. Sletzinger, Meyer (Merck and Co., Inc.). U.S. 3,438,731 (Cl. 260–326.13; C 07*d*), 06 Jan 1970, Appl. 26 Jul 1967; 2 pp. A β-haloalkanol is used for protecting the acid side chain of an indole-3-acetic acid (I) so as to allow *N*-acylation only. Thus, to 0.1 mole I (R = MeO, R^1 = H) and 0.15 mole CCl_3CH_2OH in 100 ml C_6H_6 was added 100 mg *p*-$MeC_6H_4SO_3H$ and the reaction mixt. refluxed until the theoretical amt. H_2O had been produced to give II (R = MeO, R^1 =**



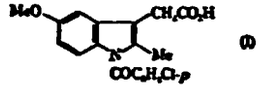
(I)



(II)

CCl_3CH_2). This (2.5 g) in 15 ml anhyd. Me_2NCHO was added to a 0.5 g 50% NaH in 5 ml Me_2NCHO under N, and the mixt. kept 1 hr, 1.9 g *p*-ClC_6H_4COCl in 5 ml Me_2NCHO added at 0–5°, and the mixt. kept 2 hr at room temp. to give II (R = MeO, R^1 = CCl_3CH_2). This (4.89 g) in 25 ml AcOH was treated at 60–80° with 2.0 g Zn powder over 15 min, and the mixt. heated 15 min at 80° to give II (R = Me, R^1 = H), m. 150° (*tert*-BuOH). The title compds. are effective in treating arthritic conditions.

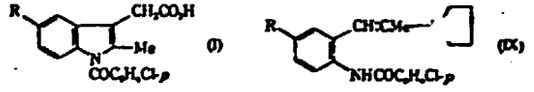
A6.38. 66515n N-(p-Chlorobenzoyl)-2-methyl-5-methoxyindole-3-acetic acid. Chemerda, John M.; Sletzinger, Meyer (Merck and Co., Inc.) Fr. Demande 2,000,747 (Cl. C 07d), 12 Sep 1969, US Appl. 25 Jan 1968; 17 pp. The title compd. (I) was prepd. To a suspension of 3.5 g NaOMe in 500 ml Et_2O was added 7 g $AcCO_2Et$, 8.2 g N-(p-chlorobenzoyl)-4-methoxyacetanilide added, and the mixt. refluxed 1 hr to give 4-methoxy-N-(p-chlorobenzoyl)-pyruvylacetanilide. This (10 g) and 40 ml anhyd. HF was heated 2 hr at 60–5° to give 4-acetyl-6-methoxy-N-(p-chlorobenzoyl)carbostyryl, 10 g of which in 50 ml EtOH was hydrogenated over 2 g 10% Pd/C to give the 3,4-dihydro deriv. This (10 g) in 150 ml MeOH was added, 7 g Na_2CO_3, and 150 ml H_2O was refluxed 1 hr to give 3-[2-(p-chlorobenzoylamino)-5-methoxyphenyl]levulinic acid, m. 173–5° (Me_2CO).



(I)

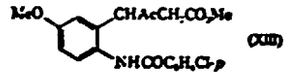
This (0.01 mole) in 35 ml Me_2CO contg. a catalytic amt. HCl was refluxed 6 hr to give I, m. 159–60° (BuOH). Gerben Sipma

A6.39. 55255d 1-(p-Chlorobenzoyl)-2-methyl-3-indolylacetic acid derivatives. Chemerda, John M.; Sletzinger, Meyer (Merck and Co., Inc.) Fr. 1,555,404 (Cl. C 07d), 24 Jan 1969, Can. Appl 09 Mar 1967; 9 pp. The prepn. of the title compds. (I) is described: exptl. details are given but no m.p.'s. To 27 g abs. MeOH contg. 1 g powd. NH_4Cl was added 0.1 equiv. 2,5-$O_2N(MeO)C_6H_3CH_2Ac$ (II) and 35 g $(MeO)_3CH$ and the mixt. heated 1 hr at 65° to give 2,5-$XRC_6H_3CH_2CMe(OMe)_2$ (III) (R = MeO, X = NO_2) (IV). Similarly prepd. was III (R = Me_2N, X = NO_2). Hydrogenation of 0.1 equiv. IV in 100 ml dioxane over 200 mg 5% Pd-C gave III (R = MeO, X = NH_2) (V). III (R = Me_2N, X = NH_2) was similarly prepd. Treatment of 0.1 mole V in 100 ml dioxane and 100 ml C_5H_5N with 0.1 mole p-ClC_6H_4COCl, heating 0.5 hr at 50°, and stirring 4 hr at 25° gave III (R = MeO, X = $NHCOC_6H_4Cl$-p) (VI). The III (R = Me_2N) analog was similarly prepd. To a soln. of 0.1 mole VI in 300 ml 50% aq. MeOH at 0° was added 2 ml concd. HCl and the mixt. kept 3 hr at 0°, to give 4,2-$R(AcCH_2)C_6H_3NHCOC_6H_4Cl$-p (VII) (R = MeO) (VIII). VII (R = Me_2N) was similarly prepd. Conversion of VIII to the pyrrolidine enamine



(I)

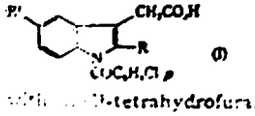
(IX)



(XIII)

IX (R = MeO) (X) was carried out by refluxing equimolar amts. VIII and pyrrolidine in C_6H_6 with removal of H_2O. To a soln. of 0.1 mole X in 100 ml $HCONMe_2$ was added, over 0.5 hr and at 10–5°, 0.1 mole $ClCH_2CO_2Na$, and the mixt. heated 0.5 hr at 100–10°, to give I (R = MeO) (XI). I (R = Me_2N) (XII) was similarly prepd. A mixt. of 0.1 mole X and 0.1 mole $ClCH_2CO_2$-Me in 300 ml C_6H_6 was refluxed 2 hr to give XIII, which on heating in 50% aq. MeOH with 1.1 equivs. KOH 2 hr at 50° gave XI. XII was similarly obtained. P. Marmalis

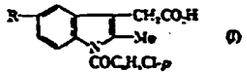
A6.40. 55254c 1-(p-Chlorobenzoyl)-2,5-disubstituted-indole-3-acetic acids. Chemerda, John M.; Sletzinger, Meyer (Merck and Co., Inc.) Fr. 1,533,160 (Cl. C 07d), 26 Jul [illegible], Appl. 20 Aug 1966; 9 pp. I (R = Me, R^1 = MeO or NMe_2) was prepd. from I (R = p-$MeC_6H_4SO_2CH_2$, R^1 = MeO or NMe_2) by



(I)

successive reactions with [illegible]-tetrahydrofuran [illegible] HCl.

A6.41. 55253b Indole-3-acetic acids and intermediates from derivatives of aryl levulinic acid. Chemerda, John M.; Sletzinger, Meyer (Merck and Co., Inc.) Fr. 1,555,402 (Cl. C 07*dc*), 24 Jan 1969, Can. Appl. 09 Mar 1967; 7 pp. Title compds. (I) were prepd. Thus, 0.3 mole *m*-methoxyphenylacetone was slowly added to 35 ml HNO_3 and 74 ml H_2SO_4 at 15–20°, and the mixt. stirred 2 hr at 20° to give 2-nitro-5-methoxyphenylacetone. This (0.1 equiv.), 300 ml benzene, and 0.2 equiv. pyrrolidine was refluxed 5 hr to give 1-(2-nitro-5-methoxyphenyl)-2-pyrrolidinylpropene. This (0.1 equiv.), 100 ml dioxane, and 0.1 equiv. $ClCH_2CO_2Et$ was refluxed 10 hr, 10 ml water added,

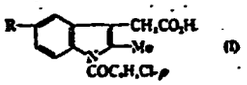


(I)

and the mixt. refluxed 3 hr to give Me 3-(2-nitro-5-methoxyphenyl)levulinate. A 5% ammoniacal soln. contg. 0.1 equiv. of this was added to a boiling soln. contg. 0.7 equiv. $FeSO_4$ in 2–3 parts water, concd. NH_4OH added dropwise until the soln. was alk., and the mixt. stirred 1 hr to give 3-(2-amino-5-methoxyphenyl)levulinic acid. This (0.1 mole), 50 ml pyridine, and 0.1 mole *p*-ClC_6H_4COCl was stirred 3 hr at 10–15° to give 3-[2-(*p*-chlorobenzamido)-5-methoxyphenyl]levulinic acid (II), m. 173–5° (the 5-dimethylaminophenyl analog m. 176–7°). II was also prepd. from 3-[2-(*p*-chlorobenzamido)-5-methoxyphenyl]-4-hydroxyvaleric acid. II (0.1 equiv.), 3 l. acetone, and 2 ml 10% HCl was refluxed 6 hr under N to give I (R = MeO), m. 153–5°. Also prepd. was I (R = Me_2N), m. 176–7°.

Gerard J. Toussaint

A6.42. 55252a Indole-3-acetic acids from α-derivatives of dialkoxyvaleric acid. Chemerda, John M.; Sletzinger, Meyer (Merck and Co., Inc.) Fr. 1,555,401 (Cl. C 07*dc*), 24 Jan 1969, Can. Appl. 09 Mar 1967; 5 pp. The title compds. (I) were prepd. Thus, to 27.6 g MeOH contg. 1 g NH_4Cl were added 0.1 mole 3-(2-nitro-5-methoxyphenyl)levulinic acid and 35 g $HC(OMe)_3$, the mixt. was refluxed 1 hr, distd., 100 ml 50% aq. MeOH contg. 6 g KOH added, and the mixt. heated 2 hr to give β-(2-nitro-5-methoxyphenyl)levulinic acid di-Me acetal. This (0.1 mole) in 100 ml MeOH was hydrogenated over 5% Pd/C (0.3 mole absorbed) to give β-(2-amino-5-methoxyphenyl)levulinic acid di-Me acetal. This (0.1 mole), 100 ml pyridine, and 0.1 mole *p*-ClC_6H_4COCl was kept 2 hr at 25° and heated 1 hr at 50° to



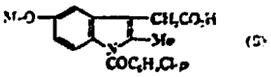
(I)

give β-[2-(*p*-chlorobenzamido)-5-methoxyphenyl]levulinic acid di-Me acetal. This (0.1 mole) in 50 ml dioxane contg. 0.2 equiv. H_2O and 0.05 equiv. HCl was heated 1 hr at 65–70° to give I (R = MeO), m. 159°. Similarly prepd. was I (R = Me_2N), m. 176–7°.

Gerard J. Toussaint

A6.43. 55250y 3-Indoleacetic acids. Chemerda, John M.; Sletzinger, Meyer (Merck and Co., Inc.) Fr. 1,555,373 (Cl. C 07*dc*), 24 Jan 1969, Can. Appl. 08 Mar 1967; 8 pp. Title compds. were prepd. Thus, 0.1 mole 5,2-$MeO(O_2N)C_6H_3CH$:$CHCO_2Et$ was reacted at 70° with 0.1 mole $EtNO_2$ in dioxane

(II)

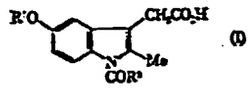


(III)

contg. 2 ml 40% $PhCH_2NMe_3OH$ to give I (R^1 = NO_2, R^2 = MeO, R^3 = $CHMeNO_2$), which with NaOH in EtOH on dropwise addn. to 2*N* H_2SO_4 gave I (R^1 = NO_2, R^2 = MeO, R^3 = Ac). The Na salt of this (0.1 mole in 100 ml H_2O) with excess NaBH, kept 4 hr at ambient temp. gave I (R^1 = NO_2, R^2 = MeO, R^3 = CHMeOH), which was hydrogenated to I (R^1 = NH_2, R^2 = MeO, R^3 = CHMeOH), 0.1 mole of which with 0.1 mole *p*-$ClC_6H_4CO_2H$ in C_6H_6 refluxed 2 hr gave I (R^1 = *p*-ClC_6H_4CONH, R^2 = MeO, R^3 = CHMeOH). This with 0.1 equiv. $MeSO_2Cl$ in 250 ml pyridine kept 3 hr at 0° gave I (R^1 = *p*-ClC_6H_4CONH, R^2 = MeO, R^3 = $CHMeO_3SMe$), which was refluxed with 5 ml F_3CCO_2H in 150 ml dioxane to give II.

Laurence M[illegible]

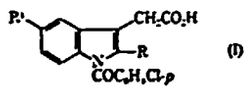
A6.44. 12563k 1-Aroyl-2-methyl-5-alkoxyindole-3-acetic acids. Pakula, Ryszard; Wojciehowski, Jani; Posliaska, Halina; Pichnej, Lidia; Ptaszynski, Leszek; Przepalkowski, Adam; Logwinienko, Roman (Lodzkie Zaklady Farmaceutyczne "Polfa") Ger., Offen. 1,816,993 (Cl. C 07d), 16 Oct 1969, Pol. Ap. 27 Dec 1967-24 May 1968; 26 pp. Derivs. of I were prepd. by acylation of a *p*-substituted phenyl-2-formylhydrazine with an acid chloride or anhydride followed by condensation with levulinic acid (II) and simultaneous cyclization in the presence of an inorg. acid. Derivs. of I possess antiinflammatory, antipyretic, and analgetic activity. Thus, 11.9 g *p*-chlorobenzoyl



(I)

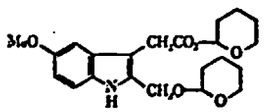
chloride was added to 35 g 1-(*p*-methoxyphenyl)-2-formylhydrazine in 160 ml abs. C_6H_6, the mixt. was boiled 2 hr, cooled, and filtered to give 47.6 g 1-(*p*-chlorobenzoyl)-1-(*p*-methoxyphenyl)-2-formylhydrazine (III), m. 102–8°. HCl (10.6 g) was bubbled through a mixt. of 47.6 g III and 160 g II, the mixt. was warmed 3 hr at 60–70°, poured into 200 ml H_2O, and filtered to give 48.6 g I (R^1 = Me, R^2 = *p*-chlorophenyl), m. 153–5° (Et_2O-petroleum ether). The following I were similarly prepd. (R^1, R^2, and m.p. given): Ph, Me, 171–2° (MeOH); *p*-chlorophenyl, Me, 154–5° (aq. EtOH); 4-pyridyl, Me, 164–5° (Me_2CO); 2-furyl, Me, 140–2° (aq. Me_2CO); 3-pyridyl, Me, 188–9° (aq. Me_2CO); 2-thienyl, Me, 141–3° (aq. Me_2CO); 2-quinolyl, Me, 198–200°; 2-pyridyl, $PhCH_2$, 202–4° (MeOH–Me_2CO); *p*-chlorophenyl, $PhCH_2$, 132–3° (70% EtOH). FDPG

A6.45. 3371u 5-Substituted-1-(p-chlorobenzoyl)-2-methylindole-3-acetic acids. Chemerda, John M.; Sletzinger, Meyer (Merck and Co., Inc.) Fr. 1,534,198 (Cl. C 07d), 26 Jul 1968, Can. Appl. 20 Aug 1966; 5 pp. The title compds. I (R = Me) are prepd. from the corresponding 2-formyl derivs. I (R = CHO) by treatment of the hydrazones with *tert*-BuOK (II) in Me_2SO. Treatment of a soln. of 3.72 g I (R = CHO, R^1 = MeO) (III) in 100 ml. EtOH with 0.64 g N_2H_4 gave the hydrazine salt (IV) of the corresponding hydrazone. To a rapidly stirred soln. of 2.24 g II in 25 ml Me_2SO, 4.19 g IV was added in small portions over 8 hr, the mixt. dild. with 200 ml H_2O and extd. with CH_2Cl_2,



(I)

(VI)



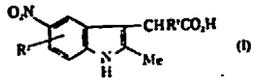
(VII)

and the aq. phase acidified to give crude I (R = Me, R^1 = MeO) (*tert*-BuOH). I (R = Me, R^1 = Me_2N) was similarly prepd. To 100 ml Me_2SO at 100° was carefully added 10 g $NaHCO_3$ followed by 5.28 g I (R = *p*-$MeC_6H_4SO_2CH_2$, R^1 = MeO) (V), the mixt. heated under N at 100° 5 min, cooled, and treated with H_2O, and the aq. phase, after extn. with CH_2Cl_2, acidified to give III. Condensation of the 5-hydroxylevulinic acid deriv. (VI) with *p*-$MeOC_6H_4NHNH_2$ in refluxing C_6H_6, filtration, and evapn. of the filtrate to give VII, acylation with *p*-ClC_6H_4COCl in Me_2NCHO in the presence of NaH, and removal of the protecting groups gave I (R = CH_2OH, R^1 = MeO), which, with *p*-$MeC_6H_4SO_2Cl$ in C_5H_5N gave V. P. Ma[illegible]alis

A6.46. 124235r α-Substituted 1-(p-chlorobenzoyl)-2-methyl-5-methoxy-3-indolylacetic acids. Chemerda, John M.; Sletzinger Meyer (Merck and Co., Inc.) U.S. 3,467,669 (Cl. 260–326.12; C 07d), 16 Sep 1969, Appl. 25 Jul 1967; 3 pp. *p*-Methoxyphenylhydrazine·HCl (10 g.), 10 g. 2-(3-butan-3-onyl)malonic acid di-*tert*-butyl ester, and 100 ml. *tert*-BuOH was refluxed 5 hrs. to give di-*tert*-butyl 2-methyl-5-methoxyindol-3-ylmalonate (I). I (5.0 g.) in 100 ml. $HCONMe_2$ was added to a slurry of 10% excess Na hydride in $HCONMe_2$, stirred at 0–5° until H evolution ceased, then 10% molar excess *p*-chlorobenzoyl chloride added

slowly, the mixt. stirred 1 hr., and quenched with H_2O to give di-*tert*-butyl 1-(*p*-chlorobenzoyl)-2-methyl-5-methoxyindol-3-ylmalonate (II). Br in Et_2O (5% excess) was added to 5 g. II in Et_2O and the soln. washed with H_2O to give di-*tert*-butyl 1-(*p*-chlorobenzoyl)-2-methyl-5-methoxyindol-3-yl-α-bromomalonate (III). III (2 g.), 100 ml. toluene, and 200 mg. *p*-toluenesulfonic acid was refluxed until isobutylene evolution ceased to give 1-(*p*-chlorobenzoyl)-2-methyl-5-methoxyindol-3-yl bromoacetic acid (IV). Pd-C (200 mg. 5%) was added to 1 g. IV in HOAc, and hydrogenated to give 1-(*p*-chlorobenzoyl)-2-methyl-5-methoxy-3-indolylacetic acid. Prepd. similarly were: *tert*-butyl-1-(*p*-chlorobenzoyl)-2-methyl-5-methoxyindol-3-yldibromoacetic acid; 1-(*p*-chlorobenzoyl)-2-methyl-5-methoxy-3-indolylacetic acid; 1-(*p*-chlorobenzoyl)-2-methyl-5-methoxyindol-3-yl-α-tosyloxyacetic acid; and 1-(*p*-chlorobenzoyl)-2-methyl-5-methoxy-3-indolylacetic acid. Aletha Kowitz

A6.47. **124232n 2-Methyl-5-nitro-3-indoleacetic acids. Carey, Daniel J.; Gal, George; Sletzinger, Meyer; Reinhold, Donald F. (Merck and Co., Inc.) Fr. 1,544,381 (Cl. C 07*d*), 31 Oct 1968, US Appl. 14 Nov 1966; 5 pp.** The title compds. (I) are intermediates in the manuf. of *N*-acylated derivs. having anti-

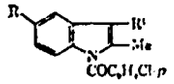


(I)

inflammatory activity. They are prepd. by reacting 4-nitrophenylhydrazine (II) (and derivs.) with levulinic acid (III) (and 2-alkyl derivs.) in the presence of concd. HCl in a sealed flask. Thus, 1.36 moles II and 1.5 moles III were added to 1.2 l. HCl and the mixt. kept 10 hrs. at 80° in a sealed system to give 29.8% I ($R^1 = R^2 = H$), which with dicyclohexylcarbodiimide was converted to the anhydride. This in *tert*-BuOH with $ZnCl_2$ was refluxed to give the *tert*-Bu ester, which (0.04 mole) in 150 ml Me_2NCHO and 0.08 mole 51% NaH (in mineral oil) in 150 ml. Me_2NCHO was stirred 1 hr. at 0° and 0.05 mole *p*-ClC_6H_4COCl in 50 ml. Me_2NCHO was added over 0.5 hr. The mixt. was stirred 0.5 hr. at 0° and kept 12 hrs. to give the 1-(*p*-chlorobenzoyl) deriv., with 10% Pd-C in *tert*-BuOH to the 5-amino analog. The ester was heated with clay chips to give the free acid. Also prepd. was [1-(*p*-thiomethyl)-2-methyl-5-dimethylamino-3-indolyl]acetic acid. M. Protiva

A6.48. **91302e 1-Benzoyl-2-methylindole-3-acetic acid derivatives. Chemerda, John M.; Sletzinger, Meyer (Merck and Co., Inc.) Fr. 1,534,488 (Cl. C 07*d*), 26 Jul 1968, Can. Appl. 25 Aug 1966; 3 pp.** To a suspension in $HCONMe_2$ of 5-methoxy-2-methyl-3-(2-nitroethyl)indole [prepd. from *p*-$MeOC_6H_4NHNH_2$.HCl and $Ac(CH_2)_2NO_2$] and 1.1 equivs. NaH, was added slowly at 0–5° 1.05 equivs. *p*-ClC_6H_4COCl, the mixt. stirred 2 hrs. at 0–5°, 100 ml. 5% AcOH added and the mixt. extd. with $CHCl_3$ to give 1-*p*-chlorobenzoyl-5-methoxy-2-methyl-3-(2-nitroethyl)indole (I). I was stirred 24 hrs. in concd. HCl at 0–10° to give 1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid. James E. Siggins

A6.49. **91208h 1-(p-Chlorobenzoyl)-2-methyl-3-indolecarbonyl halides and derivatives. Chemerda, John M.; Sletzinger, Meyer (Merck and Co., Inc.) U.S. 3,457,275 (Cl. 260-326.13; C 07*d*), 22 Jul 1969, Appl. 26 Jul 1967; 3 pp.** The title halides (I) and the corresponding III are useful in prepg. the known II. Thus, 20 g. 2-methyl-3-carboxy-5-methoxyindole, 250 ml. methylene chloride, 40 g. liq. isobutylene and 1 ml. concd. H_2SO_4 are charged into a glass autoclave and shaken 60 hrs. to give



(I, R = OX)
(II, R = CH(CO$_2$H)$_2$)
(III, R = CBr(CO$_2$H)$_2$)

tert-Bu 2-methyl-5-methoxy-3-indoleacetate (IV). To a suspension of 2.5 g. NaH in 30 ml. anhyd. Me_2NCHO (DMF) is added 12 g. IV in 100 ml. DMF at 0° under N over 50 min., then 10 g. *p*-ClC_6H_4COCl dropwise over 20 min. at 0°, let stand 1 hr. at room temp., worked up, and the product in ether treated with 1 g. *p*-$NO_2C_6H_4SO_3H$ heated to 95° under N 2 hrs. to give I (X = OH, R = MeO) (Ia). To a suspension of 5 g. (Ia) in 50 ml. anhyd. ether is added 2.5 g. freshly distd. oxalyl chloride, let stand 1.5 hr. and cooled to −10° to give I (X = Cl, R = MeO) (Ib, 5 g.) in 20 ml. ether is added dropwise to 2.8 g. CH_2N_2 in 50 ml. ether, let stand 12 hrs., the ether removed, the residue [illegible] ml. 50% $MeNH_2$ in [illegible] and [illegible] refluxed 1 hr. [illegible] cooled to [illegible] MeO). Similarly [illegible] (I, R = Me_2N). B. B. Lane

A6.50.

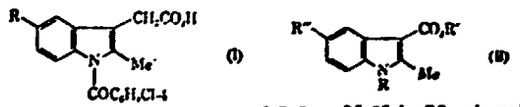
81174a 5-Methoxy- and 5-dimethylamino-1-(4-chlorobenzoyl)-2-methyl-3-indoleacetic acid Chemerda, John M.; Sletzinger, Meyer (Merck and Co., Inc.) Fr. 1,534,327 (Cl. C 07d), 26 Jul 1968, Can. Appl. 23 Aug 66; 6 pp. The title compds. (I and II) (U.S. 3,161,654, *CA* 63: 2957b) are prepd. Thus, 15.34 g. $POCl_3$ is added dropwise to 36.5 g. $HCONMe_2$ (DMF) at −5 to 0°, 8.05 g. 5-methoxy-2-methylindole are added portionwise at 20–25°, the mixt. kept 1 hr. at ambient temp., 20 g. anhyd. $CaCO_3$ added, the mixt. heated to 60° in 1 hr., cooled to 10°, added to 100 ml. 30% aq. NaOAc soln., the mixt. dild. with H_2O to 500 ml., 20 g. NaOH added, refluxed 2 hrs., cooled to 10°, and the product filtered off to give 3-formyl-5-methoxy-2-methylindole (III). III (18.92 g.) in 50 ml. DMF is added to a vigorously stirred suspension at 10° of 4.8 g. NaH (as a 50% emulsion in oil) in 25 ml. anhyd DMF, the mixt. kept 1 hr., 18 g. 4-ClC_6H_4COCl (IV) added dropwise at 0–10°, the mixt. kept 4 hrs. at 20–25°, added to 300 ml. ice water and 10 ml. HOAc, and the solid filtered off, washed, and dried in vacuo to give 1-(4-chlorobenzoyl)-3-formyl-5-methoxy-2-methylindole (V). A soln. of 2.5 g. dimethylborane in 20 ml. HOAc is added dropwise to a soln. of 10 g. V in 25 ml. HOAc, the mixt. refluxed 10 min., allowed to cool, 6 ml. cold H_2O added, and the solid filtered off, washed (H_2O), and dried in vacuo to give 1-(4-chlorobenzoyl)-5-methoxy-2-methylindole-3-methanol (VI); the 5-dimethylamino analogs of III, V, and VI are prepd. similarly. $TiCl_4$ (0.3 g.) and 2 ml. *M* PrMgBr in Et_2O is added to a soln. of 3.3 g. V in 50 ml. Et_2O, the mixt. refluxed 5 hrs. to give a soln. of 1-(4-chlorobenzoyl)-5-methoxy-2-methylindole-3-methylmagnesium bromide (VII), the latter cooled to −10°, ~10 g. finely-divided solid CO_2 added, the mixt. allowed to warm to ambient temp., added to 100 ml. iced H_2O contg. 10 ml. HOAc, the org. phase sepd., the aq. phase extd. with CH_2Cl_2, the combined org. phases washed (H_2O), dried ($MgSO_4$), concd. to dryness, and the crude I recrystd. from Me_2COH. The 5-dimethylamino analog of VII is similarly obtained and converted to II. A soln. of 17.5 g. 2,3-dimethyl-5-methoxyindole in 75 ml. anhyd. DMF is added to a suspension of 2.6 g. NaH in 15 ml. anhyd. DMF at 10° under N, and after the theoretical amt. H (2200 ml.) has evolved, the mixt. is cooled to 0°, 15.5 g. IV added dropwise (stirring) at 0–10° (external cooling), and the mixt. kept 2 hrs. at 0–10° to give 1-(4-chlorobenzoyl)-2,3-dimethyl-5-methoxyindole (VIII). A soln. of 3.14 g. VIII in 30 ml. $(CH_2OMe)_2$ contg. 2 g. PhSMe is cooled to 0°, 1.2 g. K added in small portions under N, the mixt. kept 30 min., and the PhSK filtered off to give a filtrate contg. 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-3-(potassiomethyl)indole (IX); the latter is cooled to −70°, 5 g. finely divided solid CO_2 added, the mixt. added to 50 ml. H_2O contg. 5 ml. HOAc, and the I recovered. The 5-dimethylamino analogs of VIII and IX are similarly obtained and converted to II. A soln. of 6.3 g. VIII in 50 ml. anhyd. Et_2O is cooled to 0° under Ar, and 30 ml. *M* PhLi in Et_2O added dropwise over 20 min. to give a soln. of IX 3-lithiomethyl analog which is reacted with CO_2 as for IX, to give I; II is also prepd. analogously, and PhNa or BuLi may be substituted for PhLi. $SOBr_2$ (12.8 g.) is added over 20 min. to a stirred mixt. of 3.17 g. VI, 3 g. dry $CaCO_3$, and 30 ml. anhyd. benzene, and the mixt. heated 30 min. at 40° to give 3-bromomethyl-1-(4-chlorobenzoyl)-5-methoxy-2-methylindole (X). 15 ml. *M* BuLi in Et2O is added dropwise over 5 min. to a stirred soln. of 3.2 g. X in 25 ml. tetrahydrofuran (THF) at −80°, and the soln. reacted as for IX with CO_2, to give I; the 5-dimethylamino analog of X is obtained and used similarly to give II. A soln. of 3.92 g. X in 30 ml. anhyd. THF is added over 15 min. under N to 0.5 g. Mg in 50 ml. anhyd. Et_2O to give VII, which is reacted with CO_2 to give I as before; the 5-dimethylamino analog of VII may be prepd. and reacted analogously to give II. No phys. consts. of the exemplified compds. are given.

Shirley J. Davis

A6.51. 81173z 1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-3-indoleacetic acid. Chemerda, John M.; Sletzinger, Meyer (Merck and Co., Inc.) Fr. 1,534,376 (Cl. C 07*d*), 26 Jul 1968, Can. Appl. 23 Aug 1966; 3 pp. The title compd. (I) (U.S. 3,161,654, *CA* 63: 2957b) is prepd. Thus, a mixt. of 10 g. 4-$MeOC_6H_4NHNH_2$.HCl, 10 g. $AcCH_2CH(CO_2Bu\text{-}tert)_2$, and 100 g. *tert*-BuOH is refluxed 5 hrs. to give di-*tert*-butyl 5-methoxy-2-methyl-3-indolemalonate (II); II dibenzyl ester analog is prepd. similarly. A soln. of 5 g. II in 100 ml. $HCONMe_2$ (DMF) is added to a suspension of 10% excess NaH in DMF soln., the mixt. stirred at 0–5° until evolution of H ceased, a 10% molar excess of 4-ClC_6H_4COCl added slowly, the mixt. stirred 1 hr., and excess NaH deactivated with H_2O to give di-*tert*-butyl 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-3-indolemalonate (III); III dibenzyl ester analog (IIIa) is prepd. similarly. A mixt. of 5 g. III, 100 ml. toluene, and 1 g. 4-$MeC_6H_4SO_3H$ (or $MeSO_3H$) is refluxed until the evolution of $Me_2C{:}CH_2$ ceased to give crude I, which is purified by recrystn. from *tert*-BuOH; IIIa may be decompd. similarly in HOAc until IIIa can no longer be detected with thin layer chromatog. A soln. of 5 g. IIIa in 100 ml. HOAc contg. 1 equiv. HCl is hydrogenolyzed (5% Pd-C) until absorption of H ceases, the catalyst is filtered off, the soln. heated at 30–118° until evolution of CO_2 ceases, and concd. in vacuo to give I.

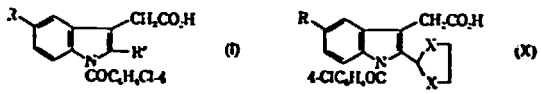
Stanley J. Davis

A6.52. 81170w 1-(*p*-Chlorobenzoyl)-2-methyl-5-(substituted)-3-indoleacetic acids. Chemerda, John M.; Sletzinger, Meyer (Merck and Co., Inc.) Fr. 1,534,328 (Cl. C 07*d*), 26 Jul 1968, Can. Appl. 23 Aug 1966; 5 pp. The title compds. (I) are prepd. by an improved process from the indole-3-carboxylic acids (II, R = R′ = H). A mixt. of 20 g. II (R = R′ = H, R″ = MeO), 250 ml. CH_2Cl_2, 40 g. isobutylene, and 1 ml. concd. H_2SO_4 was kept at room-temp. in a sealed autoclave 60 hrs. Pouring into ice-water contg. 4 g. Na_2CO_3 gave II (R = H, R′ = CMe_3, R″ =



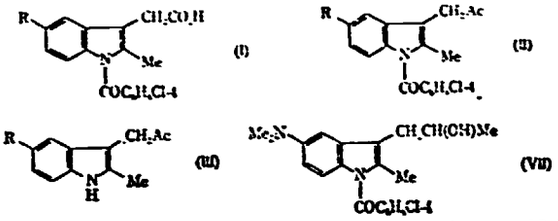
MeO) (III). To a suspension of 2.8 g. NaH in 30 ml. anhyd. Me_2NCHO was added a soln. of 26.2 g. III in 100 ml. Me_2NCHO, the mixt. stirred 0.5 hr. at 0–10°, treated dropwise with 19 g. *p*-ClC_6H_4COCl at 0–10°, and stirred 1 hr. The mixt. was poured into 400 ml. H_2O contg. 10 g. AcOH, the product extd. with PhMe, washed, dried, concd. to 100 ml., treated with 1 g. *p*-$MeC_6H_4SO_3H$, and heated under N at 90–5° for 2 hrs. to cleave the ester. Processing gave cryst. II (R = *p*-ClC_6H_4CO, R′ = H, R″ = MeO) (IV). Keeping a mixt. of 3 g. IV, 2.5 g. $(COCl)_2$, and 300 ml. dry Et_2O at room-temp. 8 hrs. and cooling to −10° gave the acid chloride, 5 g. of which in 20 ml. Et_2O was reacted with 2.8 g. CH_2N_2 in 20 ml. Et_2O to give a soln. of the diazo ketone. The resulting soln. was evapd., dissolved in 50 ml. 50% aq. MeOH, treated with 0.5 g. $PhCO_2Ag$ and 1 ml. Et_3N, and refluxed 1 hr. Acidification of the filtered soln. with 2 ml. AcOH gave I (R = MeO). By a similar process was prepd. (R = Me_2N) from II (R = R′ = H, R″ = Me_2N). P. M. Salis

AG.53. 81168b 1-(p-Chlorobenzoyl)-3-indoleacetic acid derivatives. Chemerda, John M.; Sletzinger, Meyer (Merck and Co., Inc.) Fr. 1,534,326 (Cl. C 07d), 26 Jul 1968, Can. Appl. 23 Aug 1966; 10 pp. I (R = MeO or Me_2N, R′ = Me) are prepd. by redn. of derivs. I (R = MeO or Me_2N, R = formyl or a protected formyl, or a substituted Me). Heating a mixt. of 5.28 g. I (R = MeO, R′ = $CH_2OSO_2C_6H_4Me$-*p*) (II), 70 ml. Me_2SO, and 10 g. $NaHCO_3$ 5 min. at 100°, cooling, pouring into 500 ml. H_2O, extg. with 2 × 100 ml. $CHCl_3$, and acidification gave I (R =



MeO, R′ = CHO) (III). I (R = Me_2N, R′ = CHO) (IV) was similarly prepd. Stirring a mixt. of 0.1 mole II and 0.1 mole LiCl in 100 ml. Me_2CO 48 hrs. at 25° gave I (R = MeO, R′ = CH_2Cl) (V). I (R = Me_2N, R′ = CH_2Cl) (VI) was similarly prepd. Treatment of 0.1 mole II in 200 ml. MeOH with 0.2 mole NaSMe in MeOH at 25° 48 hrs. gave I (R = MeO, R′ = CH_2SMe) (VII) from which the sulfone I (R = MeO, R′ = CH_2SO_2Me) was prepd. by oxidn. By similar methods were prepd. I (R = Me_2N, R′ = CH_2SMe and R′ = CH_2SO_2Me), I (R = MeO, R′ = CH_2NMe_2) (VIII) and I (R = Me_2N, R′ = CH_2NMe_2) (IX). To a stirred mixt. of 10 ml. $HSCH_2CH_2SH$, 1.25 g. $ZnCl_2$, and 1 g. Na_2SO_4 at 5° was added 3.72 g. III and the mixt. stirred for 24 hrs. at 5° and at room-temp. 4 hrs. to give X(X = S, R = MeO) (XI) crystd. from *tert*-BuOH. X (X = S, R = Me_2N) was similarly prepd. and crystd. from aq. EtOH. X (X = O, R = MeO) (crystd. from *tert*-BuOH) was prepd. by refluxing a mixt. of 0.01 mole III, 10 ml. $HOCH_2CH_2OH$, and 0.1 g. *p*-$MeC_6H_4SO_3H$ in 100 ml. C_6H_6 with removal of the H_2O formed. X (X = O, R = MeO) was similarly prepd. Stirring a mixt. of 0.1 mole II, 0.1 mole NaOAc, and 100 ml. AcOH for 18 hrs. at 25° gave I (R = MeO, R′ = CH_2OAc); I (R = Me_2N, R′ = CH_2OAc) was also prepd. Reacting 5-hydroxylevulinic acid (XII) in tetrahydrofuran (THF) with 2.1 equivs. dihydropyran and a few drops concd. HCl gave the *O*-(tetrahydropyranyl)ether tetrahydropyranyl ester (XIII) of XII purified by distn. Refluxing XIII with 1 equiv. *p*-$MeOC_6H_4NHNH_2$.HCl in dry C_6H_6 for 5 hrs., filtering, and evapg. gave pyranyl 5-methoxy-2-pyranyloxymethyl-3-indoleacetate which was converted to the *N*-(*p*-chlorobenzoyl) deriv., and deesterified by stirring at room-temp. with a little concd. HCl in *tert*-BuOH. The product, I (R = MeO, R′ = CH_2OH) (XIIIa) was converted to II by normal tosylation. I (R = Me_2N, R′ = CH_2OH) was prepd. by a similar process. Treating a soln. of 3.72 g. III in 100 ml. EtOH with 3 g. amalgamated Zn and 5 ml. concd. HCl and refluxing 24 hrs., gave after filtering, pouring into H_2O, collecting the solid, and crystg. from *tert*-BuOH, I (R = MeO, R′ = Me) (XIV). I (R = Me_2N, R′ = Me) (XV) was similarly prepd. from IV. XIV was also obtained by heating a soln. of 3.72 g. III in 100 ml. EtOH with 4 g. Raney Ni W2 and H at 105 bars pressure and 80°. Hydrogenation of 3.93 g. V in 200 ml. 95% EtOH contg. 10 ml. *N* NaOH with H and 0.5 g. Pd catalyst gave XIV. Similar redn. of VI gave XV. V and VI were also reduced with Zn and HCl in EtOH to give XIV and XV, resp. In a further process, XIV was prepd. by refluxing together a mixt. of 4.04 g. VII, 20 g. Raney Ni, and 300 ml. EtOH for 2 hrs. The same product was analogously obtained from XI. Hydrogenation of 5.29 g. VIII methiodide in 100 ml. H_2O contg. 2.5 g. NaOAc with 0.1 g. Pt and H gave XIV after 4 hrs. at room temp. and pressure. Catalytic redn. of 4.01 g. VIII in 100 ml. EtOH with H and 0.25 g. Pd/C catalyst also gave XIV. IX similarly yielded XV. [illegible] XIIIa. Refluxing a soln. of 3.84 g. I (R = MeO, R′ = CH_2OMe) (prepd. from II and NaOMe in MeOH) and 4 g. diisobutylaluminum hydride in 100 ml. THF for 4 hrs., pouring into 0.5 l. ice-water, and acidifying with dil. HCl gave XIV. XV was similarly prepd. XIV and XV were also prepd. by treatment of V and VI, resp., with Mg in THF. P. Mastagli

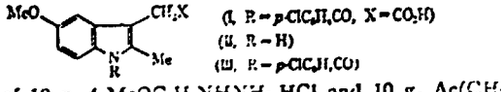
AG.54. 81166z 1-(p-Chlorobenzoyl)-2-methylindoleacetic acid derivatives. Chemerda, John M.; Sletzinger, Meyer (Merck and Co., Inc.) Fr. 1,534,375 (Cl. C 07d), 26 Jul 1968, Can. Appl. 23 Aug 1966; 4 pp. The title compds. (I) are prepd. by oxidn. of ketones (II) with a hypochlorite or hypobromite. Refluxing a mixt. of 17.4 g. *p*-$MeOC_6H_4NHNH_2$.HCl and 14 g. [illegible]-one in 100 ml. *tert*-BuOH 6 hrs. and work-up gave II. [illegible]



(IV). A soln. of 5 g. IV in Me_2NCHO contg. 10% excess NaH was treated with 1.05 equivs. *p*-ClC_6H_4COCl at 0–5°, stirred at 0–5° for 2 hrs., and treated with 5% aq. AcOH to give II (R = MeO) (V). Treatment of 2 g. V in 20 ml. dioxane with a 10% excess over theory of NaOCl and 2 g. NaOH, stirring at 35° for 1 hr., addn. of 10% $NaHSO_3$ to destroy excess reagent, adjusting to pH 2 with HCl, and extg. with $CHCl_3$ gave I (R = MeO). By similar methods were prepd. III (R = NO_2)(purified on Al_2O_3) and II (R = NO_2) (VI). A mixt. of 3.2 g. VI, 40 ml. MeOH, 17.2 ml. AcOH, 61 ml. aq. 36–8% CH_2O, and 2.1 g. Raney Ni was shaken with H at 50° and 2.8 kg./cm.^{2} 24 hrs. to give II (R = Me_2N) contg. some alc. VII. Oxidn. of 2 g. of the foregoing mixt. in 20 ml. dioxane with excess 10% aq. NaClO and 2 g. NaOH 1 hr. at 35° gave I (R = Me_2N). P. Mamalis

A6.55- 81159z High purity 1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid. Sletzinger, Meyer; Gal, George; Chemerda, John M. (Merck and Co., Inc.) Fr. 1,540,724 (Cl. C 07*d*, A 61*k*), 27 Sep 1968, US Appl. 13 Oct 1966-14 Aug 1967; 5 pp. The title compd. (I) is prepd. in higher purity and yield, compared with a prior method in which a hydrazone intermediate is used. I is a well known antiinflammatory agent, and it also prevents the formation of granuloma tissue. Thus, a soln. of *p*-$MeOC_6H_4NHNHSO_3Na$ (II) in 210 ml. water and 90 ml. *tert*-BuOH was treated with 29.7 ml. *p*-ClC_6H_4COCl, stirred 1 hr. at 25° and 1 hr. at 75–80°, and treated at 80° with 350 ml. toluene and 76.6 ml. 25% NaOH. The aq. phase was sepd. and extd. with 150 ml. toluene at 80°. The combined toluene extns. (~700 ml.) were washed with 150 ml. hot water (80°), concd. to 200 ml. at 75°/508 mm. to remove the *tert*-BuOH, dild. to 700 ml. with toluene, heated to 80°, treated with 57.7 ml. 85–9% H_3PO_4, stirred for 15 min., treated with 25.5 ml. levulinic acid, refluxed for 90 min. while the water of reaction was sepd., cooled to 80°, mixed with 250 ml. hot water (80°), and stirred 5 min. The aq. layer sepd. and extd. with 150 ml. hot toluene (80°). The ext. was washed with 150 ml. hot water. Work up gives I, m. 157–9°. I can also be prepd. without the use of *tert*-BuOH in the initial acylation step. To demonstrate the direct acylation of the α-N of II, a soln. of II in aq. dioxane contg. NaOH is treated with *p*-ClC_6H_4COCl to prep. (*p*-$MeOC_6H_4$)(*p*-ClC_6H_4CO)$NNHSO_3Na$, m. 200° (decompn.), which is also refluxed with ethanolic HCl to prep. (*p*-$MeOC_6H_4$)(*p*-ClC_6H_4CO)NNH_2.HCl, m. 179–80°. VNPF

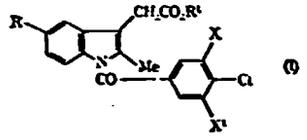
A6.56- 81158y 1-(p-Chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid. Chemerda, John M.; Sletzinger, Mayer (Merck and Co., Inc.) Fr. 1,534,459 (Cl. C 07*d*), 26 Jul 1968, Can. Appl. 23 Aug 1966; 9 pp. The title compd. (I) is prepd. Thus,



(I, R = *p*-ClC_6H_4CO, X = CO_2H)
(II, R = H)
(III, R = *p*-ClC_6H_4CO)

a mixt. of 10 g. 4-$MeOC_6H_4NHNH_2$.HCl and 10 g. $Ac(CH_2)_2CH:CMe_2$ in 100 ml. *tert*-BuOH is refluxed 6 hrs. to give II (X = $CH:CMe_2$) (IIa); similarly obtained are II [X = $CCl:CH_2$, $CH:CHCl$, $CH:CClMe$, $C(OH):CHMe$, $C:CH$, $C:CMe$, or $CH(OH)Me$]. IIa (10 g.) is added to 3 g. of a 50% NaH emulsion in 100 ml. $HCONMe_2$, followed by 8.5 g. *p*-ClC_6H_4COCl at 0–5°, the mixt. stirred 2 hrs., and excess NaH decompd. to give III (X = $CH:CMe_2$) (IIIa); similarly obtained are III (X = $CCl:CH_2$, $CH:CHCl$, $CH:CClMe$, $C:CH$, or $C:CMe$; to prep. III (X = $C(OH):CHMe$) (IIIb) or III (X = $CH(OH)Me$), the oxidopyran adduct is first formed in the presence of *p*-$MeC_6H_4SO_3H$. Powd. $KMnO_4$ is added over 5 hrs. to 2 g. IIIb in 100 ml. Me_2CO at 25° and the mixt. stirred ~16 hrs., to give III (X = $COCO_2H$) (IIIc); similarly, III (X = $CH(OH)CMe_2OH$) (IIId) is obtained from IIIa. Aq. NaOH (1 equiv.) is added to a mixt. of 2 g. IIIc in 100 ml. H_2O contg. a 10% molar excess of 30% H_2O_2 and the mixt. stirred 5 hrs. at 0° to give I. A satd. soln. of CrO_3 (10% excess) in HOAc is added to 5 g. IIId in 100 ml. HOAc and the mixt. stirred 16 hrs. to give I. IIId may also be oxidized [illegible] to give III (X = $COCMe_2OH$) (IIIe). A satd. soln. of Me_2CO with [illegible] $KMnO_4$ also gives I. NaH replace $KMnO_4$. [illegible] obtained by the $KMnO_4$ [illegible] IIIe or III (X = $CCl:CH_2$, $CH:CHCl$, $CH:CClMe$, $C:CH$, $CHMe$, $C:CH$, $C:CMe$, or $CH(OH)Me$). No phys. [illegible] the compds. are given. (Stanley [illegible]

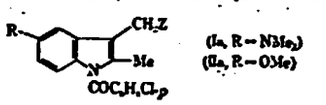
A6.57. 70494d Derivatives of 1-(p-chlorobenzoyl)-2-methyl-3-indolylacetic acid. Chemerda, John M.; Sletzinger, Meyer (Merck and Co., Inc.) Fr. 1,534,489 (Cl. C 07d), 25 Jul 1968, Can. Appl. 25 Aug 1966; 5 pp. Treatment of esters of 5-MeO or 5-Me_2N derivs. of 2-methyl-3-indolylacetic acid in Me_2NCHO with NaH, then with derivs. of *p*-chlorobenzoyl chloride gave the following title compds. (I) (R, R¹, X, and X¹ given): MeO,



(I)

$PhCH_2$, Br, H; Me_2N, $PhCH_2$, Br, H; MeO, $PhCH_2$, I, H; Me_2N, $PhCH_2$, I, H; MeO, $PhCH_2$, Br, Br; Me_2N, $PhCH_2$, Br, Br; MeO, $PhCH_2$, I, I; Me_2N, $PhCH_2$, I, I; MeO, Me_3C, Br, H; Me_2N, Me_3C, 3-Br, H. Action of *p*-$MeC_6H_4SO_3H$ in refluxing PhMe on the Me_3C esters yields the corresponding acids. Hydrogenolysis of the $PhCH_2$ esters replaces the 3- and 5-halogens and the $PhCH_2$ by H. L. R. Caswell

A6.58. 70490z 5-Dimethylamino- and 5-methoxy-1-(p-chlorobenzoyl)-2-methylindole-3-acetic acids. Chemerda, John M.; Sletzinger, Meyer (Merck and Co., Inc.) Fr. 1,534,458 (Cl. C 07d), 26 Jul 1968, Can. Appl. 23 Aug 1966; 5 pp. The title compds., Ia (Z = CO_2H) and IIa (Z = CO_2H) (II) are

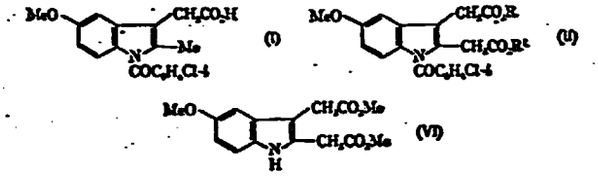


(Ia, R = NMe_2)
(IIa, R = OMe)

prepd. I was prepd. by the carbonylation of 5-dimethylamino-1-(*p*-chlorobenzoyl)-2-methyl-3-indolylmethanol Ia (Z = OH) (III), Ia (Z = Cl) (IV), or Ia (Z = Br) (V). Similarly, II are prepd. from IIa (Z = OH) (VI), IIa (Z = Cl) (VII), or IIa (Z = Br) (VIII). Thus, a mixt. of 3.2 g. III, 0.3 g. H_2O, 0.8 g. $Ni(CO)_4$, 0.2 g. $NiCl_2$, and 0.3 g. concd. HCl was placed in a stainless steel autoclave with an enamel liner, of vol. 20 ml., and CO added to 63 bars. The mixt. was heated at 200° for 6 hrs. to give I. A mixt. of 50 ml. CCl_4 and 4.8 g. III is placed in an autoclave and 1 ml. BF_3 added at 4–5 bars. CO was added to 600 bars which was held for 9 hrs. After release of gas, the product was washed with water, evapd., and crystd. from BuOH to give I. II was similarly prepd. To a mixt. of 36.5 g. Me_2NCHO and 15.34 g. $POCl_3$ at −5°, was added 8.06 g. 2-methyl-5-dimethylaminoindole at 20–25°. After 1 hr. at room temp., 20 g. $CaCO_3$ was added and the mixt. heated to 60° for 1 hr. and cooled to 10°, 100 ml. 30% NaOAc added, H_2O added to make 500 ml., and 20 g. NaOH added. Refluxing the mixt. for 2 hrs. and cooling to 10° gave 2-methyl-5-(dimethylamino)indole-3-carboxaldehyde (IX). To a mixt. of 25 ml. Me_2NCHO and 4.8 g. NaH (as 50% emulsion in oil) were added 17.5 g. IX in 50 ml. Me_2CHO at 10°. After 1 hr., 18 g. 4-chlorobenzoyl chloride was added and the mixt. stirred at 20–25° for 4 hrs. and dild. with H_2O to give the benzoyl deriv. (X) of IX. Dimethylborane (2.5 g.) was added to a suspension of 9.2 g. X in 25 ml. HOAc, the mixt. refluxed for 10 min., cooled, dild. with 6 ml. H_2O, adjusted to pH 7–7.5, and III removed by filtration. A mixt. of 31.77 g. III, 30 g. $CaCO_3$, and 300 ml. C_6H_6 was stirred and 11.9 g. $SOCl_2$ added over 30 min. The mixt. was heated to 40° for 30 min. and filtered and the cake extd. with C_6H_6 to give IV. V–VIII were prepd. by similar procedures. No phys. data or yields of any of the compds. were given. Leonard F. Dixon

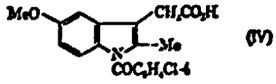
A6.59. 70466e 5-Dimethylamino- and 5-methoxy-1-(p-chlorobenzoyl)-2-methylindole-3-acetic acids. Chemerda, John M.; Sletzinger, Meyer (Merck and Co., Inc.) Fr. 1,534,460 (Cl. C 07d), 26 Jul 1968, Can. Appl. 25 Aug 1966; 3 pp. The title compds. (I and II) are prepd. by the redn. of the corresponding nitrobenzoyl compds. (III and IV) to the amines (V and VI), followed by Sandmeyer reactions. Thus, 0.01 mole IV, 100 ml. EtOH, and 1.5 g. 10% Pd/C catalyst was hydrogenated at 3 bars H to give VI. VI (0.01 mole) was dissolved in 25 ml. dil. HCl and diazotized. The soln. was added over 0.5 hr. to 10 ml. of a boiling 10% soln. of CuCl in HCl. When all the N had evolved the solid was collected and crystd. from *tert*-BuOH to give II. I was prepd. by a similar series of reactions. No phys. consts. or yields given. Leonard F. Dixon

A6.60. 61211g 1-p-Chlorobenzoyl-2-methyl-3-indolylacetic acids. Chemerda, John M.; Sletzinger, Meyer (Merck and Co., Inc.) Fr. 1,534,556 (Cl. C 07*d*), 26 Jul 1968, Can. Appl. 25 Aug 1966; 6 pp. I is prepd. by decarboxylation of II (R = R¹ = H) (III). Thus, to 0.01 mole 1-(*p*-chlorobenzoyl)-5-methoxyindole in 100 ml. tetrahydrofuran (THF) was added 0.021 mole CHN_2CO_2Me in 25 ml. THF. After 15 min. the mixt. was exposed to uv light until the evolution of N stopped to yield II (R = R¹ = Me) (IV). Similarly, reaction of 1-(*p*-chlorobenzoyl)-5-methoxy-3-indolylacetic acid with CHN_2CO_2Me in THF afforded II (R = H, R¹ = Me) (V). V (0.01 mole), 8.5 g. LiI, and 200 ml. 2,6-lutidine was refluxed 8 hrs. under N, cooled, 100 ml. $CHCl_3$ and 100 ml. 2*N* HCl added and the $CHCl_3$ layer worked up to yield III. Similar treatment of IV afforded III.



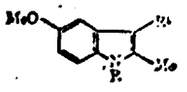
Heating 26.64 g. $4\text{-MeOC}_6H_4NH_2$ and 26.71 g. $MeO_2CCH_2CO\text{-}CHBrCH_2CO_2Me$ 3 hrs. at 100° under N yielded VI. To 5 g. 50% NaH in 50 ml. $HCONMe_2$ at 5° was added 27 g. VI in 300 ml. $HCONMe_2$. After 1 hr., 24 g. 4-ClC_6H_4COCl was added in 1 hr. to yield IV which on treatment with LiI and 2,6-lutidine yielded V. Refluxing 0.01 mole III in 100 ml. $1,2\text{-Cl}_2C_6H_4$ until the evolution of CO_2 stopped afforded I. The identical reaction sequence is described for the 5-dimethylamino compds.

A6.61. 61209n 1-(p-Chlorobenzoyl)-2-methyl-5-methoxy-3-indolacetic acid. Chemerda, John M.; Sletzinger, Meyer (Merck and Co., Inc.) Fr. 1,534,487 (Cl. C 07*d*), 26 Jul 1968, Can. Appl. 23 Aug 1966; 4 pp.; (cf. U.S. 3,161,654). From 10 g. $p\text{-MeOC}_6H_4NHNH_2$ and 10 g. $PrCOCH(CO_2CMe_3)_2$ in 100 ml. *tert*-BuOH, refluxed 5 hrs., was obtained di-*tert*-butyl 2-methyl-5-methoxy-3-indolmalonate (I). Action of a 10% mole excess $p\text{-ClC}_6H_4COCl$ on 5 g. I and 10% mole excess NaH in 100 ml. Me_2NCHO gave di-*tert*-butyl 1-(*p*-chlorobenzoyl)-2-methyl-5-methoxy-3-indolmalonate, bromination of which gave di-*tert*-butyl 1-(*p*-chlorobenzoyl)-2-methyl-5-methoxy-3-indolyl-α-bromomalonate (II). Refluxing 2 g. II in 100 ml. PhMe contg. 0.2 g. $p\text{-MeC}_6H_4SO_3H$ gave 1-(*p*-chlorobenzoyl)-2-methyl-5-methoxy-3-indolbromoacetic acid (III). Action of H on 1 g. III and 0.2 g. 5% Pd–C in HOAc gave the title compd. (IV). Action of 0.1 g. $p\text{-MeC}_6H_4SO_3H$ on 5 g. II in refluxing PhMe gave *tert*-butyl 1-



(*p*-chlorobenzoyl)-2-methyl-5-methoxy-3-indolbromoacetate, bromination of which gave *tert*-butyl 1-(*p*-chlorobenzoyl)-2-methyl-5-methoxy-3-indoldibromoacetate (V). Hydrolysis of V gave 1-(*p*-chlorobenzoyl)-2-methyl-5-methoxy-3-indoldibromoacetic acid, which was hydrogenolyzed to give IV.

A6.62. 61204g 1-(p-Chlorobenzoyl)-2-methyl-5-methoxy-3-(2-nitroethyl)indole. Chemerda, John M.; Sletzinger, Meyer (Merck and Co., Inc.) U.S. 3,449,364 (Cl. 260–325.16; C 07*d*), 10 Jun 1969, Appl. 25 Jul 1967; 2 pp. Refluxing 17.4 g. $p\text{-MeOC}_6H_4\text{-}NHNH_2.HCl$ and 15 g. 5-nitro-2-pentanone 6 hrs. in 100 ml. *tert*-BuOH gave 2-methyl-5-methoxy-3-(2-nitroethyl)indole (I, R = H, R¹ = $CH_2CH_2NO_2$) (Ia). Ia (10 g.) in $HCONMe_2$ contg. 1.1 equivs. NaH, treated slowly with 1.05 equivs. $p\text{-ClC}_6H_4COCl$ kept 2 hrs. at 0–5° before 100 ml. 5% aq. HOAc was added, gave the title compd. (I, R = $p\text{-ClC}_6H_4CO$, R¹ = $CH_2CH_2NO_2$) (II). II (2 g.) was stirred 24 hrs. in concd. HCl



at 0–10°, and H_2O was added to give 1-*p*-chlorobenzoyl-2-methyl-5-methoxyindole-3-acetic acid (I, R = $p\text{-ClC}_6H_4CO$, R¹ = CH_2CO_2H) (III). Thus, II is a useful intermediate for prepn. III (*CA* 63: 2957b).

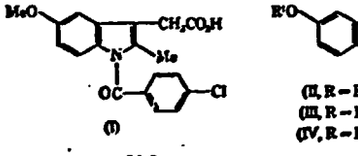
P. E. Shaw

A6.63. 115605t 1-(p-Chlorobenzoyl)-2-methyl-5-methoxyindole-3-acetic acid. Tani, Hidero; Otani, Motoharu; Mizutani, Naoshi; Mashimo, Katsumi (Kowa Co., Ltd.) Japan. 69 05,224 (Cl. 16 E 332), 04 Mar 1969, Appl. 05 Jul 1966; 2 pp. Treatment of 1-(*p*-chlorobenzoyl)-4-acetyl-6-methoxy-3,4-dihydrocarbostyril (I) with acid gives the title product (II), useful as an antiinflammatory drug. In an example, 290 mg. I in 10 ml. Me_2CO is heated 5.5 hrs. with 0.5 ml. 10% HCl and evapd., the residue dissolved in Et_2O, the soln. washed with H_2O, extd. with 5% Na_2CO_3 soln., and the ext. acidified with HCl, and extd. with Et_2O to give 170 mg. II, needles, m. 154–5° (aq. MeOH).
Hiroshi Kataoka

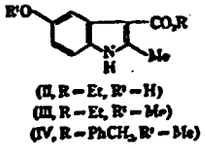
A6.64. 106381k Indole aliphatic acids. Merck and Co., Inc. Brit. Amended 1,050,735 (Cl. C 07*d*), 07 Dec 1966, US Appl. 01 Feb 1963; 5 pp. Division of Brit. 1,050,728 (See Neth. Appl. 64 00,813, *CA* 62: 4009a). Same disclosure. Changes in wording in the introduction.
SNWV

A6.65. 87569j 3-(Carboxymethyl)-1-(p-chlorobenzoyl)-5-methoxy-2-methylindole. Christensen, Svend A. (Aktieselskabet Dumex (Dumex Ltd.)) Brit. 1,130,429 (Cl. C 07*d*), 16 Oct 1968, Appl. 04 Jul 1966; 2 pp. The title compd. (I) useful as an antiinflammatory and antipyretic agent is prepd. by treatment of 4-acetyl-1-(*p*-chlorobenzoyl)-6-methoxy-3,4-dihydrocarbostyril (II) with HCl. A mixt. of 0.29 g. II, 0.5 ml. 10% HCl, and 10 ml. Me_2CO was refluxed for 5.5 hrs. and evapd. and the residue dissolved in Et_2O and filtered. Extn. of the filtrate with aq. $NaHCO_3$ and acidifying the ext. to pH 2 gave I, m. 151–3° (aq. MeOH).
P. Mamalis

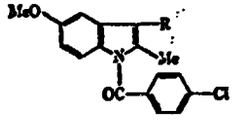
A6.66. 77786p 1-(p-Chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid. Christensen, Svend A. (Aktieselskabet Dumex (Dumex Ltd.)) Brit. 1,131,545 (Cl. C 07*d*), 23 Oct 1968, Appl. 22 Apr 1966; 4 pp. The title compd. (I) is prepd. Thus, *p*-benzoquinone is treated with $MeC(NH_2):CHCO_2Et$ to give 2-methyl-3-carbethoxy-5-hydroxyindole (II), m. 205°. II is treated with Me_2SO_4 to give III; III is treated with $PhCH_2OH$ to



(I)



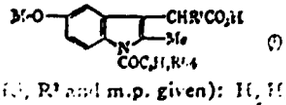
(II, R = Et, R' = H)
(III, R = Et, R' = Me)
(IV, R = $PhCH_2$, R' = Me)



(V, R = CO_2CH_2Ph)
(VI, R = CO_2H)
(VII, R = COCl)
(VIII, R = $COCHN_2$)

give benzyl ester IV. IV is treated with *p*-ClC_6H_4COCl to give benzyl 1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-carboxylate (V); V is hydrogenated over 1% Pd–C at 3 atm. to give acid VI; and VI is treated with $SOCl_2$ to give VII. VII is treated with CH_2N_2 in ether to give diazo ketone VIII; a soln. of VIII in dioxane is added to a suspension of $AgNO_3$ in 1% $Na_2S_2O_3$ at 50°, and the mixt. is acidified to yield I.
BDPN

A6.67. 77783k Antiinflammatory N-benzoylindoles and thieno[3,4-b]indoles. Sorrentino, Pasquale D. (Aktieselskabet Dumex (Dumex Ltd.)) S. African 68 01,254, 18 Jul 1968, Brit. Appl. 28 Feb 1967; 8 pp. Indole derivs. (I) are prepd. by catalytically reducing dihydrothiopheno-3',4':2,3-indole derivs. Thus, 3.2 g. *N*-(*p*-methoxyphenyl)-*N*-(*p*-chlorobenzoyl)hydrazine·HCl and 2 g. 4-thiophanone-2-carboxylic acid in 15 ml. AcOH was stirred and heated to 80° for 3 hrs., cooled to room temp. and the mixt. poured into 50 ml. H_2O to ppt. *N*-(*p*-chlorobenzoyl)-5-methoxy-2'-carboxydihydrothiopheno 3',4':2,3-indole, 3 g. of which was added to 30 g. Raney Ni suspended in 500 ml. EtOH and the mixt. boiled gently 4 hrs. to give *N*-(*p*-chlorobenzoyl)-5-methoxy-2-methyl-3-indoleacetic acid m. 151°. Similarly prepd. were

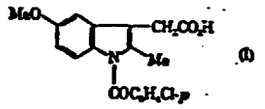


(I)

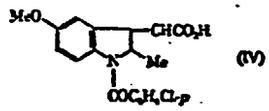
the following I (R, R' and m.p. given): H, H, [illegible], [illegible], Cl, 87–8°.
[illegible]

A6.68.

106549z 1-(p-Chlorobenzoyl)-2-methyl-5-methoxy-3-indoleacetic acid. Gal, George (Merck and Co., Inc.) U.S. 3,397,211 (Cl. 260–326.13), 13 Aug 1968, Appl. 09 Sep 1966; 3 pp. The title acid (I) is prepd. Thus, 5,2-MeO(H_2N)C_6H_3CH:CH-CO_2H is treated with *p*-ClC_6H_4COCl in the presence of 12*N*



(I)



(IV)

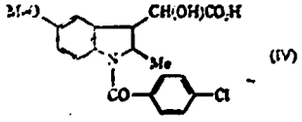
NaOH at 30–40° to give 5,2-MeO(*p*-ClC_6H_4CONH)C_6H_3CH:CH-CO_2H (II). II (33.2 g.) is treated with 5.0 g. AcH in 100 ml. HOAc 2 hrs. at 60–70° to give *N*-(α-hydroxyethyl)-2-(*p*-chlorobenzamido)-5-methoxycinnamic acid (III). A mixt. of 5 g. III, 100 mg. *p*-$MeC_6H_4SO_2H$, and 100 ml. ether is kept 12 hrs. at −20° to give IV. IV (5 g.) is added to a soln. of 0.5 g. H_3PO_4 in 20 ml. HOAc and the mixt. is refluxed 2 hrs. to give I, m. 158–60°. A mixt. of 33.2 g. II, 100 ml. HOAc, 5.0 g. AcH, and 0.5 g. 85% H_3PO_4 is agitated 2 days at room temp. to give I. The following 2,5-$RR^1C_6H_3CH(OEt)_2$ (R and R^1 given): Cl, NO_2; NH_2, NO_2; AcNH, NO_2; and the following compds.: 2,5-H_2N-(Me_2N)C_6H_3CHO, 2,5-AcNH(Me_2N)C_6H_3CH:$CHCO_2H$, 2,5-H_2N(Me_2N)C_6H_3CH:$CHCO_2H$, are prepd. according to known methods. BDPN

A6.69.

96464c N-Acylated carboxylic acid derivatives. Ecsery, Zoltan; Kosa, Ildiko; Seress, Jeno; Somfai, Eva; Milak, Mrs. Zoltan; Somfai, Zsuzsa; Daroczi, Mrs. Istvan (Chinoin Gyogyszer es Vegyeszeti Termekek Gyara Rt.) Hung. 154,933 (Cl. C 07*cd*), 25 Jul 1968, Appl. 22 Aug 1965; 7 pp. *tert*-Bu *N*-(*p*-chlorobenzoyl)-2-methyl-5-methoxyindole-3-acetate (1 g.), 10 ml. C_6H_6, and 1.5 g. CCl_3CO_2H is refluxed for 3 hrs. to give 100% *N*-(*p*-chlorobenzoyl)-2-methyl-5-methoxyindole-3-acetic acid, m. 151–3° (96% EtOH). *N*-Acetylanthranilic acid, m. 182–4°, was obtained similarly from *tert*-Bu *N*-acetylanthranilate, m. 79–81°, which was obtained from 2-methyl-3,1-benzoxazin-4-one with *tert*-BuONa. T. Mohacsi

A6.70.

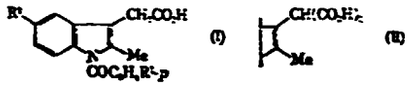
67217u Indole-3-acetic acids. Gal, George (Merck and Co., Inc.) U.S. 3,390,154 (Cl. 260–326.13), 25 Jun 1968, Appl. 09 Sep 1966; 3 pp. The title compds. are prepd. by reducing a 3-indolylglyoxalate or glyoxalic acid to form a 3-indolineglycolic acid or ester, acylating the glycolic compds., and finally heating the *N*-acyl compd. in the presence of an acid. Thus, 25 ml. oxalyl chloride was added dropwise over 30 min. to 0.25 mole 2-methyl-5-methoxyindole in 500 ml. anhyd. Et_2O at 0–5°. After 1 hr. at 0–5°, 25 g. anhyd. MeOH was added over 30 min., the solvents were removed in vacuo, and the residue was recryst.



(IV)

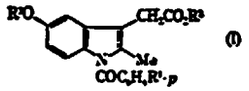
from MeOH to give Me 2-methyl-5-methoxy-3-indolylglyoxalate (I). I was reduced with Al amalgam to Me 2-methyl-5-methoxy-3-indoleglycolate (II). I and II were both hydrogenated in basic aq. soln. with Raney Ni to 2-methyl-5-methoxy-3-indoleglycolic acid (III). *p*-ClC_6H_4COCl (18 ml.) was added to 41.5 g. III in 21 ml. 1*N* NaOH which was maintained at ab. pH 9 and 40° during addn., and the mixt. worked up to give 1-(*p*-chlorobenzoyl)-2-methyl-5-methoxy-3-indolineglycolic acid (IV). A mixt. of 37.5 g. IV in 300 ml. benzene and 3.0 g. *p*-$MeC_6H_4SO_3H$ in 25 ml. glacial AcOH was refluxed and freed of water by azeotropic distn. When the theoretical amt. of water had been collected, the mixt. was worked up to give 1-(*p*-chlorobenzoyl)-2-methyl-5-methoxy-3-indoleacetic acid, m. 150–[illegible]. The 5-dimethylamino compd. can also be prepd. These compds. are useful as antiinflammatory agents.

A6.71. 35940h 1-Benzoylindole-3-acetic acid derivatives. Yamamoto, Hisao; Nakao, Masaru (Sumitomo Chemical Co., Ltd.) Japan. 67 24,501 (Cl. 16 E 332), 25 Nov 1967, Appl. 07 Dec 1965; 2 pp. Manuf. of I, useful as antiphlogistic, analgesic, and antipyretic agents, by heating II is described. In an example, 2 g. II (R^1 = Cl, R^2 = OMe) is heated 20 min., the product cooled and extd. with 5 ml. AcOH, 15 ml. H_2O added to the ext., and the ppt. washed with H_2O to give I (R^1 = Cl, R^2 = OMe), m. 151–3°



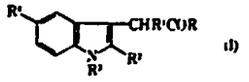
(dil. EtOH). Similarly prepd. are the following I (R^1, R^2, and m.p. given): Cl, OEt, 162–4°; H, Cl, 169–72°; Cl, F, 145–50°; Me, OMe, 154–6°; OMe, OMe, 158–60°. Hiroshi Kataoka

A6.72. 104976t N-Benzoylindole derivatives. Sumitomo Chemical Co., Ltd. (by Hisao Yamamoto, Katsu Nakao, and Isamu Maruyama). Japan. 15,092('67) (Cl. 16 E 332), Aug. 22, Appl. April 19, 1965; 3 pp. Manuf. of I, useful as analgesics is described. In an example, a mixt. of 2 g. N^1-(*p*-methoxyphenyl)-N^1-(*p'*-chlorobenzoyl)hydrazine-HCl and 8.5 g. levulinic acid is heated at 70° for 3 hrs., let stand overnight, and washed with 60 ml. cold H_2O to give I (R^1 = Cl, R^2 = H, R^3 = Me), m. 157–8° (Et_2O),



quant. Similarly prepd. are the following I (R^1, R^2, R^3, and m.p. given): Cl, Me, Me, 89–90° (50% MeOH); Cl, H, Et, 161–4° (dil. EtOH); Br, H, Me, 162–4° (dil. EtOH); F, H, Me, 148–50° (dil. EtOH). Hiroshi Kataoka

A6.73. 29596p Indolyl acid amides. Tsung-Ying Shen (to Merck & Co., Inc.). U.S. 3,336,194 (Cl. 167–65), Aug. 15, 1967, Appl. April 30 and Nov. 18, 1963; 13 pp. The title compds. (I) are useful antiinflammatory agents. A soln. of 25 g. *p*-$MeOC_6H_4$-

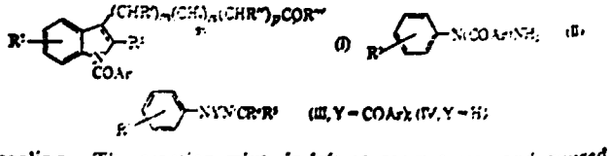


$NHNH_2$.HCl and 20 g. Et α-methyllevulinate in 250 ml. 2.N ethanolic-HCl was heated on the steam bath a few min., the spontaneous refluxing allowed to subside, the mixt. again refluxed on the steam bath 30 min., concd. in vacuo to 80 ml., dild. with 400 ml. H_2O, and extd. with Et_2O, and the Et_2O ext. worked up in the usual manner to yield an oil which was chromatographed over acid-washed alumina and distd. in a short-path distn. app. to give I (R = OEt, R^1 = Me, R^2 = Me, R^3 = H, R^4 = MeO) (Ia), $b_{0.3}$ 150–3°, m. 53–5.5° (Et_2O–petr. ether). A suspension of 2.3 g. 50% NaH–mineral oil suspension in 250 ml. $HCONMe_2$ (DMF) was stirred 20 min. under N with ice-cooling, treated with 8.64 g. Ia, stirred 20 min., treated dropwise during 30 min. with 8.6 g. *p*-$MeSC_6H_4COCl$ (II) in 50 ml. DMF, stirred 5 hrs. in an ice bath under N, and poured into a mixt. of 500 ml. Et_2O, 5 ml. AcOH, and 1 l. iced H_2O, the org. products extd. with Et_2O, the Et_2O ext. washed with a large quantity of H_2O, dried over Na_2SO_4, and filtered, the filtrate evapd. to near dryness, and the residue chromatographed over alumina to give I (R = OEt, R^1 = Me, R^2 = Me, R^3 = *p*-$MeSC_6H_4CO$, R^4 = MeO). A mixt. of 27 g. *p*-$MeSC_6H_4CO_2H$ and 21.4 g. $SOCl_2$ was heated 1 hr. on the steam bath to give II, m. 40–4°. A soln. of 15 g. I (R = MeO, R^1 = H, R^2 = Me, R^3 = H, R^4 = MeO) and 0.2 g. Na in 50 ml. $PhCH_2OH$ was slowly fractionated during 4.5 hrs. through a Vigreux column to remove MeOH. The excess $PhCH_2OH$ was distd. at 60°/2.5 mm. to leave 18.6 g. I (R = $PhCH_2O$, R^1 = H, R^2 = Me, R^3 = H, R^4 = MeO). A soln. of 1.5 g. Ib (see below) in 20 ml. EtOAc contg. a drop of AcOH was reduced catalytically at room temp. over Pd on C to give I (R = $PhCH_2O$, R^1 = H, R^2 = Me, R^3 = H, R^4 = MeO), m. 172–3°. A soln. of 1 g. dicyclohexylcarbodiimide (III) and 22 g. I (R = OH, R^1 = H, R^2 = Me, R^3 = H, R^4 = MeO) in 200 ml. tetrahydrofuran (THF) was kept 2 hrs. at room temp. and filtered, the filtrate evapd. in vacuo to a residue which was flushed with [illegible] B, treated with 25 ml. *tert*-BuOH and 0.3 g. fused $ZnCl_2$, and refluxed 16 hrs., the excess alc. removed in vacuo, and the residue dissolved in Et_2O and worked up by standard procedures to give 18 g. of an oily ester. A stirred soln. of the latter in 450 ml. dry DMF was treated with NaH and *p*-ClC_6H_4COCl as above to give I (R = *tert*-BuO, R^1 = H, R^2 = Me, R^3 = *p*-ClC_6H_4CO, R^4 = MeO) (Ic), m. 103–4° (MeOH). A stirred mixt. of [illegible]

Ic and 0.1 g. powd. porous plate was heated in an oil bath at 210° under N 2 hrs., cooled, and dissolved in C_6H_6 and the mixt. extd. with $NaHCO_3$ soln., filtered, neutralized with AcOH, and acidified with dil. HCl to give 0.1 g. I (R = R^1 = H, R^2 = Me, R^3 = *p*-ClC_6H_4CO, R^4 = MeO), m. 151° (aq. EtOH). A soln. of 29.5 g. III in 110 ml. dry THF was added during 30 min. to a soln. of 13.9 g. *p*-$O_2NC_6H_4OH$ and 12.3 g. isonicotinic acid in 250 ml. THF and the mixt. stirred overnight to give *p*-nitrophenyl isonicotinate (IV), m. 126–7°. A mixt. of 100 ml. DMF and 10.5 g. I (R = MeO, R^1 = H, R^2 = Me, R^3 = H, R^4 = MeO) under N at 0° was treated with 2.5 g. 50% NaH in mineral oil mixt., stirred 30 min., and treated during 15 min. with a soln. of 11 g. IV in 50 ml. DMF and worked up as above to give I (R = MeO, R^1 = H, R^2 = Me, R^3 = isonicotinyl, R^4 = MeO), m. 114–15°. Id (see below) (3 g.) in 300 ml. MeOH was reduced with H in an autoclave over Raney Ni to give I (R = MeO, R^1 = H, R^2 = Me, R^3 = H, R^4 = NH_2) (Ie), m. 144–5°. A stirred mixt. of 1.0 g. Ie, 0.99 g. $Br(CH_2)_4Br$, and 0.995 g. anhyd. Na_2CO_3 was refluxed 6 hrs. under N and filtered, the filtrate concd. in vacuo to a small vol., dild. with Et_2O, washed with H_2O, dried over Na_2SO_4, concd. in vacuo, and chromatographed over silica gel to give I (R = MeO, R^1 = H, R^2 = Me, R^3 = H, R^4 = 1-pyrrolidinyl), m. 117–19°. A mixt. of 0.387 g. If (see below) in 20 ml. distd. $MeOCH_2CH_2OMe$ (V), 1.5 ml. AcOH, and 0.5 ml. 37% aq. HCHO was reduced over Raney Ni at 40 psi. at room temp. to give I (R = MeO, R^1 = H, R^2 = Me, R^3 = *p*-ClC_6H_4CO, R^4 = Me_2N). A soln. of 0.388 g. If in 30 ml. anhyd. EtOAc and 0.306 g. Ac_2O was reduced over Raney Ni at room temp. and 40 psi. to give I (R = MeO, R^1 = H, R^2 = Me, R^3 = *p*-ClC_6H_4CO, R^4 = AcNH), m. 176–7°. A slurry of 80 ml. dry C_6H_6, 20 ml. $PhCH_2OH$, 3.0 g. Ig (see below), and 0.2 g. *p*-$MeC_6H_4SO_3H$ was refluxed 2 hrs. under N and the formed H_2O removed in a Dean-Stark tube. Excess alc. was removed in vacuo, the residue dissolved in C_6H_6, washed with aq. $NaHCO_3$, followed by H_2O, dried, and concd. in vacuo, and the residue chromatographed over acid-washed alumina to give I (R = $PhCH_2O$, R^1 = H, R^2 = Me, R^3 = H, R^4 = NO_2), m. 147–8° (C_6H_6–petr. ether). A soln. of 0.025 molar I (R = MeO, R^1 = Me, R^2 = Me, R^3 = *p*-ClC_6H_4CO, R^4 = NO_2) in 100 ml. EtOH was hydrogenated over 120 mg. 10% Pd on C at 40 psi. and room temp. to give I (R = MeO, R^1 = Me, R^2 = Me, R^3 = *p*-ClC_6H_4CO, R^4 = NH_2) (Ih). A cooled, stirred suspension of I (R = MeO, R^1 = H, R^2 = Me, R^3 = *p*-ClC_6H_4CO, R^4 = NH_2), NaH, and DMF was treated with MeI to give I (R = MeO, R^1 = H, R^2 = Me, R^3 = *p*-ClC_6H_4CO, R^4 = AcMeN). A mixt. of 0.02 mole Ih, 0.044 mole ethylene oxide, and 0.03 mole AcOH in 300 ml. V was heated 18 hrs. at 100° in an autoclave, dild. with H_2O, and filtered to give I [R = MeO, R^1 = Me, R^2 = Me, R^3 = *p*-ClC_6H_4CO, R^4 = $(HOCH_2CH_2)_2N$] (Ii). A stirred soln. of Ii and 2 mole proportions of *p*-$MeC_6H_4SO_2Cl$ in C_5H_5N at 0° was poured into H_2O and the 5-bis(*p*-tolylsulfonyloxyethyl)amino compd. isolated. The latter was dissolved in C_6H_6, treated with 1 mole $MeNH_2$, kept 3 days at room temp., and poured into ice–H_2O, and the product isolated in the usual manner to give I (R = MeO, R^1 = Me, R^2 = Me, R^3 = *p*-ClC_6H_4CO, R^4 = 4-methyl-1-piperazinyl). A mixt. of 36.02 g. triphenylphosphonium bromide and 94.36 ml. 0.1 *N* BuLi was stirred 1 hr. at room temp. under N and treated with 38 g. Et (2-methyl-5-methoxyindol-3-yl)-glyoxylate in 260 ml. C_6H_6 and the mixt. stirred 1 hr., transferred to a closed pressure flask, and heated 5 hrs. at 65–70° to give Et α-(1-benzoyl-2-methyl-5-methoxyindol-3-yl)acrylate (VI). A soln. of 1.8 g. VI in 10 ml. THF was treated with 4.0 g. CH_2I_2, 1.25 g. Zn–Cu couple, and iodine in 20 ml. THF, the mixt. refluxed 20 hrs. under N and filtered, the filtrate added to ice–H_2O and extd. with Et_2O, and the Et_2O ext. worked up to give Et α-(1-benzoyl-2-methyl-5-methoxyindol-3-yl)cyclopropanecarboxylate. A suspension of 1.0 g. 50% NaH in 80 ml. C_6H_6 was treated successively with 4.5 g. I (R = NH_2, R^1 = H, R^2 = Me, R^3 = H, R^4 = MeO), 20 ml. DMF, and 2.8 g. BzCl to give I (R = NH_2, R^1 = H, R^2 = Me, R^3 = Bz, R^4 = MeO) (Ij), m. 219–20° (EtOAc). A soln. of 7.2 g. Ij in 50 ml. V contg. 1 ml. 12 *N* HCl at 0° was treated with 0.7 g. NaNO2, the mixt. poured into H_2O and extd. with CH_2Cl_2, and the extr. worked up to give I (R = OH, R^1 = H, R^2 = Me, R^3 = Bz, R^4 = MeO). An ice-cold N-blanketed soln. of 0.5 g. I (R = OH, R^1 = H, R^2 = Me, R^3 = *p*-ClC_6H_4CO, R^4 = MeO) and 0.207 g. Et isocyanoacetate in 10 ml. V was treated with 0.07 g. 50% mole isobutyl chloroformate, the mixt. stirred in the cold 30 min. and filtered, the filtrate immediately ice-cooled, placed under N, and treated with 0.08 mole morpholine in 10 cc. V, and the cold mixt. stirred overnight and filtered to give I (R = morpholinyl, R^1 = H, R^2 = Me, R^3 = *p*-ClC_6H_4CO, R^4 = MeO), m. 192–3.5°. A mixt. of

0.003 mole Ik (see below) in 25 ml. anhyd. MeOH was reduced in the presence of 1 g. 5% Pd on C at room temp. and 40 psi. to give I (R = $NHCH_2CO_2H$, R^1 = H, R^2 = Me, R^3 = p-ClC_6H_4CO, R^4 = MeO), m. 152.5–54°; p-nitrophenylhydrazone m. 175–9°. The following I were similarly prepd. according to the various procedures given above (R, R^1, R^2, R^3, R^4, and m.p. given; A = p-ClC_6H_4CO): EtO, Me, Me, H, MeO, 83.0–8.5°; MeO, H, Me, A, MeO, 99–100°; EtO, Me, Me, 2-Me-4-MeSC_6H_3CO, MeO, —; EtO, Me, Me, Bz, MeO, —; EtO, Me, Me, A, MeO, —; $PhCH_2O$, H, Me, Bz, MeO (Ib), 91–2°; EtO, Me, Me, p-FC_6H_4CO, MeO, —; BuO, Me, Me, p-$MeSC_6H_4CO$, MeO, —; OH, Me, Me, p-$MeSC_6H_4CO$, MeO, 175–6°; OH, Me, Me, A, MeO, 87–9°; OH, H, Me, H, NO_2 (Ig), 238°; MeO, H, Me, H, NO_2 (Id), 132°; MeO, H, Me, A, 1-pyrrolidinyl, 62–4°; MeO, H, Me, A, NO_2 (If), 170–1°; $PhCH_2O$, H, Me, A, NO_2 (Ih), 166–7°; MeO, H, Me, A, 4-morpholino, —; MeO, H, Me, A, CN, —; MeO, H, Me, A, CH_2NH_2, —; MeO, H, Me, A, Me_2NCH_2, —; MeO, H, Ph, A, MeO, 120.0–20.5°; EtO, Me, Me, A, EtO, —; OH, H, $PhCH_2$, A, H, —; OH, H, Me, p-$MeOC_6H_4CO$, MeO, 83–9°; OH, Me, Me, p-$MeOC_6H_4CO$, MeO, 65°; MeO, H, Me, p-BrC_6H_4CO, MeO, 106–7.5°; MeO, H, Me, p-$O_2NC_6H_4CO$, MeO, 130–2°; MeO, H, Me, o-ClC_6H_4CO, MeO, 91–3°; MeO, H, Me, m-ClC_6H_4CO, MeO, 51–2°; MeO, H, Me, p-PhC_6H_4CO, MeO, 101.5–3.0°; MeO, H, Me, p-$AcOC_6H_4CO$, MeO, 99–101°; EtO, H, Me, 4-thiazolylcarboxy, MeO, 76–82°; EtO, H, Me, 2-thenoyl, MeO, —; *tert*-BuO, Me, Me, p-BrC_6H_4CO, MeO, 103–5°; MeO, H, Me, α-naphthoyl, MeO, —; MeO, H, Me, p-$PhCH_2OC_6H_4CO$, MeO, 116–18°; MeO, H, Me, p-HOC_6H_4CO, MeO, 155–8° (prepd. from the p-benzyloxybenzoyl compd. by catalytic hydrogenation over Pd); MeO, H, Me, o-$PhCH_2OC_6H_4CO$, MeO, —; MeO, H, Me, o-HOC_6H_4CO, MeO, —; MeO, H, Me, o-FC_6H_4CO, MeO, 93–9°; OH, H, Me, 2-thenoyl, MeO, 62°; MeO, H, Me, β-naphthoyl, MeO, 120–4°; MeO, H, Me, 5-chloro-2-thenoyl, MeO, —; OH, H, Me, p-$F_3CC_6H_4CO$, MeO, 169–71°; MeO, H, Me, 2,6-$(MeO)_2C_6H_3CO$, MeO, 139.5–41°; MeO, H, Me, 2,4-$Cl_2C_6H_3CO$, MeO, —; NMe_2, H, Me, A, MeO, 179.5–80.5°; $HOCH_2CH_2NH$, H, Me, A, MeO, 137–8°; $PhCH_2NH$, H, Me, A, MeO, —; $Et_2NCH_2CH_2NH$, H, Me, A, MeO, 110–11.5°; $PhCH_2O_2CCH_2NH$, H, Me, A, MeO (Ik), 133–4.5°; and morpholino, H, Me, A, F, 168–70°. I. Levi

A6.74. 90068j **Preparation of 1-acyl-3-alkoxycarbonyl alkyl-substituted indoles.** Sumitomo Chemical Co., Ltd. Neth. Appl. 6,605,169 (Cl. C 07*d*), Oct. 20, 1966; Japan. Appl. April 19, 26, Nov. 30, Dec. 7, 8, 29, 1965, Jan. 20, 31, and Feb. 7, 1966; 37 pp. Th = thienyl, Py = pyridyl, Fu = furyl, and d = decompn. throughout this abstract. The title compds. (I) are antiinflammatory, antipyretic and analgetic agents. I are prepd. by the reaction of *N*-acylated phenylhydrazine (II) with an oxo acid $R^2COCH_2(CHR')_m(CH_2)_n(CHR'')COR'''$. II is obtained by decompn. of hydrazone (III), which is obtained by acylation of IV with ArCOX (X is halogen or ester residue). Thus, to a soln. of 12 g. IV (R^3 = p-MeO, R^4 = H, R^5 = Me) in 30 ml. pyridine, 15 g. 4-ClC_6H_4COCl is added dropwise with ice-



cooling. The reaction mixt. is left at room temp. and poured into ice-H_2O to give 10 g. III (R^2 = p-MeO, R^4 = H, R^5 =

Me, Ar = p-ClC_6H_4), m. 197–8° (EtOH, H_2O). To a soln. of 3.4 g. IV (R^3 = p-MeO, R^4 = $CH_2CH_2CO_2Me$, R^5 = Me) in 30 ml. C_5H_5N, 2.8 g. 4-ClC_6H_4COCl is added with ice-cooling. The mixt. is left at room temp. and poured into ice-H_2O to give 2.5 g. II (R^3 = p-MeO, Ar = p-ClC_6H_4), m. 131–2°. A soln. of 9.5 g. V in 80 ml. EtOH is satd. with HCl. The mixt. is left at ambient temp., concd., and worked up to give VI. A soln.

III (R^3 = R^4 = H)			Corresponding II.HCl
R^5	Ar	M.p.	M.p.
4-Me	4-ClC_6H_4	124–5°	192–3° (d)
4-MeO	3-Py (V)	100–5°	(VI) 200–1° (d)
4-MeO	4-Py	134–6°	149.5° (d)
4-Me	2-Th	114–16°	164–6° (d)
4-Me	2-Fu	70–85°	180–1° (d)

Other II.HCl		
R^3	Ar	M.p.
4-MeO	2-Th	155–6° (c)
4-F	4-ClC_6H_4	209–11° (c)
3-Me	4-ClC_6H_4	162–5° (c)
H	4-MeC_6H_4	150–2° (c)
4-MeO	4-ClC_6H_4	177–9° (c)

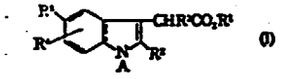
of 4.9 g. VI and 17.6 g. levulinic acid is heated 3 hrs. at 75°. The mixt. is left at ambient temp. and poured into H_2O to give 5.8 g. I (Ar = 3-Py, R^3 = Me, R^3 = 5-MeO, m = p = 0, n = 1, R'' = OH) (VII), m. 187–9° (Me_2CO, H_2O) (method *a*). In method *b* AcOH is used as the solvent. A mixt. of 9 g. VI, 4.2 g. Me levulinate, and 40 ml. MeOH is refluxed 5 hrs. with stirring. The MeOH is evapd. in vacuo and the ppt. worked up to give VII Me ester (VIII), m. 113–15° (MeOH) (method *c*). A mixt. of 1 g. II.HCl (Ar = p-ClC_6H_4, R^3 = p-MeO) and 1 g. acetonylmalonic acid is heated 5 min. at 145°, the mixt. cooled slowly, and 2 ml. AcOH and 5 ml. H_2O are added. The ppt. is worked up to give 0.6 g. IX (method *d*). A mixt. of 9.0 g. VI, 4.5 g. levulinic acid, and 60 ml. MeOH is refluxed 16 hrs. The MeOH is distd. and the residue worked up to give VIII (method *e*). III (R^3 = p-MeO, Ar = p-ClC_6H_4, R^4 = H, R^5 = Me) (IIIa) (9.1 g.) is added to 50 g. levulinic acid, and 1.46 g. dry HCl gas is passed with ice-cooling. The mixt. is heated slowly and refluxed 1.5 hrs. H_2O is added to give a resin, which is dissolved in EtOH and $CHCl_3$. Work up gives IX (method *f*). Similarly, heating a mixt. of 4.9 g. IIIa, 4.8 g. acetonylmalonic acid, 10 ml. AcOH, and 0.8 g. dry HCl at 80–100° with stirring, gives

Ar	R^3	R'	m	n	R''	p	R'''	R^5	Method	M.p.
2-Th	Me	—	0	1	—	0	OH	5-MeO	*a*	65–7°
2-Fu	Me	—	0	1	—	0	OH	5-Me	*a, d, f, g*	160–3°
2-Th	Me	H	1	1	H	1	OH	5-MeO	*e, f*	118–20°
4-Py	Me	—	0	1	—	0	OH	5-MeO	*b, d, f*	146–9°
2-Fu	Me	H	1	1	—	0	OH	5-Me	*b*	95–8°
2-Th	Me	H	1	1	H	1	OH	5-MeO 4-Me	*b*	119–20°
4-ClC_6H_4	Me	—	0	1	—	0	OH	6-Me	*b*	mixt. 152–90°
5-Cl-2-Th	Me	—	0	1	—	0	OMe	5-Me	*c*	— (oil)
2-Fu	H	—	0	1	CO_2Me	1	OMe	5-Cl	*c*	— (oil)
2-Py	Me	—	0	1	—	0	OMe	5-MeO	*c*	132–5°
4-ClC_6H_4	Me	—	0	1	—	0	OH	H	*a, d,*	124–7°
4-ClC_6H_4	Me	H	1	1	H	1	OH	5-MeO	*a, f*	106–9°
4-ClC_6H_4	Me	—	0	1	—	0	OH	5-Cl	*a, b, d*	185–7°
4-ClC_6H_4	Me	—	0	1	—	0	OH	5-Me	*a, b, d, g*	207–9°
4-ClC_6H_4	Me	—	0	1	—	0	OH	5-F	*a, f*	149–51°
Ph	Me	—	0	1	—	0	OH	5-Me	*a, f*	165–6°
4-MeC_6H_4	Me	—	0	1	—	0	OH	5-MeO	*a, b, d, f, g*	155–6°
4-$MeOC_6H_4$	Me	—	0	1	—	0	OH	5-MeO	*a, b, d, f,*	158–60°
4-ClC_6H_4	Me	H	1	1	—	0	OH	5-MeO	*a*	87–8°
Ph	Me	—	0	1	—	0	OH	5-Cl	*a, b, d, f*	170–1°
Ph	Me	—	0	1	—	0	OH	H	*a, b, f*	167–8°
4-$CF_3C_6H_4$	Me	—	0	1	—	0	OH	H	*a*	169–71°
4-$MeSC_6H_4$	Me	H	1	1	—	0	OH	5-MeO	*b, d*	172–4°
4-MeC_6H_4	Me	—	0	1	—	0	OH	H	*b*	141–3°
4-ClC_6H_4	Me	—	0	1	—	0	*tert*-BuO	5-F	*c*	65–8°
4-$MeOC_6H_4$	H	—	0	1	—	0	OEt	5-MeO	*c*	— (oil)
Ph	Me	—	0	1	—	0	OCH_2Ph	5-MeO	*c*	85–7°
4-ClC_6H_4	Me	—	0	1	—	0	OMe	5-NO_2	*c, e*	153–7°
β-naphthyl	Me	—	0	1	—	0	OMe	5-MeO	*c, e*	124–5°
4-$MeSC_6H_4$	Me	—	0	1	—	0	*tert*-BuO	5-MeO	*c*	— (oil)
4-ClC_6H_4	Me	—	0	1	CO_2Et	1	OEt	5-MeO	*c*	—
Ph	Me	—	0	0	—	0	OEt	H	*c*	96–8°
4-ClC_6H_4	Me	—	0	1	—	0	OH	5-MeO (IX)	*a, c, f, g*	150–1°
4-ClC_6H_4	Me	—	0	1	—	0	OMe	5-MeO	*c, e*	88–91°
4-ClC_6H_4	Me	—	0	1	—	0	OH	5-EtO	*a*	161–4°
4-BrC_6H_4	Me	—	0	1	—	0	OH	5-MeO	*b, d,*	162–4°
4-FC_6H_4	Me	—	0	1	—	0	OH	5-MeO	*a, f*	148–50°
4-ClC_6H_4	Me	—	0	1	—	0	NH_2	5-MeO	*b*	216–18°
2-Fu	Me	H	1	1	—	0	OH	5-Me	*d*	92–5°
2-Th	Me	—	0	1	—	0	OEt	5-MeO	*c*	—
5-Cl-2-Th	Me	—	0	1	—	0	OMe	5-MeO	*c*	—
2-Fu	Me	—	0	1	—	0	OMe	5-MeO	*c*	—
4-ClC_6H_4	Me	—	0	1	—	0	OEt	5-MeO	*c*	97–8°
4-BrC_6H_4	Me	—	0	1	—	0	OMe	5-MeO	*c*	105–7°
β-naphthyl	Me	—	0	1	—	0	OMe	5-MeO	*c*	125–8°
4-ClC_6H_4	H	H	1	1	H	1	OMe	5-Me	*c*	— (oil)
3-Py	Me	—	0	1	—	0	OMe	5-MeO		128–30°

IX (method *g*). The I prepd. are listed in the 2nd table.

S. A. Van Walle

[illegible] 82u6f Aliphatic α-[1-acylindol-3-yl]carboxylic acids. Merck & Co., Inc. Neth. Appl. 6,609,940 (Cl. C 07d), Jan. 15, 1967; U.S. Appl. July 14, 1965, 15 pp. The prepn. of aliphatic α-(1-acetylated indol-3-yl)carboxylic acids or substituted derivs. thereof by acid hydrolysis of phthalimidomethyl esters or alkyl esters of α-(1-acylated indol-3-yl)carboxylic acids or substituted derivs. thereof is described. The compds. prepd. are used as antiinflammatory agents. Thus, a soln. of 0.01 mole phthalimidomethyl α-[1-(*p*-chlorobenzoyl)-2-methyl-5-methoxyindol-3-yl]acetate in 75 ml. toluene was satd. with anhyd. HCl at 10° and the solid filtered off after 24 hrs. and recrystd. from *tert*-BuOH to yield α-[1-(*p*-chlorobenzoyl)-2-methyl-5-methoxyindol-3-yl]acetic acid. A soln. of 0.005 mole *tert*-Bu α-[1-(*p*-chlorobenzoyl)-2-methyl-5-nitroindol-3-yl]acetate in 25 ml. anhyd. C_6H_6 was cooled to 10° and satd. with anhyd. HCl, the mixt. kept overnight at 20°, and the pptd. benzene semisolvate of α-[1-(*p*-chlorobenzoyl)-2-methyl-5-nitroindol-3-yl]acetic acid filtered off, washed with 5 ml. cold C_6H_6, and dried in vacuo at 40° to yield the pure compd. A soln. of 0.01 mole Me α-[1-(*p*-chlorobenzoyl)-2-methyl-5-fluoroindol-3-yl]acetate in 15 ml. 90% HCO_2H contg. 0.01 mole $MeSO_3H$ was refluxed 5 hrs., cooled to room temp., and dild. with 30 ml. H_2O, the ppt. filtered off, washed

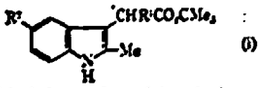


(I)

R	R^1	A
H	MeO	Bz
F	EtO	*p*-ClC_6H_4CO
H	Me	3,4,5-trimethoxybenzoyl
H	CF_3	5-nitrofuran-2-carbonyl
Cl	$PhCH_2O$	*p*-acetylbenzoyl
H	F	*p*-carbomethoxybenzoyl
Me	SH	*p*-mercaptobenzoyl
H	cyclopropyl	2-phenylthiazole-4-carbonyl
H	NO_2	*p*-carbomethoxybenzoyl
MeO	cyclopropylethoxy	*p*-methylsulfinylbenzoyl
CF_3	$PhCH_2S$	1-methylbenzimidazole-2-carbonyl
H	dimethylsulfonamido	5-fluorothiophene-2-carbonyl
H	Et	*p*-trifluoroacetylbenzoyl
H	MeO	*p*-phenoxybenzoyl
H	*p*-ethylbenzyloxy	*p*-(*N*,*N*-dimethylsulfamoyl)benzoyl
H	cyclobutyl	1-methylbenzimidazole-2-carbonyl
MeO	H	furan-3-carbonyl

with H_2O and recrystd. from *tert*-BuOH to yield α-[1-(*p*-chlorobenzoyl)-2-methyl-5-fluoroindol-3-yl]acetic acid. Similarly were prepd. the I listed in the table. (The positions of R^4 could not be checked during editing). R. Van Steen

A6.76. 32591t α-(Indol-3-yl)carboxylic acid esters. Merck & Co. Inc. Neth. Appl. 6,609,138 (Cl. C 07*a*), Jan. 2, 1967; U.S. Appl. June 30, 1965; 11 pp. The prepn. of *tert*-Bu esters of α-(2-methyl-5-alkoxyindol-3-yl)acetic acid and the α-alkyl derivs. thereof is described. The compds. have the general formula I where R^1 is an alkyl group contg. <4 C atoms and R^2 is EtO or MeO; they are valuable intermediates in the prepn. of nonsteroidal antiinflammatory compds. Thus, 2.5 g. Na *p*-methoxyphenylhydrazinesulfonate monohydrate was suspended in 10 parts *tert*-BuOH, the suspension cooled under N to <10°, 1.70



(I)

ml. concd. HCl added dropwise with stirring, the mixt. heated to room temp., stirring continued 25 hrs., concd. NH_3 added to adjust pH to 3.3–3.5, 1.98 g. *tert*-Bu levulinate added under N, the mixt. refluxed (82–3°) 5 hrs., cooled to 70°, 3 ml. H_2O added, the aq. phase sepd., the org. phase dild. with 12.5 ml. H_2O, the mixt. cooled, kept 9 hrs. in a refrigerator and filtered, and the product washed with 0.2 ml. cold 50% *tert*-BuOH and then with H_2O to give the *tert*-Bu α-(2-methyl-5-methoxyindol-3-yl)acetate. The same expt. with K *p*-ethoxyphenylhydrazinesulfonate with *tert*-Bu α-methyllevulinate gave the *tert*-Bu α-(2-methyl-5-ethoxyindol-3-yl)propionate. Other I prepd. were [R^1, R^2, the alkali metal salt of *p*-alkoxyphenylhydrazinesulfonic acid, HCl (10*N*) or HCl in anhyd. form, moles H_2O/mole sulfonic acid, temp. prepn. hydrochloride, reaction time in hrs., pH in reaction medium during conversion with levulinic acid ester, concd. aq. base, temp., and reaction time in hrs. given]: H, EtO, Na, 10*N* HCl, 20, 20°, 50, 3.0, NaOH, 70°, 7; Me, MeO, Na, 10*N* HCl, 5, 55°, 10, 5.0, NH_4OH, 80°, 4; Et, EtO, Na, 10*N* HCl, 3, 25°, 16, 3.3, Me_2NH, reflux, 5; Pr, PrO, Na salt (anhyd.), 10*N* HCl, 16, 25°, 20, 3.4, KOH, reflux, 5; Bu, EtO, K salt (anhyd.), anhyd. HCl, 5, 25°, 24, 3.5, NH_4OH, reflux, 6. In the last two expts. evacuation was eliminated. Also prepd. was α-[1-(*p*-chlorobenzoyl)-2-methyl-5-methoxyindol-3-yl]acetic acid in 47% yield, m. 151° (aq. EtOH), after drying at 65° in vacuo.

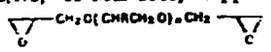
R. Van Steen

INDOMETHACIN

Miscellaneous

A6.77.

102: 5225?w Pharmaceutical complexes with cyclodextrin and glycol diglycidyl ether polymers. Mitsubishi Petrochemical Co., Ltd. Mitsubishi Yuka Pharmaceutical Co., Ltd. Jpn. Kokai Tokkyo Koho JP 59,164,728 [84,164,728] (Cl. A61K47/00), 17 Sep 1984, Appl. 83/55,473, 09 Mar 1983; 7 pp. Insol. or barely-sol.

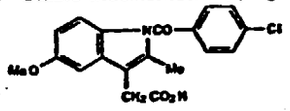


I

drugs are treated with reaction products of I (R = H or Me; n = 1–10) and cyclodextrin to give complexes that are sol. in H_2O. Thus, sol. cyclodextrin–polymers were prepd. by treating β-cyclodextrin with propylene glycol diglycidyl ether and polymg. This product was treated with insol. drugs such as phenytoin and indomethacin to give sol. complexes.

A6.78.

~~93:~~ 181506g **Hydrophilic polymers for indomethacin tablets.** Chiyoda Yakuhin K. K. Jpn. Kokai Tokkyo Koho JP 58,144,316 [83,144,316] (Cl. A61K9/20), 27 Aug 1983, Appl. 82/25,464, 18 Feb 1982; 5 pp. Stable *indomethacin* (I) [53-86-1] tablets are

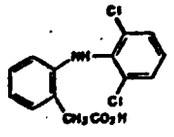


I

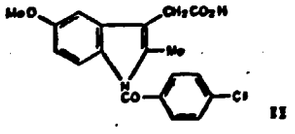
prepd. by coating I particles with hydrophilic polymers during the granulation process prior to the tablet formation. Thus, *2-hydroxypropyl cellulose* [9004-64-2] 40 and polyethylene glycol 5 parts were dissolved in a mixt. of 600 parts EtOH and 200 parts CH_2Cl_2. This soln. was sprayed over a mixt. of I 250, cryst. cellulose 150, and Mg metasilicate aluminate 50 parts. The mixt. was made into granules, dried, combined with microcryst. cellulose 250, lactose 215, Ca glycolate 30, and Mg stearate 10 parts, and made into tablets.

A6.79.

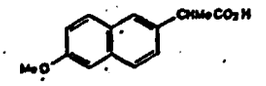
99: 53369c **Salts of 2-(2,6-dichloroanilino)phenylacetic acid, [1-(p-chlorobenzoyl)-5-methoxy-2-methyl-3-indolyl]acetic acid and 2-(6-methoxy-2-naphthyl)propionic acid with organic bases containing nitrogen.** Ciba-Geigy A.-G. Austrian AT 370,721 (Cl. C07C101/447), 25 Apr 1983, Appl. 81/709, 16 Feb 1981; 7 pp. Novel amine salts of I–III were prepd. by mixing the



I



II



III

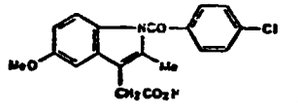
components in, e.g., Et_2O or EtOAc. Thus prepd. were salts of I with Et_2NH, $(HOCH_2)_2CNH_2$, $N(CH_2CH_2OH)_3$, $HN(CH_2CH_2OH)_2$, morpholine, diisopropanolamine, and *N*-methyl-D-glucamine; no specific examples for II and III salts were given.

A6.80.

93: 173751u **Pharmaceutical preparations containing a mollusk extract.** McFarlane, Stuart John; Croft, John Eric Eur. Pat. Appl. 10,061 (Cl. A61K35/60), 16 Apr 1980, New Zealand Appl. 188,489, 25 Sep 1978; 34 pp. The occurrence of gastric ulcers or stomach bleeding from drugs is inhibited by combination with the drugs of a mollusk *Perna canaliculus* ext. (Seatone), which is composed of proteins, carbohydrates and minerals (mineral and amino acid content given). Capsule compns. were given contg. the ext. and analgesics–inflammation inhibitors such as *acetylsalicylic acid* [50-78-2], *diclofenac Na* [15307-79-6], *phenylbutazone* [50-33-9], or *indomethacin* [53-86-1].

A6.81. 85: 1611[illegible]s Antiphlogistic composition of phenylbutazone and alkali salicylate. Chemoky, Eszter; Ezer, Elemer; Forgach, Lilla; Gidai, Katalin; Hajos, Gyorgy; Hortobagyi, Gyozo; Karpati, Egon; Palosi, Eva; Szporny, Laszio (Richter, Gedeon, Vegyeszeti Gyar Rt.) U.S. 4,193,402 (Cl. 424-232; A61K31/62), 15 Apr 1980, Appl. 641,771, 17 Dec 1975; 6 pp. The ulcerogenic side effects of antiphlogistics *indomethacin* [53-86-1], *acetylsalicylic acid* [50-78-2], *phenylbutazone* [50-33-9], and *niflumic acid* [4394-00-7] are antagonized by *Na salicylate* [54-21-7], as shown by tests on rats. Various pharmaceuticals were prepd. combining these antiphlogistics with Na salicylate approx. in a ratio of 1:1-1:10.

A6.82. 88: 197668v Submorphous drug preparations. Sakamaki, Yasuhisa; Miyamoto, Masatoshi (Sumitomo Chemical Co., Ltd.; Hayashibara Biochemical Laboratories, Inc.) Japan. Kokai 78 12,417 (Cl. A61K9/14), 03 Feb 1978, Appl. 76/87,002, 20 Jul 1976; 3 pp. Submorphous drugs are prepd. by adding *pullulan*



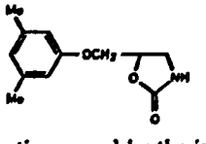
I

[9057-02-7] to aq. drug solns. and freeze-drying. The products dissolve in gastric juice more rapidly than do cryst. drugs. Thus, 2 g *indomethacin* (I) [53-86-1] was dissolved in 109 mL water, and 2 g pullulan (mol. wt. 7,0000) was added. The soln. was freeze-dried. An increase in the soly. of the product was demonstrated, as compared to the soly. of crystd. I.

A6.83. 87: 172896j Water-soluble salt of indomethacin. Gallardo, Antonio, S. A. Span. 438,121 (Cl. C07D), 01 Feb 1977, Appl. 02 Jun 1975; 4 pp. The *indomethacin meglumine salt* [36798-16-0] is prepd. by reacting *indomethacin* [53-86-1] and *meglumine* [6284-40-8] in water at 10-80°, filtering the soln., and subjecting it to a process of atomization at the rate of 120 mL/min, velocity of centrifugal disks of 10,000 revolutions/min, temp. of air at entry of 140-90°, and exit temp. of 70-100°.

A6.84. 86: 127271v Antiinflammatory agents coprecipitated with lignosulfonic acid. Lybrand, Robert A.; Bell, Louis Gary (Robins, A. H., Co.) U.S. 4,004,002 (Cl. 424-230; A61K31/60), 18 Jan 1977, Appl. 89,999, 16 Nov 1970; 9 pp. Antiinflammatory agents were copptd. with lignosulfonic acid and the resulting coppts. retained the therapeutic activity of the antiinflammatory agent while preventing the gastric irritation. The prepn., formulation, and pharmacol. of the coppts. were described. E.g., ammonium lignosulfonate was treated with aspirin in a basic medium and the coppt. formed after acidification contained 89% by wt. aspirin and 9.8% by wt. lignosulfonate. This coppt. reduced bleeding in cat stomach mucosa 100% compared to aspirin.

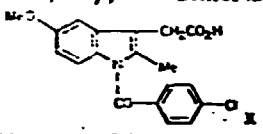
A6.85. 86: 60537r Compositions to suppress gastric bleeding in indomethacin and phenylbutazone therapy. Alphin, Reevis S.; Droppleman, David A. (Robins, A. H., Co., Inc.) U.S. 3,993,767 (Cl. 424-272; A61K31/40), 23 Nov 1976, Appl. 633,043, 18 Nov 1975; 10 pp. The incidence of intestinal



I

ulceration and perforation caused by the inflammation inhibitors *indomethacin* [53-86-1] or *phenylbutazone* [50-33-9] are minimized by concomitant administration of a 5-phenoxymethyl-3-oxazolidinone such as *metaxalone* (I) [1665-48-1]. Thus, in rats receiving 20 mg/kg oral indomethacin, none died when pretreated with 200 mg/kg oral I while 86% died in a control group pretreated with acacia suspension. Gastrointestinal ulceration protection from phenylbutazone by I was also shown. Formulations were given contg. combinations of I with indomethacin or I with phenylbutazone. E.g., capsules contain indomethacin 25 and metaxalone 250 mg/capsule.

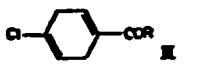
A6.86. 57305m Antiinflammatory indomethacin preparations for external use. Umemura, Koshiro; Shomura, Tomoko (Meiji Confectionary Co., Ltd.) Ger. 1,617,653 (Cl. A 61k), 18 Jun 1970, Appl. 08 Sep 1970; 5 pp. Indomethacin (I) is dissolved



in a dicarboxylic acid ester which penetrates the skin easily and from which I is readily absorbed by the organism. I is dissolved in malonic, succinic, glutaric, adipic, pimelic, suberic, azelaic, or sebacic diesters and used as a soln. of transformed into a suspension or cream with the usual pharmaceutical agents. The equiv. of the normal oral dose of 25–50 mg/day is absorbed by the organism when 1–2 g of the prepn. contg. 5–10% I is used externally. A. Mangels

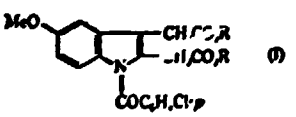
A6.87. 85: 177045z N-(p-Chlorobenzoyl)-N-(p-methoxyphenyl)-hydrazine hydrochloride. Fisnerova, Ludmila; Nemecek, Oldrich Czech. 162,229 (Cl. C09C109/10), 15 Feb 1976, Appl. 72/6,622, 29 Sep 1972; 2 pp. *p*-$MeOC_6H_4NHNH_2$ was reacted with *p*-ClC_6H_4COCl in chilled CH_2Cl_2 in the presence of Et_3N to give 69% *N*-(*p*-chlorobenzoyl)-*N*-(*p*-methoxyphenyl)hydrazine, an intermediate for the prepn. of indomethacin. L. J. Urbanek

A6.88. 34333r 1-(4-Chloro-1,4-cyclohexadien-1-ylcarbonyl)-2-methyl-5-methoxy-3-indoleacetic acid. Levine, Seymour David; Diassi, Patrick A.; Vogt, Berthold R.; Weisenborn, Frank L. (Squibb, E. R., and Sons, Inc.) Ger. Offen. 2,151,798 (Cl. C 07dc, A 61k), 27 Apr 1972, US Appl. 82,512, 20 Oct 1970; 60 pp.



The title compd. (I), useful as antiinflammatory, antipyretic, and analgesic agent and as intermediate in the prepn. of 1-(*p*-chlorobenzoyl)-5-methoxy-2-methyl-3-indoleacetic acid (II), was prepd. Thus, reaction of 2.4 g III (R = Cl) with 2 g $MeCH{:}NNHC_6H_4OMe$-*p* in dioxane contg. pyridine 5 hr at 6° gave 1.25 g III [R = $N(C_6H_4OMe$-*p*$)N{:}CHMe$] (IV). Treatment of 1.25 g IV with HCl(g) in MeOH/EtOAc 20 min on an ice bath gave 1.01 g III [R = $N(C_6H_4OMe$-*p*$)NH_2.HCl$] (V). Heating 1.75 g V and 0.76 g levulinic acid in HOAc 3 hr at 80° gave 1.8 g I. Redn. of I with H over Pd-C or with S gave II.

A6.89. 101708h 1-(p-Chlorobenzoyl)-2,3-bis(carboxymethyl)-5-methoxyindole and esters. Chemerda, John M.; Sletzinger, Meyer (Merck and Co., Inc.) U.S. 3,454,594 (Cl. 260-326.13; C 07d), 08 Jul 1969, Appl. 26 Jul 1967; 3 pp. The di-Me ester (I, R = R¹ = Me) (Ia) [useful intermediate in the prepn. of 1-(*p*-chlorobenzoyl)-2-methylindole-3-acetic acid, of the title compd. (I, R = R¹ = H) (Ib)] was prepd. Thus, to 0.01 mole 1-(*p*-chlorobenzoyl)-5-methoxyindole in 100 ml. tetrahydrofuran (THF) was added 0.021 mole Me diazoacetate in 25 ml. THF over 15 min., and the mixt. irradiated at 20–5° to give Ia. Simi-



larly prepd. was I (R = H, R¹ = Me) (II). A mixt. of 0.01 mole II, 8.5 g. anhyd. LiI, and 2.0 ml. 2,6-lutidine was refluxed 8 hrs. under N to give Ib, also prepd. from Ia by this procedure. II was prepd. in a 3-stage reaction from di-Me 3-oxo-4-bromoadipate. F. J. Sprules

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A7

MEBENDAZOLE

PATENTS

1967-1985

APPENDIX P7

ANALYSIS OF THE ABSTRACTS OF PATENTS

Patents of the compound mebendazole are still valid !

Apart from the standard process (A7.6.) other interesting synthetic alternatives are described in patents A7.1. to A7.5. among which A7.3. amd A7.4. seem particularly interesting because of the use of calcium cyanamide.

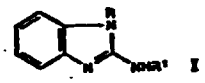
ABSTRACTS OF PATENTS

A7

MEBENDAZOLE

Preparation

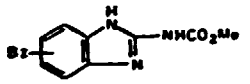
A7.1. 99: 38464m N-Acylaminoazoles. Martin, Dieter; Graubaum, Heinz; Schumann, Hiltraud (Akademie der Wissenschaften der DDR) Ger. (East) DD 158,358 (Cl. C07D235/32), 12 Jan 1983, Appl. 220,703, 25 Apr 1980; 11 pp. 2-Aminoazoles were transacylated



I

by heating in an inert solvent with an *N*-acylazole to give *N*-acyl-2-amino(or imino)azoles, which underwent rearrangement to give 2-(acylamino)azoles. Thus, benzimidazole I (R = R¹ = H) (II) was heated 15 min in THF with 1-(ethoxycarbonyl)imidazole to give 87% I (R = CO_2Et, R¹ = H). II was heated in PhMe with 1-(isopropoxycarbonyl)imidazole to give 70% I (R = H, R¹ = CO_2CHMe_2).

A7.2. 25669k Methyl 5(6)-benzoylbenzimidazol-2-ylcarbamate. Barker, Alan Charles; Foster, Richard Gregory (Imperial Chemical Industries Ltd.) Brit. 1,350,277 (Cl. C 07d), 18 Apr 1974, Appl. 44,203/71, 22 Sep 1971; 5 pp. The title compd.

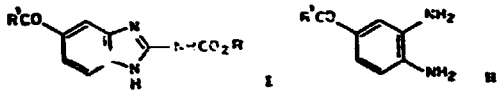


I

(I) was prepd. by decompn. of 1*H*-2,1,4-benzothiadiazine derivs. with acid or Ph_3P. E.g., decompn. of Me 7-benzoyl-1*H*-2,1,4-benzothiazin-3-ylcarbamate (II) in MeOH with 2*N* HCl gave 52% I. II was prepd. in 2 stages from 4-benzoyl-2-nitroaniline.

A7.3. 3936t Preparation of alkyl 5(6)-acylbenzimidazolyl carbamates. Harsanyi, Kalman; Toth, Geza; Simay, Antal; Gonczi, Csaba; Takacs, Kalman; Ajzert, Ilona K. (Chinoin Gyogyszer es Vegyeszeti Termekek Gyara Rt.) Brit. 1,348,460 (Cl. C 07d), 20 Mar 1974, Hung. Appl. 14,618, 06 Oct 1971; 5 pp. The title compds. were prepd. by reaction of (alkoxycarbonyl)-cyanamides with acyl-*o*-phenylenediamines. Thus, $NCNHCO_2Me$ reacted with 4-benzoyl-*o*-phenylenediamine at 90–5° for 45 min with pH kept at 3.5–4.0 by addn. of HCl to give 81.5 % Me 5(6)-benzoyl-2-benzimidazolylcarbamate. $NCNHCO_2Me$ had been prepd. by reaction of Ca cyanamide (in tech. Ca_2N_2) with $ClCO_2Me$.

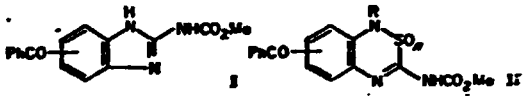
A7.4. 76801n 5(6)-Acylbenzimidazolyl alkyl carbamates. Harsanyi, Kalman; Toth, Geza; Simay, Antal; Gonczi, Csaba; Takacs, Kalman; Ajzert, Ilona K. (Chinoin Gyogyszer es Vegyeszeti Termekek Gyara Rt.) Hung. Teljes 5600 (Cl. C 07d), 28 Feb 1973, Appl. Ci-1172, 06 Oct 1971; 14 pp. I



I II

(R = Me, Et; R¹ = Me, Ph, *p*-tolyl, *p*-ClC$_6$H$_4$) were prepd. by treating II with NCNHCO$_2$R in aq. medium at 30–10° and pH 3.0–4.5. Thus, CaNCN was treated with ClCO$_2$Me in aq. EtOH at 30–40°, and the mixt. heated 45 min at 90–5° with II (R¹ = Ph) at pH 3.5–4 (HCl) to give 83% I (R = Me, R¹ = Ph). T. Mohacsi

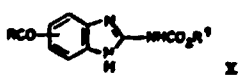
A7.5. 5341c Methyl [5(6)-benzoyl-2-benzimidazolyl]carbamate. Barker, Alan Charles; Foster, Richard G. (Imperial Chemical Industries Ltd.) Ger. Offen. 2,246,605 (Cl. C 07d), 29 Mar 1973, Brit. Appl. 44,203/71, 22 Sep 1971; 16 pp. The title compd. (I),



I II

useful as anthelmintic, was prepd. from the benzothiadiazines II (PhCO connected in position 6 or 7; *n* = 0 or 1; R = H, Ac, or Bz). Thus, II (PhCO connected in position 7, *n* = 0, R = H), prepd. from 4,2-PhCO(O$_2$N)C$_6$H$_2$NH$_2$ and SCNCO$_2$Me via 4,2-PhCO(O$_2$N)C$_6$H$_3$NHCSNHCO$_2$Me, was refluxed in 2*N* HCl and MeOH for 17 hr to give 52% I.

A7.6. 100047s Anthelmintic alkyl N-[5(6)-acyl-2-benzimidazolyl] carbamates. Van Gelder, Josephus L. H.; Raeymaekers, Alfons H. M.; Roevens, Leopold F. C. (Janssen Pharmaceutica N.V.) Ger. Offen. 2,029,637 (Cl. C 07d), 18 Feb 1971, US Appl. 20 Jun 1969; 28 pp. The title compds. (I), active against e.g.



I

Syphacia muris, *Trichostrongylus*, were prepd. according to U.S. 3,010,968 from 3,4-(H$_2$N)$_2$C$_6$H$_3$COR (II) and H$_2$N(MeS)C:NCO$_2$R¹. II were prepd. from PhF and RCOCl in the presence of AlCl$_3$ via *p*-FC$_6$H$_4$COR, nitration and ammonolysis to give 4,3-H$_2$N(O$_2$N)C$_6$H$_3$COR, which were hydrogenated over Pd/C. Among 14 compds. prepd. were I (R and R¹ given): Ph, Me (III); Et, Me; cyclopropyl, Me; *p*-MeOC$_6$H$_4$, Me; 2-thienyl, Me; Ph, Et. III had LD$_{50}$ >80 mg/kg in sheep and >40 mg/kg in mice, rats, chicks, and chickens on oral administration. KRPG

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A8

NALIDIXIC ACID

PATENTS

1967-1985

ANALYSIS OF THE ABSTRACTS OF PATENTS

Among the patents cited A8.25. seems to be an interesting alternative to the standard process. In this process ethylamino-methyl-pyridine is used so that the ethylation step of the standard process can be omitted. Also patents A8.8., A8.10. and A8.17. are similar to the standard process. (in A8.8. there is an obvious misprint in the first reaction step.)

The process given in A8.18 seems to be of particular interest because it makes use of relatively cheap starting materials (acetoacetic ester and orthoformic acid).

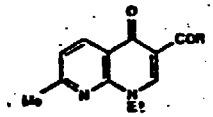
In A8.21. different alkylation procedures for 1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridin-3-carboxylicester and subsequent hydrolysis to nalidixid acid are described.

ABSTRACTS OF PATENTS

NALIDIXIC ACID

Preparation

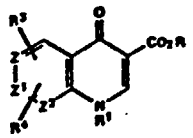
A8.1. 101: 130678e 1-Ethyl-4-oxo-1,4-dihydro-7-methyl-1,8-naphthyridine derivatives. Garemszegi, Ferenc; Leboczky, Gabor; Somfai, Eva; Ban, Karoly; Hernadi, Gyula, Mrs. (Chinoin Gyogyszer es Vegyeszeti Termekek Gyara Rt.) Hung. Teljes HU 30,014 (Cl. C07D471/04), 28 Feb 1984, Appl. 80/2,819, 26 Nov 1980, 14 pp. The title compds. I (R = C1-2 alkyl or alkoxy) were



I

prepd. Thus, 75 kg I (R = H) was ethylated with 90 kg Et_3PO_4 in the presence of 23 kg K_2CO_3 in 30 kg ligroine for 1 h at 140–160°; the azeotrope was distd. simultaneously and the mixt. was heated at 210° to give 76 kg I (R = Et). The latter was saponf. to give nalidixic acid.

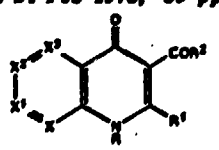
A8.2. 92: 76479h 1-Substituted-1,4-dihydro-4-oxo-3-pyridinecarboxylic acid derivatives. Agui, Hideo; Saji, Ikutaro; Nakashita, Mitsuo (Sumitomo Chemical Co., Ltd.) Jpn. Kokai Tokkyo Koho 79,112,877 (Cl. C07D215/48), 04 Sep 1979. Appl. 78/18,794, 20 Feb 1978; 5 pp. Fifty-one title derivs. I [R^2 = alkyl, OH- or halo-substituted alkyl, alkenyl; R^3, R^4 = H, halo, NO_2, alkyl, alkenyl, aryl, R^5R^6N (R^5, R^6 = H, alkyl; R^5R^6N may form a ring); Z, Z^1, Z^2 = CH, N] were prepd. by e.g.,



I, R=R^2, R^1=H
II, R=H, R^1=R^7

alkylation of II (R^7 = H, alkyl) in the presence of quaternary ammonium salts or KF followed by hydrolysis. Thus, 11.65 g II (R^3R^4 = 6,7-OCH_2O, R^7 = H, Z = Z^1 = Z^2 = CH) was stirred in H_2O 30 min at 20–5°, 0.59 g Bu_4N^+ Br^- added, 27 g Et_2SO_4 added, 55 g 20% aq. KOH added over 30 min, the mixt. heated 1 h at 40–5°, 68 g 20% H_2SO_4 added, and the mixt. heated 2 h at 90–5° to give 12.8 g I (R^2 = Et, R^3R^4 = 6,7-OCH_2O, Z = Z^1 = Z^2 = CH). K. Sempuku

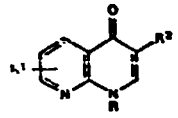
A8.3. 92: 41916w 4-Pyridinone-3-carboxylic acids and/or their derivatives. Grohe, Klaus; Zeiler, Hans Joachim; Metzger, Karl (Bayer A.-G.) Ger. Offen. 2,808,070 (Cl. C07D471/04), 30 Aug 1979, Appl. 24 Feb 1978; 39 pp. The title compds. I



I

(1–3 of X–X^3 = N, the rest optionally substituted CH; R = *tert*-alkyl, cycloalkyl, optionally substituted NH_2, heterocyclyl; R^1 = H, alkyl, aryl, aralkyl; R^2 = OH, ester or amide group) were prepd. for use as bactericides and feed additives (no data). Thus, 2-chloro-6-methylnicotinoyl chloride reacted with MeN=HCMe:$CHCO_2H$ in dioxane in the presence of 1,8-diazabicyclo=[5.4.0]undec-7-ene to give 54% I (X = N, X^1 = CMe, X^2 = X^3 = CH, R = R^1 = Me, R^2 = OMe).

A8.4. 85: 9[illegible] 1-Alkyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acids. Otaka, Hiroshi; Miura, Susumu; Nagai, Kunio (Kanebo, Ltd.) Japan. Kokai 76 32,594 (Cl. C07D[illegible]), 19 Mar 1976, Appl. 74/[illegible]264, 11 Sep 1974; 3 pp. Naphthyridines I (R = alkyl; R¹ = H, alkyl, alkoxy,

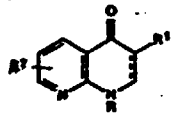


I. R¹=H
II. R¹=CO₂H

nitrofuryl, nitrofuryvinyl, OCH_2O) were treated with $COCl_2$ or its derivs. and hydrolyzed to give title carboxylic acids II. Thus, 1.2 g I [R = Et, R¹ = $CH(MeO)_2$] in THF was stirred with 1.2 ml $ClCO_2Et$ at room temp. 0.5 hr and hydrolyzed with *N* NaOH to give 0.4 g corresponding II. Among 7 more II prepd. were (R, R¹ given): Et, 7-[illegible]; Me, 7-Me; Et, 7-Et; Et, 7-nitrofuryivinyl.

I. Matsumoto

A8.5. 85: 94340r 1-Alkyl-1,4-dihydro-4-oxo-1,8-naphthyridines. Tayama, Tatsuya; Nagai, Kunio; Iizuka, Yasuhiro (Kanebo, Ltd.) Japan. Kokai 76 32,593 (Cl. C07D471/04), 19 Mar 1976, Appl. 74/104,526, 10 Sep 1974; 3 pp. Tetrahydrona-



I. 2,3-satd.
II. 2,3-unsatd.

phthyridines I (R = alkyl; R¹ = alkyl, hydroxyalkyl, carboxy, substituted carboxy; R² = H, alkyl, alkoxy, alkylthio, alkylsulfinyl, amino, nitro, alkylamino, hydrazino, carboxyacylamino, nitrofuryivinyl, pyrrolidino, piperazino) were dehydrogenated to give 1,4-dihydro-4-oxonaphthyridines II. Thus, 2 g I (R = Et, R¹ = CO_2H, R² = 7-Me) was refluxed with 6 g 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in C_6H_6 1.5 hr to give 1.71 g corresponding II. Also prepd. were II (R¹ = CO_2H, R² = 7-Me, R = Me, Bu). Chloranil was also the dehydrogenating agent. I. Matsumoto

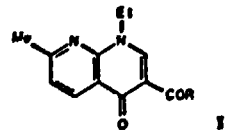
A8.6. 85: 94339x 1-Alkyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acids. Aikawa, Norio; Tayama, Tatsuya; Otaka, Hiroshi (Kanebo, Ltd.) Japan. Kokai 76 32,592 (Cl. C07D471/04), 19 Mar 1976, Appl. 74/104,525, 10 Sep 1974; 3 pp. Naphthyridine ketals I (R = alkyl; R¹ = H, alkyl, alkoxy,

I II

alkylthio, alkylsulfinyl, amino, nitro, alkylamino, hydrazino, carboxyacylamino, pyrrolidino, piperazino; R², R³ = alkyl, R^2R^3 = alkylene) were carboxylated with $COCl_2$ or its derivs. and the ketals hydrolyzed to give title carboxylic acids II. Thus, 1 g I (R = Et, R¹ = 7-Me, $R^2R^3 = CH_2CH_2$) in $CHCl_3$ was treated with 1 g $COCl_2$ at 0°, kept at room temp. 3 hr, and hydrolyzed with *p*-toluenesulfonic acid in Me_2CO to give 0.4 g II (R = Et, R¹ = 7-Me). Also prepd. was II (R = Me, R¹ = 7-Me). The carboxylation was also effected with $ClCO_2Et$ in DMF.

I. Matsumoto

A8.7. 85: 5609v 1-Ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid. Chinoin Gyogyszer- es Vegyeszeti Termekek Gyara Rt. Neth. Appl. 74 16,927 (Cl. C07D, A61K), 01 Jul 1975, Hung. Appl. CL-1430, 29 Dec 1973; 7 pp. The title compd. I (R = OH) was prepd. in 97.5%



I

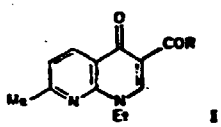
yield by the alk. hydrolysis of I (R = CH_2N^+Z,I^-, where N^+Z = pyridinium, α-picolinium, quinolinium, or isoquinolinium).

A8

84: 121798j 3-Acetyl-1,4-dihydro-4-oxo-1,8-naphthyridines. Lesher, George Y.; Brundage, Ruth P. (Sterling Drug, Inc.) U.S. 3,925,398 (Cl. 260-295N; C07D), 09 Dec 1975, Appl. 333,541, 20 Feb 1973; 9 pp. Division of U.S. 3,875,017. 2-Amino-6-methylpyridine was treated with EtOCH:CHCOC=H₂CO₂Et and the α-(6-methyl-2-pyridylaminomethylene)aceto-acetate cyclized to give 3-acetyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine which was ethylated followed by treatment with NaOH and Br to give 1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid. The naphthyridines were bactericidal (no data).

A8.9.

84: 59431d 1,8-Naphthyridine derivatives. Chinoin Gyogyszer-es Vegyeszeti Termekek Gyara Rt. Neth. Appl. 74 15,925 (Cl. C07D, A61K), 01 Jul 1975, Hung. Appl. CL-1430, 29 Dec 1973; 11 pp. The bactericidal (no data) acid I (R = CO₂H) was

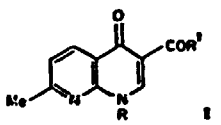


I

prepd. by treating I (R = CHMe₂, CH₂R¹, R¹ = Me, Et, Pr, Ph, CH₂Ph, cyclohexyl, cyclohexylmethyl) with pyridine, picoline, isoquinoline, quinoline, or NMe₃ and iodine to give the quaternary iodides I (R = quaternary ammoniomethyl) and hydrolyzing with base.

A8.10.

179028d 3-Acetyl-1-alkyl-1,4-dihydro-4-oxo-1,8-naphthy=ridines and intermediates. Lesher, George Y.; Brundage, Ruth P. (Sterling Drug, Inc.) U.S. 3,895,017 (Cl. 260-295R; C07D), 15 Jul 1975, Appl. 333,541, 20 Feb 1973; 9 pp. Division of U.S. 3,875,172. 2-Amino-6-methylpyridine was treated with

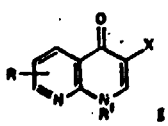


I

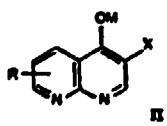
EtOCH:C(CO₂Et)COMe and the α-(6-methyl-2-pyridylaminome=thylene)acetoacetate, cyclized to the naphthyridine I (R = H, R¹ = Me), which was ethylated and the I (R = Et, R¹ = Me) brominated in NaOH to give I (R = Et, R¹ = OH).

A8.11.

131562w 1-Alkyl-3-substituted-4-oxo-1,8-naphthyridine derivatives. Morita, Yoshiharu; Wagatsuma, Kazuo (Mitsubishi Chemical Industries Co., Ltd.) Japan. Kokai 75 24,292 (Cl. 16E612), 15 Mar 1975, Appl. 73 74,658, 02 Jul 1973; 6 pp.



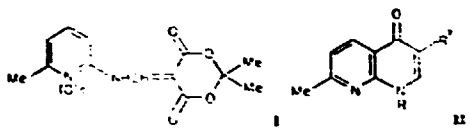
I



II

1-Alkyl-3-substituted-4-oxo-1,8-naphthyridines I (R = H, alkyl, alkoxy; R¹ = alkyl; X = alkoxycarbonyl, carboxylic acid alkali metal salts) were prepd. by reaction of 3-substituted-4-h=ydroxy-1,8-naphthyridine alkali metal salts II (M = alkali metals) with alkyl trifluor methanesulfonates followed by hydrolysis of the resulting complexes. Thus, 2 g 3-ethoxycarbon=yl-4-hydroxy-7-methyl-1,8-naphthyridine (III) was added to a mixt. of PhMe, EtOH, and 0.37 g K and the whole refluxed 2 hr to give 2.45 g III K salt. Reflux of a mixt. of III K salt and 3.5 g Et trifluoromethanesulfonate in Et₂O 2 hr and hydrolysis with 5% aq. NaOH 2 hr with reflux gave 87.2% 1-ethyl-3-carboxy-4-=oxo-7-methyl-1,8-naphthyridine (nalidixic acid) (IV). Also, 3-ethoxycarbonyl-1-ethyl-4-oxo-7-methyl-1,8-naphthyridine was prepd. IV was antibacterial. K. Sempuku

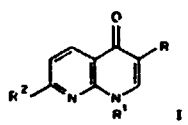
97253m [illegible] 1-oxo-1,8-naphthyridines from cyclic alkylidenemalonates and (pyridylaminomethylene)malonates. Hair, Robert K. (Sterling Drug, Inc.) U.S. 3,856,800 (Cl. 260-295N; C07d), 24 Dec 1974, Appl. 335,733, 26 Feb 1973; 9 pp.



I II

The isopropylidenyl methylenemalonate I (n = 0) was oxidized and the resulting I (n = 1) was cyclized by heat and hydrogenated to give the naphthyridine II (R = R^1 = H), which was hydroxymethylated and the resulting II (R = H, R^1 = $HOCH_2$) alkylated with EtI and oxidized with $KMnO_4$ to give II (R = Et, R^1 = CO_2H). Correction of *CA* 82: 140101b.

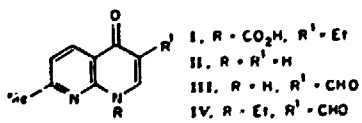
A8.13. **97252h 1-Alkyl-1,4-dihydro-7-substituted-4-oxo-1,8-naphthyridine-3-carboxylic acids via the 3-aminomethyl analogs.** Lesher, George Y.; Gruett, Monte D. (Sterling Drug, Inc.) U.S. 3,882,132 (Cl. 260-295.5R; C07d), 06 May 1975, Appl. 339,090, 08 Mar 1973; 11 pp. The naphthyridines I (R =



I

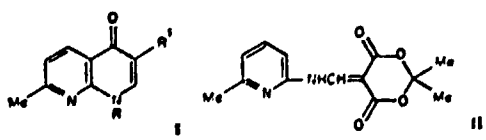
Et_2NCH_2, H, CO_2H; R^1 = H, Et; R^2 = H, Me) were prepd. Thus I (R = R^1 = H, R^2 = Me) was treated with Et_2NH and HCHO and the resulting I (R = Et_2NCH_2) ethylated to give I (R = Et_2NCH_2, R^1 = Et, R^2 = Me), which was oxidized with $KMnO_4$ to give I (R = CO_2H).

A8.14. **97250f 1-Alkyl-1,4-dihydro-7-substituted-4-oxo-1,8-naphthyridine-3-carboxylic acids via the 3-carboxaldehyde analogs.** Lesher, George Y.; Gruett, Monte D. (Sterling Drug, Inc.) U.S. 3,873,554 (Cl. 260-295.5B; C07d), 25 Mar 1975, Appl. 338,613, 06 Mar 1973; 10 pp. 1,8-Naphthyridine-3-carboxylic



acid (I), useful as a bactericide (no data) was prepd. by formylating naphthyridine II, ethylating the formyl deriv. III, and oxidizing IV. Thus, 3.8 g III, obtained by formylation of II, was heated with 3.8 g EtI in DMF contg. K_2CO_3 for 90 min to give IV, which was oxidized ($KMnO_4$) to give I.

A8.15. **79218x 1-Alkyl-1,4-dihydro-7-substituted-4-oxo-1,8-naphthyridine-3-carboxylic acids via the 3-hydroxymethyl analogs.** Lesher, George Y.; Gruett, Monte D. (Sterling Drug, Inc.) U.S. 3,869,464 (Cl. 260-295.5B; C07d), 04 Mar 1975, Appl. 335,734, 26 Feb 1973; 10 pp. 1,8-Naphthyridine-3-carboxylic

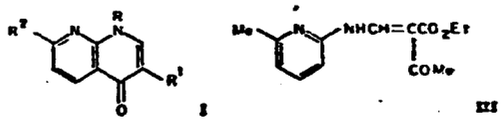


I II

acid (I, R = Et, R^1 = CO_2H), useful as a bactericide (no data), was prepd. from cyclic isopropylidenyl malonate II via cyclization, hydroxymethylation, ethylation, and oxidn. Thus, I (R = R^1 = H) obtained by cyclization of II, was hydroxymethylated with HCHO to give I (R = H, R^1 = CH_2OH), which was ethylated (EtI) to I (R = Et, R^1 = CH_2OH). Oxidn. of the latter with $KMnO_4$ gave I (R = Et, R^1 = CO_2H).

...16. 557...p 3-Dialkylaminomethyl-1,4-dihydro-4-ox...-1,8-naphthyridines. Lesher, George Y.; Gruett, Monte D. (Sterling Drug, Inc.) U.S. 3,876,650 (Cl. 260-295N; C07d), 08 Apr 1975, Appl. 329,692, 06 Mar 1973; 11 pp. Aminomethylation of 1,4-dihydro-4-oxo-1,8-naphthyridines followed by alkylation and oxidn. gave 1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acids, useful as bactericides (no data). Thus, 1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine was refluxed with Et2N in aq. CH2O to give the 3-(diethylaminomethyl) deriv. which was alkylated with EtI and then oxidized with KMnO4 in aq. pyridine to yield 1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid.

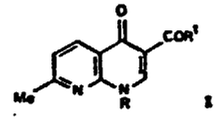
A8.17. 55783n 1-Alkyl-1,4-dihydro-7-substituted-4-oxo-1,8-naphthyridine-3-carboxylic acids via the 3-acetyl analogs. Lesher, George Y.; Brundage, R. Pauline (Sterling Drug, Inc.) U.S. 3,875,172 (Cl. 260-295.5B; C07d), 01 Apr 1975, Appl. 333,541, 20 Feb 1973; 10 pp. Antibacterial (no data)



I III

naphthyridinecarboxylate I (R = Et, R1 = CO2H, R2 = Me) (II) was prepd. from acetoacetate III. Thus, heating a mixt. of III and mineral oil for 30 sec at 300° gave I (R = H, R1 = Ac, R2 = Me) (IV). To a suspension of IV and DMF was added EtI to give I (R = Et, R1 = Ac, R2 = Me) (V). The addn. of V to a cooled soln. of NaOH-H2O-Br gave II. The condensation of 6-methyl-2-pyridinamine with EtOCH:CAcCO2Et gave III.

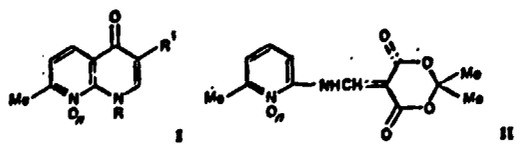
A8.18. 43292c 1,4-Dihydro-1,8-naphthyridin-4-ones. Meszaros, Zoltan; Hermecz, Istvan; Vasvari, Lelle; Horvath, Agnes; Rittli, Peter; Mandi, Atilla (Chinoin Gyogyszer es Vegyeszeti Termekek Gyara Rt.) Ger. Offen. 2,432,730 (Cl. C 07d), 06 Feb 1975, Hung. Appl. CI-1397, 17 Jul 1973; 16 pp.



I

Four naphthyridinones I (R = H, Et; R1 = Me, CF3, OH), useful as bactericides (no data), were prepd. from 2-amino-6-methylpyridine (II). Thus, II, MeCOCH2CO2Et, and HC(OEt)3 were heated in the presence of AlCl3 to give 82% Et 2-[[(6-methyl-2-pyridyl)amino]methylene]acetoacetate, which was heated in paraffin oil to give 79.5% I (R = H, R1 = Me) (III). III was ethylated with EtI and K2CO3 in DMF to give 95.7% I (R = Et, R1 = Me), which on treatment with Br in aq. NaOH and dioxane at 5-10° gave 65% I (R = Et, R1 = OH).

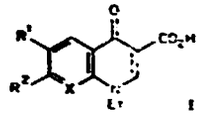
A8.19. 170564v 1,4-Dihydro-4-oxo-1,8-naphthyridine-3-carboxaldehydes. Lesher, George Y.; Gruett, Monte D. (Sterling Drug, Inc.) U.S. 3,857,851 (Cl. 260-295N; C 07d), 31 Dec 1974, Appl. 338,613, 06 Mar 1973; 10 pp. The title carboxaldehyde I



I II

(R = H, R1 = CHO, n = 0) was prepd., ethylated to I (R = Et), and oxidized to I (R = Et, R1 = CO2H, n = 0). Thus, II (n = 0) was oxidized to II (n = 1) with m-ClC6H4CO2OH, the product cyclized to I (R = R1 = H, n = 1) (III) at 275° in di-Et phthalate and III hydrogenated to give I (R = R1 = H, n = 0) (IV). Formylation of IV (DMF, POCl3) gave I (R = H, R1 = CHO, n = 0). This was ethylated to I (R = Et, R1 = CHO, n = 0) with EtI and the product oxidized with KMnO4 to give I (R = Et, R1 = CO2H, n = 0).

A8.20. [illegible] 4-Oxo-1,4-dihydro-3-quinolinecarboxylic acids and 3-aza derivatives. Budesinsky, Zdenek; Roubinek, Frantisek Czech. 154,546 (Cl. C 07d), 15 Aug 1974, Appl. 7365/72, 01 Nov 1972; 5 pp. The title compds. I (R^1R^2 = OCH_2O, X = CH; R^1 = H, R^2 = Me, X = N) were prepd. in 94.2% and 60% yields, resp., by reaction of the corresponding 3-acetylidihydroquinoline or 3-acetylnaphthyridine with NaOCl or NaOBr in aq. NaOH-dioxane. I are antibacterial (no data).



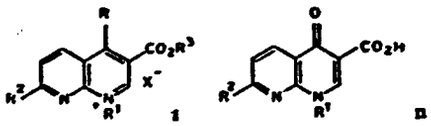
I

L. J. Urbanek

A8.21. 49668k 1-Ethyl-1,4-dihydro-4-oxo-7-methyl-1,8-naphthyridine-3-carboxylic acid (nalidixic acid). Veza, Lucia M.; Badea, Veronica; Radulescu, Nora; Ambrus, Ivan P. (Institutul de Cercetari Chimico-Farmaceutice) Rom. 56,228 (Cl. C 07d), 08 Nov 1973, Appl. 63,979, 20 Jul 1970; 2 pp. Nalidixic acid was prepd. by ethylation of Et 1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylate with Et_2SO_4, $MeC_6H_4SO_2Et$, $PhSO_2Et$ (1:1.5–3 molar). The product was hydrolyzed without sepn. of the intermediate. The ethylation was conducted either without a solvent or in the presence of hydrocarbons inert to the alkylating agents, preferably xylene. Reaction time was 0.5–5 hrs.

Lola Brodfeld

A8.22. 133409p 1-Ethyl-1,4-dihydro-7-methyl-1,8-naphthyridine-3-carboxylic acid. Domori, Renzo; Yoshimura, Ryuichi (Daiichi Seiyaku Co., Ltd.) Japan. Kokai 73 80,597 (Cl. 16 E612), 29 Oct 1973, Appl. 72 12,411, 03 Feb 1972; 3 pp. 1-Substituted

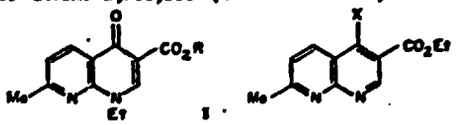


I II

1,8-naphthyridinium salts I, (R^1 and R^2 = lower alkyl; R^3 = H or lower alkyl; X = halogen; R = NH_2 or substituted amino) were hydrolyzed to give the naphthyridines II. II are bactericides. Thus, 2.31 g Et 4-R^4-7-methyl-1,8-naphthyridine-3-carboxylate (III) (R^4 = NH_2) and EtI was refluxed in EtOH for 12 hr to give 2 g I (R = NH_2, R^2 = Me, R^1 = Et, X = I), which (3.87 g) was heated 1 hr at 100° in 5% NaOH to give 81.2% II (R^1 = Et, R^2 = Me) (IV). III (R^4 = piperidino) and Me_2SO_4 was similarly treated to give IV.

Hiroshi Kataoka

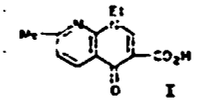
A8.23. 3486a 1-Ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid and ester. Nakagome, Takenari; Agui, Hideo; Mitani, Toru; Nakashita, Mitsuo (Sumitomo Chemical Co., Ltd.) Ger. Offen. 2,166,375 (Cl. C 07d), 18 Oct 1973, Japan. Appl. 70 7895, 28 Jan 1970; 25 pp. Division of Ger. Offen. 2,103,805 (*CA* 75: 98458b). The 1-substituted



I II, X = OEt III, X = Cl

oxonaphthyridine (I, R = Et or H), useful as antibacterial or central nervous system-stimulating drug, was prepd. from the ethoxy deriv. II with Et group migration either by heating without solvent at 155–60° in an oil bath, or in the presence of EtI on a water bath, or in the presence of EtBr in a closed tube at 130°, optionally followed by sapon. II was prepd. by treating III with EtONa.

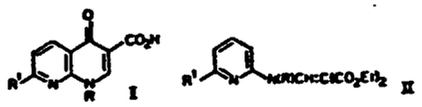
A8.24. 38530a 1-Ethyl-7-methyl-1,4-dihydro-1,8-naphthyridin-4-one-3-carboxylic acid. Kovacs, Gabor; Meszaros, Zoltan; Bodnar, Janos; Kadas, Istvan (Chinoin Gyogyszer es Vegyeszeti Termekek Gyara Rt.) Ger. Offen. 2,110,066 (Cl. C 07d), 23 Sep 1971, Hung. Appl. 11 Mar 1970; 10 pp. Title compd. (I).



I

useful as a bactericide for gram-neg. bacteria, was prepd. from Et 4-chloro-7-methyl-1,8-naphthyridine-3-carboxylate (II). Thus, II was refluxed 1 hr with $(EtO)_3PO$ and 7–8 hr with addnl. aq. NaOH to give 80% I.

A8.25. 3829g 1-Alkyl-1,8-naphthyridine-3-carboxylic acid derivatives. Wada, Yasuo; Watanabe, Nanao (Koei Chemical Co., Ltd.) Ger. Offen. 2,168,046 (Cl. C 07d), 07 Oct 1971, Japan. Appl. 20 Feb 1970; 14 pp. Title compds. (I), useful against



I II

gram-neg. bacteria, were prepd. by cyclization of aminomethyl enemalonates (II) prepd. by condensing corresponding 3-alkyl-2-(alkylamino)pyridines with $EtOCH{:}C(CO_2Et)_2$ (III) in polyphosphoric acid (IV). Thus, a mixt. contg. 102 g II (R = R^1 = Me) prepd. by heating 85 g 6-methyl-2-(methylamino)pyridine (V) and 151 g III at 100–10° and 88 g IV was heated 10 min at 200–30°. After cooling the mixt. was made alk. with 20% NaOH, extd. with Et_2O, and HOAc was added to give 42 g I (R = R^1 = Me). V was recovered from the ether phase. Similarly prepd. were 8 other I, e.g. (R and R^1 given): Et, Me; Pr, Me; Bu, Me; pentyl, Me; Et, Et.

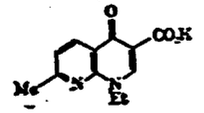
A8.26. 87933f 1-Ethyl-7-methyl-1,4-dihydro-1,8-naphthyridin-4-one-3-carboxylic acid. Kovacs, Gabor; Meszaros, Zoltan; Bodnar, Janos; Kadas, Istvan (Chinoin Gyogyszer es Vegyeszeti Termekek Gyara Rt.) Hung. Teljes 1161 (Cl. C 07d), 24 Oct 1970, Appl. 11 Mar 1970; 8 pp. The title compd. (I) was prepd. by alkylation of Et 4-chloro-7-methyl-1,8-naphthyridine-3-carboxylate (II) with Et_3PO_4 and subsequent alk. hydrolysis. Thus, a soln. of 2.5 g II in 10 ml Et_3PO_4 was refluxed 1 hr, 25 ml 10% NaOH soln. added at 100°, the mixt. refluxed until homogeneous (6–7 hr), and acidified with HCl to pH 2 to ppt 80% I, m. 225–8° (DMF–MeOH). T. Mohacsi

A8.27. 64379w 1-Ethyl-7-methyl-1,8-naphthyridin-4-one-3-carboxylic acid. Chinoin Gyogyszer es Vegyeszeti Termekek Gyara Rt. (by Zoltan Meszaros, Gabor Kovacs, Peter Szentmiklosi, and Iren Czibula). Hung. 153,292 (Cl. C 07d), Nov. 22, 1966, Appl. June 23, 1965; 3 pp. Et 4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylate (m. 272–3°, 116 g.) was heated with stirring in 273 g. Et_3PO_4 to 210° in about 1 hr., the mixt. was kept at 210–15° for 30–40 min., allowed to cool with stirring to 50–60° and 300 g. NaOH in 2000 ml. H_2O added. The soln. was heated with stirring and refluxed for 2 hrs., acidified with dil. HCl to pH 3–4 at room temp., the ppt. collected, washed, suspended in 1000 ml. H_2O, and treated with 20% NaOH (pH 9), decolorized, and acidified again, to yield 100 g. title product, m. 225–6° (AcOH or $HCONMe_2$). T. Mohacsi

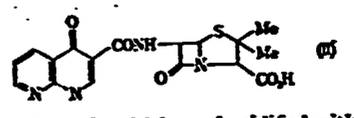
NALIDIXIC ACID

Use

A8.28. 111464k 6-(Nalidixamido)penicillanic acid. Uglesic, Ana; Seiwerth, Rativoj (Pliva Pharmazeutische und Chemische Fabrik) Ger. Offen. 1,940,511 (Cl. C 07*d*), 26 Mar 1970, Yugoslavia Appl. 08 Aug 1968; 6 pp. Nalidixic acid (I) (0.01 mole) dispersed in a 1:3 Me_2CO-dioxane mixt. and 2.0 ml Et_3N was treated 15 min with 0.01 mole iso-BuO_2CCl in 10 ml dioxane in an ice bath, 0.01 mole 6-aminopenicillanic acid and 2 ml Et_3N



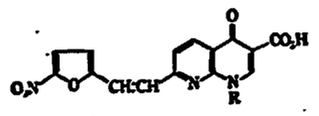
(I)



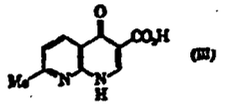
(II)

in 20 ml H_2O added, and the mixt. stirred 1 hr and acidified with 1*M* HCl to pH 3.5 to give 59% antimicrobial title compd. (II). KHPG

A8.29. 66551u Bactericidal 1-ethyl-7-[β-(5-nitro-2-furyl)vinyl]-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid. Kovacs, Gabor; Meszaros, Zoltan; Szentmiklosi, Peter; Bodnar, Janos; Simonidesz, Vilmos (Chinoin Gyogyszer es Vegyeszeti Termekek Gyara Rt.) Ger. Offen. 1,933,463 (Cl. C 07*d*, A 61*k*), 30 Jul 1970, Hung. Appl. 15 Jul 1968; 17 pp. The bactericidal title compd. (I, R = Et) was prepd. by reaction of 5-nitrofurfural (II) and III and subsequent ethylation. Thus, refluxing II and III in HOAc, Ac_2O, and NaOAc for 4 hr gave 72% I (R = H).



(I)



(III)

which was treated with $(EtO)_2PO$ to give 87.5% I (R = Et) (IV). IV was active against bacteria. KSPG

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A9

NICOTINAMIDE

PATENTS

1967-1985

APPENDIX P9

ANALYSIS OF THE ABSTRACTS OF PATENTS

15 Synthetic patents were analysed, 11 of which proceed from the nitrile (A9.1., A9.4. - A9.13.).

Hydration is frequently carried out in presence of metal oxide catalysts In A9.9. a copper catalyst leads to 99.9% yield.

In patent A9.13. the reaction is carried out in absence of a catalyst only using water at 150-200°C and 5-20 bar pressure.

The use of an ion exchanger is claimed in two patents: A9.4. describes hydration with DOWEX 1X4 in OH form, A9.6. describes the use of strongly basic ion exchanger, e.g. WOFATIT SBW in OH form.

In A9.3. nicotinamide is synthesized from 3-pyridylmethanol and ammonia, in A9.2. from pyridine-3-aldehyde, ammonia and oxygen.

The process nicotinic acid and ammonia is not described.

In A9.19. a catalyst is given, which allows transformation of a nitril to the amide with 100% selectivity in the case of acrylamide.

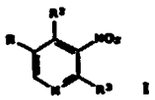
ABSTRACTS OF PATENTS

A9

NICOTINAMIDE

Preparation

A9.1. 100: 120889b Nicotinic acid derivatives. Simonovitch, Chaim (ABIC Ltd.) Israeli IL 56,965 (Cl. C07D213/64), 31 Dec 1982, Appl. 28 Mar 1979; 13 pp. The title compds. I [R = cyano, $CONH_2$,



I

CO_2R^1; R^1 = alkyl; R^2 = halo; R^3 = Cl; R ≠ CO_2R^2, R^2,R^3 = OH, R^2 = NH_2] were prepd. Thus, chlorination of II by $POCl_3$ at 5° followed by overnight refluxing gave the dichloro deriv. I (R = CO_2Me, R^2 = R^3 = Cl) which was converted into the nitrile followed by hydrolysis to give the amide.

A9.2. 94: 65475u Carboxylic acid amides. Asahi Chemical Industry Co., Ltd. Jpn. Kokai Tokkyo Koho 80 69,518 (Cl. C07B29/00), 26 May 1980, Appl. 78/141,216, 17 Nov 1978; 3 pp. Carboxylic acid amides were prepd. by reaction of aldehydes with NH_3 or Me_2NH in the presence of O-contg. gases and Pd or Pt catalysts. Thus, a mixt. of pyridine-3-carboxaldehyde 2, 28% aq. NH_3 50, and 5% Pd/C 2 g was kept 2 h at 40° with introduction of 10 L/h O to give 57% nicotinic acid amide. $PhCONH_2$, nicotinic acid dimethylamide, and DMF were similarly prepd.
K. Sempuku

A9.3. 93: 113984n Carboxylic acid amides. Tamura, Watahiko; Fukuoka, Yohei; Nishikido, Joji; Yamamatsu, Setsuo; Suzuki, Yoshio (Asahi Chemical Industry Co., Ltd.) Jpn. Kokai Tokkyo Koho 80 22,611 (Cl. C07C102/00), 18 Feb 1980, Appl. 78/94,135, 03 Aug 1978; 3 pp. The amides were prepd. by treating primary alcs. with O and NH_3 (o primary and secondary amines) in the presence of Pd or Pt catalysts. Thus, treating aq. Me_2NH in MeOH with 5% Pd-C and air 2 h at 40° gave 78% DMF with 92% conversion of Me_2NH. Similarly prepd. were nicotinamide [from 3-(hydroxymethyl)pyridine and NH_3] and $AcONMe_2$ (from Me_2NH and EtOH).

A9.4. 90: 186814e Nicotinamide. Suverkropp, Geertrudes; Hofman, Johannes H. A. (Stamicarbon B. V.) Neth. Appl. 77 06,612 (Cl. C07D213/80), 19 Dec 1978, Appl. 77/6,612, 16 Jun 1977; 8 pp. Nicotinamide (I) was prepd. with 94% selectivity at 62% conversion by hydrolyzing aq. 3-cyanopyridine on Dowex 1X4 in the OH- form and extg. I with PhMe.

A9.5. 89: 179552u Hydrolysis of nitriles. Feldman, Julian; Smith, David W. (National Distillers and Chemical Corp.) U.S. 4,096,149 (Cl. 260-295.5A; C07D213/57), 20 Jun 1978, Appl. 521,014, 05 Nov 1974; 7 pp. The catalytic hydrolysis of nicotinonitrile or RCN (R = substituted or unsubstituted C_{1-30} alkyl, alkenyl, cycloalkyl, aryl, or alkaryl) to the corresponding amides was improved by using reaction product of $RhCl_3$ and a trialkyl trithiophosphate on a solid support such as C, Al_2O_3, SiO_2, mol. sieve, or a ligand functionalized polymer. Thus, heating $RhCl_3$, trilauryl trithiophosphite, pyridine, H_2O, and H_2C:CHCN at 120° and 225 psig initial N pressure for 18 h gave H_2C:CHCONH$_2$. Benzamide was similarly prepd.

A9.6. 85: 193568r Preparation of nicotinic acid amide from 3-cyanopyridine. Zieborak, Kazimierz; Ratajczak, Wlodzimierz; Treszczanowicz, Edward; Teichert, Andrzej; Musierowicz, Jerzy; Stefaniak, Lech (Instytut Chemii Przemysłowej) Pol. 78,808 (Cl. C07D31/44), 31 Dec 1975, Appl. 149,254, 06 Jul 1971; 4 pp. Nicotinamide (I) was obtained by incomplete hydrolysis of 3-cyanopyridine (II) by using strongly basic anion exchangers as catalysts. Thus, a mixt. contg. II 24, H_2O 33.2, and MeOH 42.8 g was passed at 50° through a column filled with Wofatit SBW in the OH^- form; 79% I was crystd. from the eluate.

A9.7. 85: 62938a Nicotinic acid amide from 3-cyanopyridine. Treszczanowicz, Edward; Teichert, Andrzej; Ratajczak, Wlodzimierz; Musierowicz, Jerzy; Zieborak, Kazimierz; Misiewicz, Leonard; Stefaniak, Lech; Bellen, Natalia (Instytut Chemii Przemysłowej) Pol. 77,202 (Cl. C07D), 31 Jul 1975, Appl. 162,442, 09 May 1973; 3 pp. An aq. 45–60% soln. of 3-cyanopyridine was treated at 90–105° with NaOH (the rate of NaOH addn. was increased continuously), the mixt. was heated at 105° for 30 min, and the hydrolysis product was purified and crystd. to give nicotinamide (I) suitable for fodder. Then the product was dissolved in H_2O, the soln. was passed through an anionite, and crystd. to give I suitable for pharmaceutical purposes. K. Butkiewicz

A9.8. 85: 21134s Nicotinic acid amide and isonicotinic acid amide. Ishioka, Ryoji; Kametaka, Norio; Marumo, Kuniomi (Showa Denko K. K.) Ger. Offen. 2,539,435 (Cl. C07D), 08 Apr 1976, Japan. Appl. 74 103,789, 11 Sep 1974; 19 pp. Nicotinamide was manufd. with selectivity of 97.9% and 3-cyanopyridine (I) conversion of 98.6% by hydrating I over Fe oxide–Ni oxide catalyst, prepd. by treating 291 g $Ni(NO_3)_2.6H_2O$ and 81 g $Fe(NO_3)_3.9H_2O$ with 219 g $(NH_4)_2CO_3$ and calcining the ppt. Isonicotinamide was similarly obtained with a selectivity of 97.2%.

A9.9. 84: 135478s Nicotinamide from 3-cyanopyridine. Okano, Takeshi; Tamaru, Akio; Umeno, Koichi (Mitsubishi Chemical Industries Co., Ltd.) Japan. Kokai 75,111,077 (Cl. C07D, B01J), 01 Sep 1975, Appl. 74 18,851, 16 Feb 1974; 6 pp. Nicotinamide (I) was prepd. by catalytic hydration of 3-cyanopyridine (II) with a Cu catalyst, prepd. by decompn. of Cu hydride. Cu hydride was decompd. in the presence of an acid amide or a compd. contg. Cr, V, Si, Fe, Ru, Ti or Zr. Thus, 398 g Na hypophosphite and 28 g H_2SO_4 in H_2O was treated at 50° with 627 g $CuSO_4.5H_2O$ and 5 g $Cr(NO_3)_3.9H_2O$ in H_2O, and 25% aq. AcOH added at 50° to give a Cu catalyst. The catalyst (1 g) was heated with 0.5 g II in H_2O at 95° for 0.5 hr to give 99.9% I. Similarly, Cu catalysts were prepd. from Cu hydride in the presence of Na_2SiO_3, NH_4VO_3, $Ti(SO_4)_2$, acrylamide or $BzNH_2$. I. Matsumoto

A9.10. 192601c Acid amides and catalyst for use in preparing them. Watanabe, Yoshihiro; Yamahara, Takeshi; Inokuma, Shun; Tokumaru, Tooru (Sumitomo Chemical Co., Ltd.) Ger. Offen. 2,429,269 (Cl. C07C, B01J), 20 Mar 1975, Japan. Appl. 73 69,555, 19 Jun 1973; 26 pp. A catalyst for hydrolyzing nitriles to amides was prepd. by polymg. 4-vinylpyridine with divinylbenzene or styrene and treating the polymer with a Cu salt, such as $Cu(O_2CH)_2.4H_2O$. Acrylonitrile was 78.8% hydrolyzed by the catalyst in 5 hr at 100° with 99.1% selectivity for acrylamide. $AcNH_2$, $H_2NCO(CH_2)_4CONH_2$, $NC(CH_2)_4CONH_2$, $BzNH_2$, $C_6H_4(CONH_2)_2$-*o*, *o*-$NCC_6H_4CONH_2$, $HOCMe_2CONH_2$, $H_2N(CH_2)_5CONH_2$, $HCONH_2$, $H_2NCOCONH_2$, and nicotinamide were similarly prepd.

A9.11.

28110y Pyridinecarboxamides from cyanopyridines. Watabiki, Yukio; Sugimoto, Nobutaka; Miyoshi, Masamitsu; Uehara, Yoshihiro; Sakai, Koji (Yuki Gosei Kogyo Co., Ltd.) Japan. Kokai 74,127,976 (Cl. 16 E431), 07 Dec 1974, Appl. 73 43,624, 19 Apr 1973; 3 pp. Cyanopyridines were hydrated to pyridinecarboxamides with a Cr oxide catalyst contg. Ni, Cu, Zn, Co, Fe, Sn, and (or) Ce oxides. Thus, 250 g $(NH_4)_2Cr_2O_7$ was mixed with 110 g basic Cu carbonate and heated at 250° for 2 hr. The catalyst (0.5 g) was heated with 50 g 3-cyanopyridine in 200 ml H_2O at 96° for 8 hr to give 99.87% nicotinamide and 0.13% nicotinic acid. 2- And 4-cyanopyridines were similarly hydrated to pyridinecarboxamides in high yields. I. Matsumoto

A9.12.

170694q Amides. Asano, Shiro; Yoshimura, Kiyotaka; Hashimoto, Masao (Mitsui Toatsu Chemicals, Inc.) Ger. Offen. 2,427,204 (Cl. C 07*cd*), 19 Dec 1974, Japan. Appl. 73 62,510, 05 Jun 1973; 18 pp. Five amides were prepd. in high conversion from RCN (R = CH_2=CH, CH_2=CMe, Ph, Et, or 3-pyridyl) by treatment with H_2O in the presence of long active Cu catalysts contg. Na, Cs, Zn, or Fe nitrates as promoters. Thus, aq. CH_2=CHCN was freed from O and then heated with Raney Cu and 20 ppm $NaNO_3$ at 120° to give CH_2=$CHCONH_2$ and ≤0.5% by-products at 68% conversion rate.

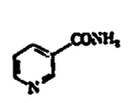
A9.13.

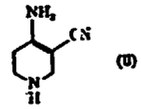
147816q Nicotinamide. Sugihara, Akira; Kakei, Minoru; Mitsuno, Shinya (Fujisawa Pharmaceutical Co., Ltd.) Japan. 73 03,625 (Cl. C 07*d*), 01 Feb 1973, Appl. 70 127,208, 29 Dec 1970; 2 pp. Nicotinamide was prepd. in 35.5–62.7% yield by treating 3-pyridinecarbonitrile with H_2O at 5–29 kg/cm² and 150–200° in the absence of a catalyst. S. Morita

A9.14.

81206n Nicotinamide. Wendler, Norman L.; Taub, David; Kuo, Chan Hwa (Merck and Co., Inc.) U.S. 3,450,706 (Cl. 260-295.5; C 07*d*), 17 Jun 1969, Appl. 03 Jun 1966; 4 pp. The title compd. was prepd. from 1-acyl-3-cyano-4-oxohexahydropyridine by (*1*) a Ritter reaction to give a *tert*-butyl amide, (*2*) redn. to a 4-OH compd., (*3*) acylation, (*4*) aromatization with loss of the 1- and 4-substituents, and (*5*) hydrolysis. Thus, to a soln. of 13.2 g. 1-acetyl-3-cyano-4-oxohexahydropyridine in 350 ml. AcOH was added 37 ml. concd. H_2SO_4 at 20°; iso-C_4H_8 was bubbled in to give *N-tert*-butyl-1-acetyl-4-oxohexahydronicotinamide (I), m. 90–8°. I (2.2 g.) in 40 ml. H_2O was reduced with 0.5 g. $NaBH_4$ in 20 ml. H_2O contg. 2 drops 2.5*N* NaOH to give *trans*-*N*-*tert*-butyl-1-acetyl-4-hydroxyhexahydronicotinamide (II), m. 167–8°. II (1 g.) mixed with 2.5 ml. Ac_2O and 5 ml. C_5H_5N gave *trans*-*N*-*tert*-butyl-1-acetyl-4-acetoxyhexahydronicotinamide (III), m. 165–6°. A mixt. of 0.8 g. III, 0.8 g. 30% Pd/C, and 50 ml. Decalin was refluxed to give *N-tert*-butylnicotinamide, m. 85–6°, which, on hydrolysis, gave nicotinamide. Also prepd. were 1-acetyl-3-cyano-4-amino-1,2,5,6-tetrahydropyridine, m. 177–8°, *cis*-*N*-*tert*-butyl-1-acetyl-4-acetoxyhexahydronicotinamide, m. 184–7°, and 1-acetylhexahydronicotinamide, m. 141–2°. Carl Osuch

A9.15: 81191d 1-Acetylhydronicotinamides. Wendler, Norman L.; Taub, David; Kuo, Chan Hwa (Merck and Co., Inc.) U.S. 3,441,568 (Cl. 260-294.9; C 07d), 29 Apr 1969, Appl. 03 Jun 1966; 5 pp. Nicotinamide (I) is prepd. from 3-cyano-4-amino-1,2,5,6-tetrahydropyridine (II). Thus, 150 ml. Ac_2O is added to 32.0 g. II in 300 ml. C_5H_5N at 30° to give 1-acetyl-4-amino-3-cyano-1,2,5,6-tetrahydropyridine (III), m. 177–8°. III (1.0 g.), 10 ml. C_5H_5N, and 5 ml. Ac_2O is heated 16 hrs. at 100° under N to give 1-acetyl-4-acetamido-3-cyano-1,2,5,6-tetrahydropyridine, m. 163–5°. The 4-propionamido analog was prepd. from


(I)


(II)

III and $(EtCO)_2O$. III (5.1 g.) is added portionwise to 30 ml. concd. H_2SO_4 at 10–15° over 30 min. After 2 hrs. the mixt. is added dropwise to 250 ml. H_2O at 0–5° and worked up to give 1-acetyl-4-oxohexahydronicotinamide (IV), m. 155–7°. 4-Amino-3-cyano-1,2,5,6-tetrahydropyridine is similarly converted into 4-oxohexahydronicotinamide. IV (2.0 g.) in 35 ml. MeOH is hydrogenated in 20 ml. MeOH over 500 mg. PtO_2 to give *cis*-1-acetyl-4-hydroxyhexahydronicotinamide (V), m. 135–40 and 150–5°. V is acetylated to give *cis*-4-acetoxy-1-acetylhexahydronicotinamide (VI), m. 154–8°. IV (1 g.) in 10 ml. H_2O is reduced with 350 mg. $NaBH_4$ in 7 ml. H_2O contg. 1 drop 2*N* NaOH to give *trans*-1-acetyl-4-hydroxyhexahydronicotinamide (VII), m. 190–2°. VII is acetylated to give the di-Ac deriv. (VIII), m. 204–5°. VI (160 mg.) and 100 mg. 30% Pd/C is heated under 1 atm. N 2 hrs. at 235–40°, during which cryst. I (m. 124–6°) sublimes from the mixt. VIII (250 mg.) and 200 mg. 30% Pd/C is refluxed in 7 ml. Decalin 18 hrs. to give I. VIII (456 mg.) in 8 ml. *tert*.-BuOH under N is treated with 2.00 ml. 1.09*N* *tert*-BuOK in *tert*-BuOH. After 18 hrs. at 25° the soln. is worked up to give 1-acetyl-1,2,5,6-tetrahydronicotinamide (IX), m. 153–5°, which with Pd/C gives I. VI (600 mg.) and 450 mg. 30% Pd/C at 200° 2 hrs. under N give 1-acetyl-1,4,5,6-tetrahydronicotinamide, m. 201–3°. VIII (500 mg.) and 400 mg. 30% Pd/C is kept 2 hrs. at 200° under N in a sublimation app. The pot residue is extd. with Me_2CO to give 1-acetyl-1,2-dihydronicotinamide, m. 175–80°, dehydrogenated to I. IV (1.00 g.) in 30 ml. 10% NH_3 in EtOH is kept in a sealed vessel 6 hrs. at 80° to give *cis*-4-hydroxyhexahydronicotinamide. All of the above reactions can also be performed starting from other lower acylates of II. Diana B. Rosen

NICOTINAMIDE

Miscellaneous

A9.16. 133056w Carbonyl and sulfonyl chlorides. Keil, Guenther (Farbwerke Hoechst A.-G.) Ger. Offen. 2,210,883 (Cl. C 07*d*), 28 Feb 1974, Appl. P 22 40 883.9, 19 Aug 1972; 15 pp. Ten carbonyl and sulfonyl chlorides, e.g. BzCl, 4-$MeC_6H_4SO_2Cl$, cyclohexanecarbonyl chloride, adipoyl chloride, or nicotinoyl chloride, were manufd. by reaction of the *N*-methylpyrrolidinone (I) or $AcNMe_2$ adduct of the appropriate acids with $COCl_2$ in MeCN. Some of the chlorides were converted in situ into amides or esters. Thus, 60 parts $COCl_2$ was passed into 61 parts BzOH, 49.5 parts I, and 200 parts by vol. MeCN within ~30 min at −15 to −10° and the temp. raised within 2 hr to ~20° to give 85% BzCl.

A9.17. 49785q Nicotinic acid. Suvorov, B. V.; et al. (Institute of Chemical Sciences, Academy of Sciences, Kazakh S.S.R. and Karaganda Metallurgical Plant) U.S.S.R. 235,764 (Cl. C 07*d*), 24 Jan 1969, Appl. 04 Nov 1966; From *Otkrytiya, Izobret., Prom. Obraztsy, Tovarnye Znaki* 1969, 46(6), 27. The title compd. is prepd. by oxidative ammonolysis of 3-picoline in the presence of a V oxide catalyst modified with Sn oxides, or promoted with W oxides followed by hydrolysis of the nicotinamide and nicotinonitrile. MGCL

A9.18. 16037p Separating an acid from an amide via an anion-exchange resin mechanism. Finkelstein, Ehud (Merck and Co., Inc.) U.S. 3,678,069 (Cl. 260/295.5A; C 07*d*), 18 Jul 1972, Appl. 60,057, 03 Aug 1970; 3 pp. The use of $CO_3^=$ in place of OH^- on strong anion exchange resins seps. acidic substances from others equally well and without hydrolysis of compds. such as niacinamide. D. E. Nettleton, Jr.

A9.19. 87: 185236u Catalyst for the manufacture of acid amides. Nakamura, Shinji; Inokuma, Shun; Tanaka, Shin; Hirose, Kenichi; Deguchi, Takashi (Sumitomo Chemical Co., Ltd.) Ger. Offen. 2,702,014 (Cl. C07C103/133), 21 Jul 1977, Japan. Appl. 76/5,289, 19 Jan 1976; 31 pp. A vanadate is treated with a cupric salt, Cu and a cupric salt, Cu and a cuprous salt, or a cupric salt and a cuprous salt to prep. catalyst for the hydration of nitriles to amides, e.g., of *acrylonitrile* (I) [107-13-1] to *acrylamide* (II) [79-06-1]. Thus, $CuCl_2$ 2.25, Na orthovanadate 1.5, and Cu 2.25 mmol. were mixed with 20 mL water, mixed with 1.2 g I, and heated at 80° for 1 h to give 85% conversion to II. The selectivity was 100%.

NICOTINAMIDE

Use

A9.20. 101: 116583a Vitamin-containing composition for hair regeneration and hair care. Agoston, Laszlo Hung. Teljes TU 31,556 (Cl. A61K7/06), 28 May 1984, Appl. 81/2,985. 15 Oct 1981; 10 pp. A hair prepn. contains an aq. ext. of wheat germ or bran and the usual vitamins. Thus, *vitamin A* [11103-57-4] 2,000,000, *vitamin D*$_3$ [67-97-0] 10,000, and *vitamin D*$_2$ [50-14-6] 12,000 IU, *vitamin C* [50-81-7] 2900, *vitamin B*$_{12}$ [68-19-9] 0.25, *vitamin B*$_6$ [8059-24-3] 225, *testosterone propionate* [57-85-2] 25, *vitamin B*$_1$ [59-43-8] 3.5, *vitamin B*$_2$ [83-88-5]50, and *vitamin E* [1406-18-4] 50 mg, 125 ng *vitamin K* [12001-79-5], 750 mg *nicotinamide* [98-92-0] and 5000 mg *choline iodide* [17773-10-3] in 200 mL water was added to 1 L wheat bran ext., to give a hair prepn. active in controlling dandruff and preventing baldness.

A9.21. 101: 97664j Antidepressants containing L-tryptophan and a monoamine oxidase inhibitor. Coppen, Alec James Brit. UK Pat. Appl. GB 2,129,299 (Cl. A61K45/06), 16 May 1984, Appl. 82/31,975, 09 Nov 1982; 3 pp. Antidepressants contain *L-tryptophan* [73-22-3] at lower doses when combined with a *monoamine oxidase* [9001-66-5] inhibitor, e.g., *phenelzine* [51-71-8] or *tranylcypromine* [155-09-9]. The antidepressant action of the compn. is greater than either compd. alone in their usual dosages. The compns. may also contain *folic acid* [59-30-3], *ascorbic acid* [50-81-7], *pyridoxine* [65-23-6], *thiamine* [59-43-8], *riboflavin* [83-88-5], *nicotinic acid* [59-67-6] or *nicotinamide* [98-92-0].

A9.22. 96: 35094t Preparation of pyridine. Organic Chemicals Co., Inc. Jpn. Kokai Tokkyo Koho JP 81 86,161 (Cl. C07D213/127), 13 Jul 1981, Appl. 79/163,942, 17 Dec 1979; 4 pp. Pyridine was prepd. from pyridinecarboxamides or cyanopyridines. E.g., treating 61 g nicotinamide with 3.14 g $Cu(OAc)_2 \cdot H_2O$ in H_2O at 310° in an autoclave gave 37.4 g pyridine.

A9.23. 91: 62750g Synthesis of a glucose tolerance factor. Silio, Fernando (Consejo Superior de Investigaciones Cientificas) Span. 472,034 (Cl. A61K), 16 Feb 1979, Appl. 26 Jul 1978; 8 pp. A synthetic glucose tolerance factor was prepd. by complexing nicotinamide with Co^{2+} and treating the resulting 2:1 complex with reduced glutathione. The product had hypoglycemic activity of 4×10^{-8} M in vitro.

A9.24. 90: 29008c Polymer of formaldehyde and carbohydrates. Blaszczak, Joseph W. Ger. Offen. 2,707,069 (Cl. C07D487/04), 24 Aug 1978, Appl. 18 Feb 1977; 18 pp. Addn. to Ger. Offen. 1,568,121. Liq., resinous or cryst. reaction products of riboflavin, nicotinamide, vitamin B_1, ribose and HCOH, and optionally contg. pyridoxine, citric acid, adenine or metal salts are prepd. by mixing the starting materials, suspending the mixt. in H_2O, and polymg. it by heating to ≤350° and/or exposing it to UV light optionally in the presence of a peroxide catalyst. These produced are useful in compns. for prevention and treatment of abnormal cell metab., including neoplasia. For example, a mixt. of riboflavin 300, ribose 25, thiamine 75, adenine 10, pyridoxine 10, Co glycinate, K carbonate 25, Mg perchlorate 10, Ca lactate 25, K permanganate 5, ferrous sulfate 25, manganese dioxide 5, ascorbic acid 50, citric acid 25, 95% paraformaldehyde 600 and nicotinamide 50 g was mixed into 2000 mL warm H_2O and then adding an O donor substance. The exothermic reaction bubbled and developed a temp. of ~80° and gave a pasty orange product. The reaction mixt. was polymd. under UV light for 3 days, held at −20° to promote stronger bonding, and then heated until it reached 150°. The cryst. polymn. product was dissolved in hot H_2O, treated with Bz_2O_2 for 1 h, cooled, heated to 100° for 1 h, and then heated to 350° to give a heat-stable, H_2O-sol. cryst. polymer product. The product formed dark cherry-red aq. solns.

A9.25. 89: 48915s Pharmaceuticals containing minerals and vitamins. Liesche Pharmaceutical Corp. Japan. Kokai 78 38,630 (Cl. A61K31/315), 08 Apr 1978, US Appl. 724,311, 17 Sep 1976; 5 pp. Mineral and vitamin complex compns. contain, e.g., $MgSO_4$ 14.47, *zinc gluconate* [4468-02-4] (as base) 23.15, $MnCl_2$ 1.16, *pyridoxine* [65-23-6] 7.23, *nicotinamide* [98-92-0] 14.47, *vitamin A* [11103-57-4] 0.87, *vitamin E* [1406-18-4] 9.69, *vitamin C* [50-81-7] 28.93, and *biotin* [58-85-5] 0.03%.

A9.26. 90046r Stable, aqueous, multivitamin preparations. Maekawa, Hideyuki; Egawa, Shohei (Shionogi and Co., Ltd.) U.S. 3,626,065 (Cl. 424/255; A 61k), 07 Dec 1971, Japan. Appl. 25 May 1967; 4 pp. Stable aq. multivitamin prepns. are obtained by formulating 2 liqs., one contg. vitamin A palmitate, niacinamide, and ascorbic acid, the other contg. thiamine. The liqs. contain the usual stabilizing and flavoring agents and are filled into sep. chambers of a partitioned container. The two liqs. are admixed just prior to use. Robert F. Doerge

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A10

OXYPHENBUTAZONE

PATENTS

1967-1985

APPENDIX P10

ANALYSIS OF THE ABSTRACTS OF PATENTS

Only 1 patent for synthesis is given which comes from a Hungarian group. In the first step 4-hydroxyazobenzene is tosylated to protect the hydroxy function. There are obviously 2 mistakes in the abstract: tosylation with toluenesulfonic acid at pH 8.5-9 will probably not succeed and butylmalonicacidchloride has to be reacted with compound III and not II.

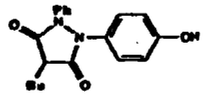
ABSTRACTS OF PATENTS

A10

OXYPHENBUTAZONE

Preparation

A10.1. 97: 38934y 1-Phenyl-2-(4-hydroxyphenyl)-3,5-dioxo-4-n-= butylpyrazolidine. Urogdi, Laszlo; Kisfaludy, Lajos; Gyuran, Janos; Patthy, Mrs. Andras; Trischler, Ferenc; Illes, Sandor (Richter, Gedeon, Vegyeszeti Gyar Rt.) Hung. Teljes HU 21,369 (Cl. C07D231/34), 28 Nov 1981, Appl. 78/Ri695, 29 Dec 1978; 13 pp. The title compd. (I) was prepd. from



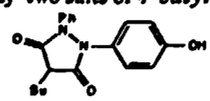
I

4-(tosyloxy)azobenzene (II) by redn. with Na_2S/AcOH, Zn/NaOH, Zn/NH_4OH, or Zn/HCl, treatment with $BuCH(COCl)_2$ or $BuCH(CO_2H)_2$, and alk. deprotection. Thus, a mixt. of *p*-HO=C_6H_4N:NPh and *p*-$MeC_6H_4SO_3H$ in Me_2CO was stirred at pH 8.5-9 and dild. with H_2O to give 96-9% II. The latter in Me_2CO was added to aq. Na_2S and stirred 30 min with AcOH to give 99.5% 4-(tosyloxy)hydrazobenzene (III). A mixt. of $BuCH(COCl)_2$, II, and pyridine in THF stirred 2 h at room temp. gave 85% product, which was stirred with NaOH in MeOH 3 h at room temp. to give 85% I. T. Mohacsi

OXYPHENBUTAZONE

Salts

A10.2. 86: 95992n Antiinflammatory compounds. Laboratorios Miquel S. A. Span. 423,379 (Cl. A61K), 16 May 1976, 19 Feb 1974; 12 pp. Twenty-two salts of *4-butyl-2-(p-hydroxyphenyl*=



I

)-1-phenyl-3,5-pyrazolidinedione (I) [129-20-4] were prepd. by the reaction of I with the appropriate basic compd., e.g. 1-benzyl-3-(3-dimethylaminopropoxy)-1*H*-indazole, *N,N*-di= ethylaminoethanol, and pyrrolidine. These derivs. showed a greater antiinflammatory activity and lower gastric toxicity than I.

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A11

PARACETAMOL

PATENTS

1967-1985

APPENDIX P11

ANALYSIS OF THE ABSTRACTS OF PATENTS

The standard process is claimed in patents A10.2., A10.5., A10.8., A10.9., A10.11., A10.14. and A11.16..

Reduction is carried out chemically or catalytically, in most cases a one pot reaction is carried out, in A11.2. and A11.16. a yield of 90% is given.

In the following patents p-nitrosophenol is used with the reduction in one case (A11.14.) carried out electrolytically, in other cases the method of reduction not being indicated: A11.1., A11.4., A11.6., A11.14. - A11.16.. In most cases one pot reaction is carried out, the yield in A11.16. being 88%.

A11.10. and A11.12. start from p-aminophenol.

In the patents A11.17. - A11.20. purification methods are described.

ABSTRACTS OF PATENTS

A11

PARACETAMOL

Preparation

A11.1. 101: 130381q N-Acetyl-p-aminophenol. Benzaria, Jacques Raphael Fr. Demande FR 2,533,559 (Cl. C07C103/38), 30 Mar 1984, Appl. 82/16,227, 27 Sep 1982; 8 pp. 4-Nitrosophenol underwent simultaneous redn. and *N*-acetylation to yield 4-AcNHC$_6$H$_4$OH. Thus, H was introduced into a mixt. of 4-ONC$_6$H$_4$OH, Pd/C, Me$_2$CHOAc, HOAc, and Ac$_2$O to give 4-AcNHC$_6$H$_4$OH.

A11.2. 101: 110547v N-Acetyl-p-aminophenol. Monsanto Co. Jpn. Kokai Tokkyo Koho JP 59 98,048 [84 98,048] (Cl. C07C103/35), 06 Jun 1984, US Appl. 439,244, 04 Nov 1982; 7 pp. 4-HOC$_6$H$_4$NHAc (I) was prepd. by simultaneous redn. and acetylation of 4-HOC$_6$H$_4$NO$_2$ (II). Thus, a mixt. of 220 g II, 80 g Me$_2$CHOH, 140 g H$_2$O, and 0.1 wt. % (based on II) 3% Pd/C was autoclaved at H 585 kPa and 110° for 8 min, 180 g Ac$_2$O was added in 59 min (at the rate of H consumption), and the mixt. was kept at H 585 kPa and 110° for another 53 min to give 90% I.

A11.3. 101: 6815v Hydroxylation of phenol and aniline derivatives by hydrogen peroxide in a superacidic medium. Morellet, Guy; Jacquesy, Jean Claude; Jouannetaud, Marie Paule (Produits Chimiques Ugine Kuhlmann) Eur. Pat. Appl. EP 97,564 (Cl. C07C69/157), 04 Jan 1984, FR Appl. 82/10,644, 18 Jun 1982; 25 pp. Phenol and aniline derivs. were treated with H$_2$O$_2$ in superacids at between −80° and 0° to yield hydroxylated isomers contg. significant amts. of the meta isomers. Thus, PhOAc and H$_2$O$_2$ were introduced into a HF-SbF$_5$ mixt. at −40°, and the mixt. was worked up after 30 min to give hydroxylated product contg. 3-HOC$_6$H$_4$OAc 51, 4-HOC$_6$H$_4$OAc 43, and 2-HOC$_6$H$_4$OAc 6%.

A11.4. 100: 191599t Purification of N-acetyl-p-aminophenol. Horyna, Jaroslav; Sadlo, Lubos Czech. CS 203,892 (Cl. C07C85/26), 15 Nov 1983, Appl. 79/6,680, 03 Oct 1979; 2 pp. The crude mixt. from redn. of *p*-ONC$_6$H$_4$OH and subsequent acetylation of *p*-H$_2$NC$_6$H$_4$OH was aerated or treated with oxidants, such as aq. H$_2$O$_2$ and AcO$_2$H, and stirred with C which removed Fe oxides and oxidn. by-products. From the decolorized filtrate 85–95% cryst. *p*-AcHNC$_6$H$_4$OH was sepd. after evapn. and cooling. L. J. Urbanek

A11.5. 99: 122018b N-Acetyl-p-aminophenol. Vitan, Marin; Dobrescu, Dumitru; Bibian, Stefan Cilianu; Cilianu, Stefan (Intreprinderea de Coloranti "Colorom") Rom. RO 76,864 (Cl. C07C91/44), 30 Aug 1981, Appl. 97,483, 11 May 1979; 2 pp. 4-Aminophenol hydrochloride was treated with NH$_3$ and Ac$_2$O to yield 4-AcNHC$_6$H$_4$OH. Thus, 4-O$_2$NC$_6$H$_4$OH was reduced, HCl was added to give 4-H$_2$NC$_6$H$_4$OH.HCl, and the product was treated with NH$_3$ and Ac$_2$O at 5–20° to give 4-acetamidophenol.

A11.6. 97: 23459y Paracetamol. Domide, Aneta; Harles, Lucian; Prejmereanu, Ion; Anghel, Dumitru (Intreprinderea de Medicamente si Coloranti "Sintofarm") Rom. RO 74,084 (Cl. C07C103/10), 08 Dec 1980, Appl. 92,381, 08 Dec 1977; 3 pp. 4-Nitrosophenol was converted to paracetamol by Na$_2$S redn. to 4-H$_2$NC$_6$H$_4$OH and subsequent *N*-acetylation.

A11.7. 96: 217499m **N-Acetyl-p-aminophenol.** Horyna, Jaroslav; Sadlo, Lubos Czech. CS 197,100 (Cl. C07C91/44), 30 Apr 1982, Appl. 78/4,877, 21 Jul 1978; 5 pp. *p*-$AcNHC_6H_4OH$ (I) was prepd. by feeding simultaneously an aq. $FeSO_4$ soln. and NH_4OH at 60–80° into an aq. suspension of *p*-ZC_6H_4OH (II) (Z = O or *m*-$HO_3SC_6H_4N$) and treating the mixt. with Ac_2O. I was salted out with NaCl or crystd. from a concd. soln. Alternatively, II was added portionwise with stirring at 50–60° into an aq. suspension contg. powd. Fe and HCl, the mixt. was treated with Ac_2O and worked up as above. L. J. Urbanek

A11.8. 95: 61757k **Stepwise reduction of p-nitrophenol.** Huber, John, Jr. (Penick Corp.) U.S. 4,264,525 (Cl. 564-223; C07C103/32), 28 Apr 1981, Appl. 53,688, 02 Jul 1979; 6 pp. The redn. of a portion of 4-$O_2NC_6H_4OH$ (I) by H to 4-$H_2NC_6H_4OH$ (II) at pH < 7.0 was followed by the addn. of Ac_2O to acylate II and give HOAc by-product, the remainder of the I was reduced at pH < 7.0, and the newly formed II was *N*-acylated to give 4-$AcNHC_6H_4OH$ at pH < 7.0. I was reduced by H over Pd/charcoal, the mixt. was cooled, Ac_2O was added, the redn. was continued until H uptake stopped, and Ac_2O was added with heating to 95° to give 4-$AcNHC_6H_4OH$.

A11.9. 95: 42649k **Borate reduction of nitrophenols.** Ruopp, Donald C.; Thorn, Mark A. (Penick Corp.) U.S. 4,264,526 (Cl. 564-223; C07C103/32), 28 Apr 1981, Appl. 54,388, 02 Jul 1979; 5 pp. Halonitrobenzenes were converted to aminophenol by alk. hydrolysis to nitrophenol and hydrogenation of the latter in media contg. borate ion, strong acids, and metal catalysts, i.e., Pd. Thus, 4-$O_2NC_6H_4Cl$ was hydrolyzed by NaOH, the 4-$O_2NC_6H_4OH$ obtained was mixed with H_2SO_4, H_3BO_3, and Pd, H was introduced, and the product was acetylated to give 4-$AcNHC_6H_4OH$, useful as an analgesic and antipyretic (no data).

A11.10. 87: 102059q **Preparation of paracetamol.** Hope, Peter; Gourley, Robert N.; Gray, John; Knight, David Hulliwell (Kodak Ltd.) Brit. 1,469,099 (Cl. C07C103/38), 30 Mar 1977, Appl. 73/50,331, 30 Oct 1973; 2 pp. Paracetamol (I) was prepd. (86%) by treating an aq. soln. of *p*-aminophenol sulfate and aniline sulfate with NH_3 to pH 5, removing the $PhNH_2$ by distn., and acetylating the *p*-aminophenol with Ac_2O at 20°, the pH being maintained at 5 with NH_3. The product comprised 95% I and 1.4% PhNHAc.

A11.11. 84: 164381k **p-Acetamidophenol.** Kulda, Drahomir; Fuka, Josef; Ott, Jan; Misar, Zdenek Czech. 159,564 (Cl. C07C), 15 Aug 1975, Appl. 9010/72, 28 Dec 1972; 2 pp. *p*-$HOC_6H_4NO_2$ was reduced with Fe in HCl and *p*-$HOC_6H_4NH_2$ (I) acetylated under conditions which minimized contamination of *p*-HOC_6H_4NHAc (II) with by products. Thus, the mixt. contg. I was neutralized with Na_2CO_3 and a portion of the I (30–80%) acetylated with Ac_2O at 55–60°, the insol. contaminants and Fe sludge were trapped by active C, and the mixt. filtered at 85–90°. The filtrate was treated with the necessary amt. of Ac_2O to complete the acetylation and II was salted out with NaCl. L. J. Urbanek

A11.12. 84: 16992v **N-Acetyl-p-aminophenol.** Schulman, Hyman L.; Baron, Frank A.; Weinberg, Alan E. (Mallinckrodt, Inc.) U.S. 3,917,695 (Cl. 260-562A; C07C), 04 Nov 1975, Appl. 33,080, 29 Apr 1970; 4 pp. Pure *p*-$AcNHC_6H_4OH$ (I) was prepd. from *p*-$H_2NC_6H_4OH$ (II) by dissolving it in HOAc, treating it with C, filtering it; the filtrate was treated with Ac_2O to form N.F. grade I which was sepd. The mother liquor was recycled after I sepn. for use as a solvent for treatment of II.

A11.13. 146250j p-Acetamidophenol. Kulda, Drahomir; Fuka, Josef; Ott, Jan; Misar, Zdenek; Liska, Karel Czech. 149,293 (Cl. C 07c), 15 Jun 1973, Appl. 3979-69, 05 Jun 1969; 2 pp. PhOH was coupled with diazotized $PhNH_2$ in dil. NaOH, the mixt. acidified, and the pptd. p-$HOC_6H_4N{:}NPh$ hydrogenolyzed in MeOH over Pd/C at <60° and 1.5–3 kg/cm² H. Unreacted $PhNH_2$ was steam distd. and the residual p-$HOC_6H_4NH_2$ treated with Ac_2O in AcOH at 15–30° to yield 95–8% p-HOC_6H_4NHAc.
L. J. Urbanek

A11.14. 65995d Electrolytic reduction of nitrosophenols to aminophenols. Greener, George Pallister; Porter, Alan Sidney (Albright and Wilson Ltd.) Ger. Offen. 2,256,003 (Cl. C 07c), 07 Jun 1973, Brit. Appl. 53,169-71, 16 Nov 1971; 33 pp. p-Nitrosophenol (I) and 4-nitroso-m-cresol (prepd. from the phenol and $NaNO_2$) were reduced electrochem. to the corresponding aminophenol; 1-nitroso-2-naphthol was similarly reduced. Addn. of Ac_2O in the rem. of I gave $AcNHC_6H_4OH$-p.

A11.15. 27009w p-Acetamidophenol. Bialik, Jozef; Jedrzejewski, Andrzej (Farmaceutyczna Spoldzielnia Pracy "Galena") Pol. 54,012 (Cl. C 07d), 31 Oct 1967, Appl. 20 Apr 1965; 2 pp. The title compd. (I) is prepd. according to the method described by redn. of p-nitrosophenol (II) with satd. aq. soln. of Na_2S at pH 8.8–10.2. Thus, 50 kg. II, contg. 45% H_2O, was added portionwise at a temp. below 45° to 75 l. aq. soln. Na_2S (sp. gr. 1.19 at 20°), the mixt. was stirred at this temp. for 1 hr., and then at 50° for another 1 hr. Aq. soln. (60 l.) of tech. pure $(NH_4)_2SO_4$ (sp. gr. 1.200 at 20°) was added to the warm mixt., the mixt. was heated at 50° for 1 hr., and cooled to 15°. Pptd. tech. pure p-aminophenol (III) was sepd. by filtration and washed with ice-water. III was acetylated with Ac_2O (0.3 kg. per 1 kg. wet III in 0.2 kg. H_2O). For this purpose III was added to H_2O, the mixt. stirred, Ac_2O added, and the mixt. stirred for 3 hrs. and cooled to 15° to crystallize. The crude I was recrystd. from H_2O. Pure I (0.49 kg.) was obtained from 1 kg. wet II in 80% yield.
Karol Butkiewicz

A11.16. 99876h N-Acetyl-p-aminophenol. Bernard F. Duessel and Godfrey Wilbert (to Nepera Chemical Co., Inc.). U.S. 3,341,587 (Cl. 260–562), Sept. 12, 1967, Appl. March 16, 1962, and Oct. 15, 1964; 2 pp. The title compd. (I) was obtained in excellent yield of high purity by the direct acylation of p-$H_2NC_6H_4OH$ formed by the catalytic redn. of certain nitrophenols in an Ac_2O reaction solvent. Thus, 350 lb. p-$O_2NC_6H_4OH$ (II) in 297 lb. Ac_2O was hydrogenated in a N purged autoclave over 770 g. 5% Pd-C catalyst under 40–60 psig. at 80–90°. After 10 hrs. reaction time, unreacted H was vented and the vessel again purged with N. To complete the acylation, 56 lb. Ac_2O was added, the mixt. heated rapidly to 80–90°, making due allowance for the exothermic reaction which takes place. After ~2 hrs. the mixt. was cooled to ~50°, treated with 35 gal. demineralized H_2O, the mass heated again to ~90°, and 100 g. $NaHSO_3$ added to prevent coloration of the product. The mixt. was then filtered at 75–80° to remove the catalyst and the filtrate cooled to 0–5° to yield (during 4 hrs.) 90% I. Using p-ONC_6H_4OH in place of II gave 88% I. With PtO_2 as hydrogenation catalyst comparable results were obtained. I is widely used as an analgesic and antipyretic in various therapeutic compns.

PARACETAMOL

Purification

A11.17. 89: 23947r **Purification of phenols.** Boecker, Ernst; Mannes, Karl; Trescher, Viktor (Bayer A.-G.) Ger. Offen. 2,644,318 (Cl. C07C37/22), 06 Apr 1978, Appl. 01 Oct 1976; 18 pp. Tech. phenols are purified by treatment with Al powder. Thus 300 g 4-$AcNHC_6H_4OH$ in 1600 mL H_2O was treated with 4 g low-FeC, 5 mL HOAc, and 2 g Al powder under N under reflux for 45 min. to give 270 g pure white 4-$AcNHC_6H_4OH$. 2-$HOC_6H_4CO_2Na$, 4-$HOC_6H_4CO_2K$, and *p*-$(HO)_2C_6H_4$ were similarly purified.

A11.18. 9491g **Purification of p-aminophenol.** Harmetz, Ronald; Ruopp, Donald C.; Brown, Bernard Beau (CPC International Inc.) U.S. 3,876,703 (Cl. 260-575; C07c), 08 Apr 1975, Appl. 367,263, 05 Jun 1973; 4 pp. *p*-Aminophenol, prepd. by electrolytic or catalytic redn. of $PhNO_2$ in aq. H_2SO_4, was obtained as a pure product by adding more $PhNO_2$ to the reaction mixt. (if the reaction had gone to completion), adjusting the pH to ~ 5-6.5, and sepg. the $PhNO_2$ phase and the purified *p*-aminophenol phase. The product after acetylation with Ac_2O gave the *N*-acetyl deriv. which met all National Formulary specifications.

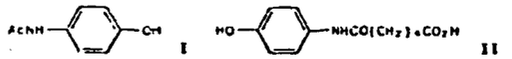
A11.19. 82385t **Purification of N-acetyl-p-aminophenol.** Kosak, John R. (du Pont de Nemours, E. I., and Co.) U.S. 3,781,354 (Cl. 260-562B; C 07c), 25 Dec 1973, Appl. 88,179, 09 Nov 1970; 2 pp. Crude light-pink-colored *p*-$AcNHC_6H_4OH$ (I), prepd. by acetylation of *p*-$H_2NC_6H_4OH$, was refluxed with aq. $FeCl_3$ soln. for 1.5 hr and then treated with activated C to give white cryst. I.

A11.20. 78380z **Purification of N-acetyl-p-aminophenol.** Baron, Frank A. (Mallinckrodt Chemical Works) U.S. 3,748,358 (Cl. 260-562P; C 07c), 24 Jul 1973, Appl. 46,840, 16 Jun 1970; 4 pp. *p*-$AcNHC_6H_4OH$ (I) was purified to N.F. specifications by treating the crude product of acetylation of *p*-$H_2NC_6H_4OH$ (contg. 80% I) in aq. soln. with charcoal, which had been previously washed with an acidic soln., and crystg. I. The Fe content of I was reduced by including a chelating agent (e.g., citric acid, gluconic acid) in the crystn. solvent or in the acid soln. used for washing the charcoal.

PARACETAMOL

Miscellaneous

A11.21. 101: 685g Acetaminophen analogs, antigens, and antibodies. Khanna, Pyare (Syva Co.) Eur. Pat. Appl. EP 95,229 (Cl. C07C103/35), 30 Nov 1983, US Appl. 364,836, 02 Apr 1982; 28 pp.

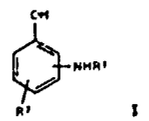


I II

Antisera can be prepd. to protein antigens or enzymes conjugated to carbonyl derivs. of acetaminophen (I). These antisera can be used as reagents in sensitive, highly specific immunoassays for monitoring I levels in biol. fluids. Thus, *adipaminophen* (II) [89519-10-3] was prepd., conjugated to *glucose-6-phosphate dehydrogenase* [9001-40-5], and antisera were prepd. in sheep. By means of the antibodies thus obtained, I at very low concns. in human serum could be detd., with very little cross-reactivity with I-metabolites or with other drugs.

A11.22. 100: 145038b Tablets by a modified 'wet-granulation' technique. Rogerson, Alan George (Sterwin A.-G.) Eur. Pat. Appl. EP 100,168 (Cl. A61K9/16), 08 Feb 1984, GB Appl. 82/19,487, 06 Jul 1982; 51 pp. A modified wet granulation method (slurry granulator) is described for prepg. good quality tablets with high dosages of active ingredient and minimal excipients. One or more drugs and excipients are moistened with a predetd. amt. of nonsolvent granulating fluid to form a uniform, moist, coherent, nonpasty mass which is subdivided into individual granules and dried. The dried granules are compressed into tablets. The amt. of granulating fluid comprises ≥90% by wt. of the predetd. amt. of fluid so as to form a homogeneous slurry where the percentage by wt. of solids in the slurry is [total solids (both dissolved and undissolved) × 100/total slurry (fluids + total solids)] = 25% wt./wt. The remaining part of the particulate solid material is moistened by wet granulation with the slurry so as to form the desired pasty mass. Tablets were prepd. from (total quantity in mixt. in milligrams and amt. in slurry in grams given): DL-*methionine* [59-51-8] 250, 125; *paracetamol* [103-90-2] 500, –; *PVP* [9003-39-8] 30, 30; stearic acid 10, –; Na starch glycolate 50, –; and 200 mL H_2O as granulating fluid.

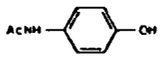
A11.23. 98: 22273a Accelerators of drug absorption in the intestine. Sawai Pharmaceutical Co., Ltd. Jpn. Kokai Tokkyo Koho JP 57,145,809 [82,145,809] (Cl. A61K31/60), 09 Sep 1982, Appl. 81/31,713, 04 Mar 1981; 5 pp. The phenol derivs. I (R^1 = H or



I

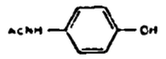
acyl; R^2 = H or CO_2H) are accelerators of drug absorption in the intestine. Thus, a suppository was prepd. by combining ampicillin Na 1.5, *4-hexanamidosalicylic acid* [83936-13-4] 1.2, and Witepsol H-15 9.3 g. Nineteen I were synthesized and their effects on drug absorption demonstrated in dogs.

A11.24. 96: 74634p **Spray dried-N-acetyl-p-aminophenol compositions.** Salpekar, Anil M. (Mallinckrodt, Inc.) Eur. Pat. Appl. EP 40,472 (Cl. A61K9/14), 25 Nov 1981, US Appl. 152,052, 20 May 1980; 17 pp. A spray-dried *N-acetyl-p-aminophenol*



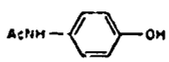
(I) [103-90-2] compn. is prepd. by forming a slurry of finely divided I and *starch* [9005-25-8] and spray-drying the slurry such that the spray-dried particles have a moisture content between 0.3 and 1.5% by wt.; the starch being gelatinized prior to or during spraying. The spray-dried compns., which may contain other active ingredients, have good compressibility and flow properties facilitating the formation of tablets, capsules, or other dosage forms. Thus, pregelatinized starch 1.5 parts was mixed with an equal quantity of I and charged to a high shear mixer contg. 100 parts H_2O. I had a particle size such that all of it passed through a 200 mesh screen and 75% through a 325 mesh screen. Addnl. I 96.5 parts was added and mixing continued until a smooth slurry was obtained which was sprayed using countercurrent conditions. This spray-dried product was formulated into tablets.

A11.25. 90: 123119y **Paracetamol granulate.** Rupp, Roland; Buecheler, Manfred; Ernst, Joachim; Vosteen, Bernhard (Bayer A.-G.) Ger. Offen. 2,713,197 (Cl. C07C103/38), 05 Oct 1978, Appl. 25 Mar 1977; 8 pp. Preservative-free *paracetamol* (I)



[103-90-2] granules (av. particle size 80-200μ) comprise 0.5-3% *poly(vinylpyrrolidone)* (PVP) [9003-39-8] and > 0.3% H_2O, and are prepd. by spray-drying an aq. suspension of 40-60% I contg. 0.5-3% PVP. The spray-drying process was conducted in an inert gas atm. by a direct flow process with an inlet temp. of 150-300° and outlet temp. of 80-150°. For example, a suspension of 500 kg powd. I and 10 kg PVP in 490 kg H_2O was spray-dried with inlet and outlet temps. of 280 and 110°. The granulate had 130 μm diam. spherical particles and contained 0.1% H_2O.

A11.26. 84: 35323u **Paracetamol tablets.** Sterwin A.-G. Fr. Demande 2,247,206 (Cl. A61K), 09 May 1975, Brit. Appl. 40,428/71, 24 Jan 1973; 17 pp. *Paracetamol* (I) [103-90-2], an analgesic, was



prepd. for tabletting by crystn. with a polymer, [*GAF S630* (vinylpyrrolidone-vinyl acetate copolymer)(II) [25086-89-9]], without grinding or the addn. of adhesives. Thus, 3500 cm^3 of an aq. soln. contg. 2 Kg I at 100° was added to 60 g II in 200 cm^3 water, underwent crystn. followed by filtration. The filtrate 1000, Solkafloc 20, and Mg stearate 2.5 g were combined and then tabletted.

A11.27. 52896q **Anti-migraine composition.** Wild, Henry Ger. Offen. 2,059,747 (Cl. A 61k, C 07d), 09 Jun 1971, Brit. App. 05 Dec 1969. The title compn. consisted of 1:70-100 1-(*p*-chlorobenzhydryl)-4-(*p*-tert-butylbenzyl)piperazine (Buclizine) and *p*-$AcNHC_6H_4OH$ (Paracetamol).

A11.28. 21900h L-Hydroxyproline and its medicinal combinations in the treatment of rheumatic diseases. Denis, J. C.; Rambaud, J. (Tecpan S. A.). Fr. M4,727 (Cl. A 61k); 06 Feb 1967, Appl. 04 Nov 1965; 2 pp. Hydroxyproline (I) in assocn. with glucosamine–HCl (II) or an antirheumatic (acetylsalicylic acid, acetyl-*p*-aminophenol (III), or 3,5-dihydroxy-1,2-diphenyl-4-butylpyrazolidine (IV)) can be used successfully in different rheumatic affections. Animal tests show that I and esp. I and II together potentiate the effects of antirheumatics and prolong their effects and permit the use of lower and less toxic doses. Thus, pills were prepd. contg. the following: II 0.200, I 0.020 g.; III 0.400, I 0.010 g.; IV 0.100, II 0.1000, I 0.010 g., for use in acute articular rheumatism, rheumatoid polyarthritis, arthrosis, periarthritis, and phlebitis. Janet D. Scott

A11.29. 21894j Medication based on a combination of N-acetyl-p-aminophenol and an enzymic product. Riviere, Jean Fr. M4,825 (Cl. A 61k), 20 Mar 1967, Appl. 13 Sep 1965; 5 pp. Mixts. of varying amts. of *p*-AcNHC$_6$H$_4$OH (I) and 3 enzymic prepns. in a suitable pharmaceutical medium have, by oral or rectal administration, analgesic, antipyretic, anti-inflammatory, and antiedemic actions superior to the individual components. Cited for oral use was a compn. contg. 300 mg. I, 1250 units CEIP amylase, 5000 units Hummel chymotrypsin, and mucopolysaccharidase (100 turbidity redn. units chondrosulfatase and 500 I.U. hyaluronidase) in a base contg. talc 0.02, levilite 0.015, and lactose, q.s.p. 0.6 g. Other formulations plus pharmacol. data, including 9 case histories, are given. D. E. Nettleton, Jr.

A11.30. 1965j Antipyretic and analgesic composition with N-acetyl-p-aminophenol. Jean Riviere. Fr. M3852 (Cl. A 61k), Feb. 21, 1966, Appl. Sept. 4, 1964; 7 pp. An antipyretic and analgesic compd. is prepd. using *N*-acetyl-*p*-aminophenol as active compound, assocd. with a barbiturate (phenobarbital), an antihistamine (promethazine), and a diffusion agent. A study of its toxicity, and pharmacol. activity is also performed.
Juan Castaner Gargallo

A11.31. 88659t Granulating materials for tableting. Lawrence Lowy and William O. Wurtz. U.S. 3,308,217 (Cl. 264–117); Mar 7, 1967, Appl. Feb. 9, 1964; 4 pp. A granulation proce[illegible] scribed that gives tablets of low friability from uniform[illegible] granules. A mixt. of physiol. active material wi[illegible] inactive thermoplastic material is heated to soften the th[illegible] plastic material and cause it to agglomerate and the mix[illegible] cooled to form uniform granules. Thus, ascorbic acid 82, co[illegible] starch 10, and poly(oxyethylene)–polypropylene copolymer (I) 8 parts were blended, heated to 80° for 5 min., cooled to room temp., and compressed into tablets. The tablets were not friable and had high hardness and soln. rates. Similarly, tablets were prepd. from thiamine, riboflavine, *N*-acetyl-*p*-aminophenol pyridoxine, and niacinamide with glyceryl tristearate instead of cornstarch, and poly(oxyethylene) glycol instead of I. COPN

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A12

PROCAINE.HCL

PATENTS

1967-1985

APPENDIX P12

ANALYSIS OF THE ABSTRACTS OF PATENTS

In patents A12.1. and A12.4. only the formation of the chlorohydrate from the base is described.

The same inventor describes in patents A12.2. and A12.3. the direct ester formation of p-nitrobenzoic acid with diethylaminoethanol with subsequent reduction and formation of chlorohydrate with a yield of 90% given in A12.3..

ABSTRACTS OF PATENTS

A12

PROCAINE.HCL

Preparation

A12.1. 102: 119707a Hydrochlorides. Szarvas, Niklos; Horvath, Eva; Cseke, Laszlo; Balint, Janos; Fabian, Ferenc; Kun, Lajos (Biogal Gyogyszergyar) Eur. Pat. Appl. EP 125,542 (Cl. C07C29/00), 21 Nov 1984, HU Appl. 83/1,497, 02 May 1983; 16 pp. HCl salts of compds. contg. protonizable N atoms are formed by incubating the compd. with a sulfonyl chloride, QSO_2Cl, where Q is OH, C_{1-4} alkyl, aryl, or C_{1-4} alkyl-substituted aryl, in an alc. medium. The method is esp. suited for prepg. pharmaceutical salts. Thus, oxytetracycline–Ca silicate complex was stirred with MeOH [67-56-1] and anhyd. $CaCl_2$, followed by gradual addn. of *chlorosulfonic acid* [7790-94-5] in MeOH. Activated C was added, the mixt. was filtered, concd. HCl was added to pH 0.4, and crystals of *oxytetracycline-HCl* [2058-46-0] were obtained by cooling.

A12.2. 48063q Esterification of a benzoic acid with a tert-amino alcohol. Levy, Joseph; Walker, William (Universal Oil Products Co.) U.S. 3,660,411 (Cl. 260-293.81; C07d), 02 May 1972, Appl. 46,514, 15 Jun 1970; 2 pp. *p*-$O_2NC_6H_4CO_2H$ was esterified with diethylaminoethanol by refluxing in xylene with HCO_2H catalyst to give diethylaminoethyl *p*-nitrobenzoate (I). I was hydrogenated with Pd/C catalyst and the product was acidified with HCl to give procaine hydrochloride.

A12.3. 5138s Catalytic reduction of ester of a nitrobenzoic acid and tertiary-amino alcohol to the corresponding amine. Levy, Joseph; Walker, William (Universal Oil Products Co.) U.S. 3,728,376 (Cl. 260/472; C 07c), 17 Apr 1973, Appl. 46,513, 15 Jun 1970; 4 pp. Procaine.HCl (I) was prepd. by esterifying *p*-$O_2NC_6H_4CO_2H$ (II) with $Et_2NCH_2CH_2OH$, reducing the ester by gradually adding it in ~7 hr to a stirred suspension of Pd/C in xylene under 30 psi H at 80–90°, and acidifying the product with HCl. The overall yield of I based on II was ~90%.

A12.4. 35455c Purification of diethylaminoethyl ester of p-aminobenzoic acid. Shitov, G. G.; Myznikova, M. A.; Klimov, V. A. (Novokuznetsk Chemical-Pharmaceutical Plant) U.S.S.R. 292,-963 (Cl. C 07c), 15 Jan 1971, Appl. 10 Jun 1968; From *Otkrytiya, Izobret., Prom. Obraztsy, Tovarnye Znaki* 1971, 48(5), 97–8. The title ester was purified by its conversion into the hydrochloride deriv., followed by sepn. of the product as a base. The reaction mass was pretreated with alkali at 50–5° and the resulting mixt. was dild. with water.

PROCAINE.HCL

Miscellaneous

A12.5. 98: 31645s Liquid crystals. Cachita, Dorina M. (Centrul de Cercetari Biologice) Rom. RO 77,251 (Cl. C09K3/34), 30 Aug 1981, P.O Appl. 88,423, 15 Nov 1976; 2 pp. Addn. to Rom. 69,633. Liq. crystals are obtained from pure phosphatides from plant parts or from plant aq. exts. by mixing the exts. with an aq. soln. of procaine chlorhydrate of 1–1000 g/L concn. at room temp. To enhance the chem. stability of the liq. crystals, some anhyd. glycerol or glycerol + sucrose soln. in water are added during the prepn. process. A change in the proportion of lecithin, procaine, and glycerol leads to a change in the d. of liq. crystals in a vol. unit. Increased concn. of procaine causes an increase in the d. and size of the formed liq. crystals. Liq. crystals obtained by this procedure are stable at room temp. for ~6 mo. L. Orlowska

A12.6. 95: 39337b Liquid crystals used in an optical display device. Cachita, Dorina Marioara Rom. 69,638 (Cl. C09K3/34), 15 Jan 1980, Appl. 88,423, 15 Nov 1976; 2 pp. Liq. crystals are prepd. from phospholipid- or lipoprotein-contg. aq. plant exts. by treatment with procaine–HCl and eventually cholesterol. Thus, rose or peony tissues (10 g) were mixed with procaine–HCl (1 g/L) followed by filtration and centrifuging. Liq. crystals were obsd. microscopically in the supernatant. For colored tissues, the color of the crystals changed with the pH.

A12.7. 100: 47033f Composition with a rhizogenic action. Cachita, Dorina; Micu, Mircea; Henegariu, Octavinn; Baloiu, Ioan; Fiell, Ingrid (Administratia Parcurilor si Strazilor) Rom. RO 79,825 (Cl. A01N5/00), 30 Aug 1982, Appl. 93,727, 21 Sep 1979; 6 pp. *Procaine-HCl* [51-05-8] enhances the rooting-stimulating activity of *NAA* [86-87-3]. Thus, a powder contg. 1000 ppm NAA and 100 ppm procaine–HCl increased rooting of carnation cuttings by 17%.

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A13

PROPRANOLOL

PATENTS

1967-1985

APPENDIX P13

ANALYSIS OF THE ABSTRACTS OF PATENTS

Most of the patents claim processes which are similar to the standard process.

A13.3. and A13.9. start from sodium naphtholate, epichlorohydrine and isopropylamine (in A13.3. wrongly indicated as ethylamine).

Patents A13.2. and A13.6. procees from the intermediate 1-(1-naphthyl-oxy)-2,3-epoxypropane which reacts with isopropylamine carbonate and isopropyaminmagnesiumbromide or isopropylamine lithium respectively

A13.1., A12.4. and A13.10. are interesting alternatives which differ significantly from the standard process.

Patents A13.5. and A13.7. seem to be rather complicated.

In A13.8. dihydropropranolol is claimed and described, according to the abstract. Dehydrogenation to propranolol is probably described in the patent itself.

ABSTRACTS OF PATENTS

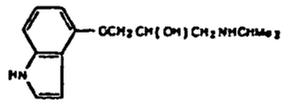
A13

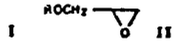
PROPRANOLOL

Preparation

A13.1. 95: 150272r Alkanolamines. Kyowa Hakko Kogyo Co., Ltd. Jpn. Kokai Tokkyo Koho 81 63,945 (Cl. C07C93/06), 30 May 1981, Appl. 79/138,684, 29 Oct 1979; 6 pp. $ROCH_2CH(OH)=CH_2NHCHMe_2$ I (R = 1-naphthyl, 4-indolyl) were prepd. by reaction of $Me_2CHN:CHZR^1$ II (R^1 = alkyl; Z = O, NH) with $ROCH_2R^2$ (III; R^2 = oxiranyl) followed by hydrolysis of the resulting $ROCH_2CH(OH)CH_2N(CHO)CHMe_2$ (IV). Thus, 0.26 g $SnCl_4$ in $CHCl_3$ was added to a mixt. of 2.3 g II (R^1 = Et, Z = O) and 3.56 g III (R = 4-indolyl) in $CHCl_3$ at <15°, the mixt. refluxed 8 h, 3 N NaOH added, and the mixt. stirred at room temp. to give 2.4 g IV (R = 4-indolyl) (V). Refluxing 1 g V in 1.5 N NaOH 1.5 h gave 0.7 g I (R = 4-indolyl). K. Sempuku

A13.2. 95: 80723n Pindolol and propranolol. Kunishige, Tsutomu Jpn. Kokai Tokkyo Koho 81 29,547 (Cl. C07C91/10), 24 Mar 1981, Appl. 79/105,353, 18 Aug 1979; 3 pp. Pindolol (I) and





I II

propranolol were prepd. by treating epoxides II (R = indol-4-yl, 1-naphthyl) with Me_2CHNHM (M = $MgBr$, Li). Thus, 2.4 g Mg was converted to EtMgBr in THF, treated with 6 g Me_2CHNH_2 at 30° for 0.5 h, and evapd. The residue was stirred with 15 g II (R = indol-4-yl) in THF at 10–33° for 3 h and poured into aq. NH_4Cl to give 14 g I. I. Matsumoto

A13.3. 94: 15445p 1-(Naphthoxy)-3-isopropylamino-2-propanol. Maftei-Mihai, G.; Moldovan, Augustin V.; Popa, Ilie I. (Centrala Industriala de Medicamente, Cosmetice, Coloranti si Lacuri) Ger. Offen. 3,005,562 (Cl. C07C93/06), 28 Aug 1980, Rom. Appl. 96,711, 23 Feb 1979; 6 pp. Propanolol (182 g) of improved purity was obtained by converting 144 g 1-naphthol to its Na salt, adding 185 g epichlorohydrin (I) stepwise with removal of unreacted I by azeotropic distn. with H_2O, adding 337 g $MeCH_2NH_2$ as a 70% aq. soln., and extg. the propranolol into PhMe.

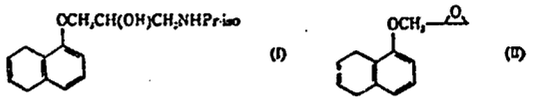
A13.4. 170489b Phenolic ethers. Instituto Luso-Farmaco, S.a r.l. Span. 398,313 (Cl. C 07c), 16 Sep 1974, Appl. 398,313, 13 Dec 1971; 6 pp. The reaction of α-naphthol with 2,3-epoxypropyl(isopropyl)amine or with 2,3-epoxypropyl(propyl)amine gave 1-isopropylamino- and 1-propylamino-3-(1-naphthoxy)-2-propanol, resp. J. Castaner-Gargallo

A13.5. 97382x 1-Isopropylamino-3-(1-naphthoxy)-2-propanol. Kudo, Shiro; Tamaki, Kentaro; Yada, Seiichi (Kyowa Fermentation Industry Co., Ltd.) Japan. Kokai 72 42,636 (Cl. 16 C412), 16 Dec 1972, Appl. 71 28,868, 04 May 1971; 3 pp. 3-(1-Naphthoxy)-1-tosyloxy-2-propanol, prepd. from 3-(1-naphthoxy)-1,2-propanediol (I) by reaction with p-$MeC_6H_4SO_2Cl$, was treated with 2,3-dihydropyran and concd. HCl in C_6H_6 to give 3-(1-naphthoxy)-1-tosyloxy-2-propanol tetrahydropyranyl ether, which with Me_2CHNH_2 gave 3-(1-naphthoxy)-1-isopropylamino-2-propanol tetrahydropyranyl ether (II). Refluxing II in Me_2CO at pH <1 gave 50% the title compd. (based on I) of 99.0% purity, a β-adrenergic inhibitor. Y. Tsuji

A13.6. 120306h 1-Aryloxy-3-(isopropylamino)-2-propanols. Daniewski, Wlodzimierz; Borowka, Marian (Przedsiebiorstwo Doswiadczalne Przemyslu Farmaceutycznego POLFA) Ger. Offen. 2,013,527 (Cl. C 07c), 08 Oct 1970, Pol. Appl. 29 Mar 1969; 7 pp. The title compds. $ROCH_2CH(OH)CH_2NHPr$-iso (I) were prepd. Thus, heating 24 g 1-(α-naphthyloxy)-2,3-epoxypropane and 10 g (iso-$PrNH_3$)$_2CO_3$ in 25 g isoamyl alc. 45 min at 90–100° gave 15 g I (R = α-naphthyl). I (R = p-AcNH-C_6H_4) and I (R = o-CH_2:$CHCH_2OC_6H_4$) were similarly prepd. KCPG

A13.7. 120082g β-Adrenergic blocking 1-alkoxy-3-amino-2-propanols. Yoshizue, Keiro; Saito, Hideo (Sankyo Chemical Industries Co., Ltd.) Ger. Offen. 2,018,263 (Cl. C 07cd, A 61k), 08 Oct 1970, Japan. Appl. 14 Apr 1969; 24 pp. The β-adrenergic blocking title compds., $ROCH_2CH(OH)CH_2NHR^1$ (I) were prepd. by reaction of epichlorohydrin (II) with Schiff bases to give 5-(chloromethyl)oxazolidines, reaction with phenols, and hydrolysis or by reaction of II with phenols, subsequent reaction with Schiff bases and hydrolysis. Thus, reaction of PhCH:NPr-iso with II in the presence of $SnCl_4$ in CCl_4 3 hr at 20° gave 74% 2-phenyl-3-isopropyl-5-(chloromethyl)oxazolidine, which on reaction with PhOH in the presence of NaOMe gave 75% 2-phenyl-3-isopropyl-5-(phenoxymethyl)oxazolidine (III). III was also prepd. by reaction of II with PhOH via 1-phenoxy-2,3-epoxypropane and reaction with PhCH:NPr-iso. Hydrolysis of III with 10% HCl 1 hr at 90–5° gave 93.7% I (R = Ph, R^1 = iso-Pr). Similarly prepd. were I (R and R^1 given): α-naphthyl, iso-Pr; m-tolyl, iso-Pr; o-$MeOC_6H_4$, iso-Pr; m-tolyl, cyclohexyl; p-Cl-C_6H_4, iso-Pr; o-iso-$PrOC_6H_4$, iso-Pr; Ph, Bu; m-tolyl, Et; p-ClC_6H_4, Et. KTPG

A13.8. 37032 1-(5,8-Dihydro-1-naphthyloxy)-3-(isopropylamino)-2-propanol. Narayanan, Venkatachala L.; Setescak, Linda L.; Weisenborn, Frank L. (Squibb, E. R., and Sons, Inc.) Ger. Offen. 1,950,742 (Cl. C 07cd), 30 Apr 1970, US Appl. 16 Oct 1968; 21 pp. The title compd. (I) and its acetate were prepd. and could be used as water softening or as antifibrillatory agents.



5,8-Dihydro-1-naphthol, prepd. in ~98% yield by redn. of 1-naphthol with Li in liq. NH_3, reacted with epichlorohydrin to give II. Reaction of II with iso-$PrNH_2$ gave I. KBPG

A13.9. 99907u Manufacture of propanolamine derivatives. Leslie H. Smith and Imperial Chemical Industries Ltd. Brit. 1,079,534 (Cl. C 07c), Aug. 16, 1967, Appl. Feb. 24, 1965; 2 pp. The relevant alc., epoxide and amine are reacted to form the propanolamine deriv.; $R^2OCH_2CH(OH)CH_2NHR^1$, where R^1 is an alkyl group of ≤10 C atoms and R^2 is a naphthyl or tolyl group. Thus, 2.8 parts 1-naphthol, 2 parts epichlorohydrin, 1.7 parts isopropylamine, 0.8 part NaOH, and 20 parts EtOH are heated at 100° in a sealed vessel for 10 hrs. The mixt. is evapd. to dryness in vacuo and shaken with 25 parts 2N HCl and 25 parts ether. The aq. phase is basified with 2N NaOH and filtered to yield 1-isopropylamino-3-(1-naphthyloxy)-2-propanol, m. 96° (cyclohexane). Similarly prepd. is 1-isopropylamino-3-(3-tolyloxy)-2-propanol, m. 78–80°. The derivs. are used in treatment or prophylaxis of heart diseases. H.Carline Barlow

A13.10. 85646a Naphthalene derivatives. Imperial Chemical Industries Ltd. Neth. Appl. 6,604,255 (Cl. C 07c), Oct. 3, 1966; Brit. Appl. March 31, 1965, and Feb. 3, 1966; 5 pp.; cf. preceding abstr. The title compds. I have β-adrenergic blocking activity and are used for the treatment or prophylaxis of heart diseases such as angina pectoris and cardiac arrythmias and for the treatment of hypertensia and pheochromocytoma. Their prepn. is given. Thus, a mixt. of 2.5 parts 1-amino-3-(1-naphthoxy)-2-propanol hydrochloride, 1.23 parts iso-PrBr, 1.68 parts Na_2CO_3, and 20 parts EtOH is heated in a closed tube 20 hrs. at 130°. After filtering, the mixt. is evapd. and the residue is extd.

(I)

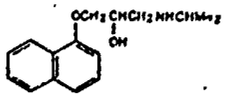
with 25 parts AcOEt. The ext. is filtered and treated with HCl in Et_2O to give the HCl salt of I (R^1 = iso-Pr), m. 162–4° (iso-PrOH). C. van de Westeringh

PROPANOLOL

Miscellaneous

A13.11. 98: 2496p Reagents and method for determining ligands in a sample of biological liquids. Wang, Chao Huie Jeffrey; Stroupe, Stephen Denham; Jolley, Michael Ernest (Abbott Laboratories) Ger. Offen. DE 3,205,506 (Cl. G01N33/54), 16 Sep 1982, US Appl. 235,259, 17 Feb 1981; 49 pp. Tracers are described for ligand (esp. drugs and hormones) detn. in body fluids by fluorescence polarization immunoassay. The tracers are ligand analogs with a single reactive primary or secondary amino group which are bound to carboxyfluorescein. For example, prepn. of an aminophenobarbital–carboxyfluorescein conjugate is described, as well as assay procedures, for detn. of phenobarbital. Numerous other examples are given.

A13.12. 95: 55037j Propanolol antigen conjugates and antibodies. Pirio, Marcel R.; Singh, Prithipal (Syva Co.) U.S. 4,241,177 (Cl. 435-7; C12Q1/66), 23 Dec 1980, Appl. 937,248, 28 Aug 1978; 7 pp. *Propranolol* (I) [525-66-6] was derivatized and



I

these derivs. were conjugated to various protein carriers (i.e. bovine serum albumin and globulin, glucose-6-phosphate dehydrogenase). These conjugates were useful as immunogens for the induction of I-specific antibodies and as indicator mols. in I enzyme immunoassays.

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B1

DIPHENYLHYDANTOIN

PATENTS

1967-1985

ANALYSIS OF THE ABSTRACTS OF PATENTS

There is only one synthesis patent starting from benzoin which reacts with urea in presence of potassiumhydroxide and sulfur.

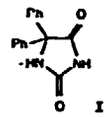
ABSTRACTS OF PATENTS

B1

DIPHENYLHYDANTOIN

Preparation

B1.1. 140814n 5,5-Diphenylhydantoin. Kolbeck, Winfried; Bayerlein, Friedrich (Diamalt A.-G.) U.S. 3,646,056 (Cl. 260-309.5; C 07d), 29 Feb 1972, Appl. 10,317, 10 Feb 1970; 2 pp.



I

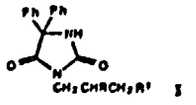
Treatment of benzoin and NH_2CONH_2 with aq. KOH and S gave 67-8[illegible]% 5,5-diphenylhydantoin (I).

DIPHENYLHYDANTOIN

Miscellaneous

B1.2. 99: 209278k Assay method. Allen, Gerald John (Amersham International PLC) Eur. Pat. Appl. EP 92,344 (Cl. G01N33/53), 26 Oct 1983, GB Appl. 82/10,928, 15 Apr 1982; 14 pp. Assays for analytes (esp. antigens) are described which employ a specific binding partner for the analyte (esp. antibodies), a fluorescent compd.-analyte conjugate, and solid particles which have a material which is not a member of the binding pair but which controls the extent of binding of the labeled deriv. The solid particles are preferably of C, either coated with albumin or carrying a receptor for the binding partner. The albumin coating acts as a mol. sieve to accept labeled analytes but not antiserums and complexes thereof. For example, phenytoin amine was detd. with a phenytoin-fluorescein label, antiserum, and albumin-coated charcoal. Fluorescence was measured at 490 nm excitation and 520 nm emission. Serum phenytoin amine was detd. in the range 0-100 μg/mL.

B1.3. 99: 22468e 3-(γ-Amino-β-hydroxypropyl)-5,5-diphenylhydantoin derivatives. Zejc, Alfred; Kiec-Kononowicz, Katarzyna (Polska Akademia Nauk, Instytut Farmakologii) Pol. PL 114,751 (Cl. C07D403/06), 30 Dec 1982, Appl. 202,530, 30 Nov 1977; 4 pp.



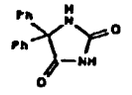
I

The title compds. I [R = OH, R^1 = 4-(R^2-substituted) piperazino, R^2 = CH_2CH_2OH, $CH_2CHMeOH$, Me, CH_2Ph, Ph, C_6H_4Cl-*p*, *p*-tolyl] were prepd. by treating I (R = OH, R^1 = Cl; RR^1 = O) with the corresponding *N*-substituted piperazine. Thus, 5,5-diphenylhydantoin Na salt 27.2 and then epichlorohydrin 9.2 g were dissolved in H_2O 100 mL and the mixt. refluxed 1 h and then frozen. After 24 h the soln. was decanted and the solid recrystd. from PrOH to give 23 g (73%) I (RR^1 = O), which (3.1 g) was refluxed 6 h with *N*-(β-hydroxyethyl)piperazine 1.4 g in PhMe 20 mL to give 2.7 g (65%) I [R = OH, R^1 = 4-(β-hydroxyethyl)piperazino].

B1.4. 98: 122427p **Stabilization of glucose oxidase apoenzyme.** Rupchock, Patricia A.; Tyhach, Richard J. (Miles Laboratories, Inc.) U.S. US 4,366,243 (Cl. 435-7; C12N9/04), 28 Dec 1982, Appl. 255,310, 17 Apr 1981; 17 pp. Glucose oxidase apoenzyme is stabilized by poly(vinyl alc.) and serum albumin for ligand binding assays. The stabilized apoenzyme can be incorporated into test strips for immunoassays. In such assays an FAD-antigen conjugate is the label, and FAD-antigen conjugate which is not bound to the antibody is available for glucose oxidase apoenzyme activation. For example, test strips were prepd. for dinitrophenyl caproate immunoassay which contained buffer, a glucose oxidase detection system, apoglucose oxidase, dinitrophenol antibody, and dinitrophenol-FAD conjugate. Inclusion of poly(vinyl alc.) and albumin increased the heat stability of the test strips. Test strips for theophylline and phenytoin are also described.

B1.5. 98: 65454e **Homogeneous specific binding assay test device having a copolymer enhancing substance.** Tabb, David L.; Tyhach, Richard J. (Miles Laboratories, Inc.) U.S. US 4,362,697 (Cl. 422-56; G01N33/52), 07 Dec 1982, Appl. 255,759, 20 Apr 1981; 15 pp. Test strips are described for ligand detn. by homogeneous specific binding assays with reflection spectrometric detection. The test strips are impregnated with the appropriate reagents and an enhancer substance (e.g. Gafquat). For example, *N*-(2,4-dinitrophenyl)-6-aminocaproic acid was detd. by test strips impregnated with apoglucose oxidase, 2,4-DNP-FAD conjugate, antibody, and a glucose oxidase detection reagents. This system responded to 2,4 DNP by exhibiting color due to the activation of apoglucose oxidase by the 2,4-DNP-FAD conjugate. The presence of Gafquat 734 markedly improved the color response. Theophylline and phenytoin were also detd. by the title system.

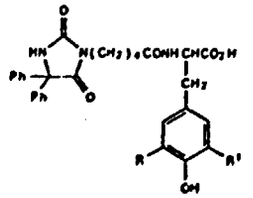
B1.6. 97: 66393q **Fluorescent reagent and method for determining immunofluorescence.** Tsay, Yuh Geng; Chen, Janet H.; Palmer, Richard J. (International Diagnostic Technology, Inc.) Eur. Pat. Appl. EP 47,459 (Cl. G01N33/58), 17 Mar 1982, US Appl. 185,225, 08 Sep 1980; 23 pp. Fluorescent diagnostic



I

reagents are prepd. which contain a hydrophobic hapten, a hydrophilic compd. such as an aminoglycoside, peptide, protein, or *polyacrylamide hydrazine* [30601-03-7], and a hydrophobic fluorescent compd. such as a deriv. of *fluorescein* [2321-07-5], *umbelliferone* [93-35-6], or *fluorescamine* [38183-12-9]. The hydrophobic hapten and the hydrophobic fluorescent compd. are both bound to the hydrophilic compd. but sepd. from each other. The reagents are used in the solid-phase fluorescence immunoassay of e.g. *diphenylhydantoin* (I) [57-41-0], *phenobarbital* [50-06-6], and *primidone* [125-33-7] in blood serum and eliminate the disadvantages of previously used reagents. Thus, for the detn. of the hydrophobic compd. I, a reagent was prepd. by coupling a carboxylated deriv. of I and *FITC* [27072-45-3] with the hydrophilic compd. *gentamicin* [1403-66-3]. The resulting hydrophilic conjugate has increased water soly., less susceptibility to fluorescence quenching by albumin and other serum proteins, and improved antigenicity.

B1.7. 89: 129930v **Labeled 5,5-diphenylhydantoin derivatives for radioimmunoassay.** Parsons, George H., Jr.; Eller, Thomas (Baxter Travenol Laboratories, Inc.) U.S. 4,092,479 (Cl. 548-312; C07D233/72), 30 May 1978, Appl. 673,853, 05 Apr 1976; 4 pp. Radioiodinated derivs. of hydantoin I (R = R¹ = H)



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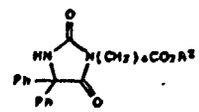

III

(II), useful in radioimmunoassays, were prepd. Thus, 5,5-diphenylhydantoin 3-Na salt was treated with $Br(CH_2)_4CO_2Me$ to give hydantoinvaleric acid ester III (R^2 = Me), which was hydrolyzed to III (R^2 = H), which was condensed with tyrosine via the $ClCO_2Et$ mixed anhydride method to give II. II was iodinated with $Na^{125}I$ to give I (R = ^{125}I, R^1 = H; R = R^1 = ^{125}I). The radioiodinated derivs. were used in the radioimmunoassay of 5,5-diphenylhydantoin in rabbits.

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B2

ISONIAZID

PATENTS

1967-1985

ANALYSIS OF THE ABSTRACTS OF PATENTS

Two patents are claimed for the preparation of isoniazid. B2.1. starts from isonicotinic acid and B2.2. from isonicotinic nitrile.

ABSTRACTS OF PATENTS

B2

ISONIAZID

Preparation

B2.1. 120269p Carboxamides and carbohydrazides. Stanley, Robert H.; Shaw, Barry Leigh (British Titan Ltd.) Ger. Offen. 2,364,059 (Cl. C 07c, B 01j), 18 Jul 1974, Brit. Appl. 513/73, 04 Jan 1973; 10 pp. Five $RCOR^1$ (R = Me, Ph, or 4-pyridyl; R^1 = NHPh or $NHNH_2$) were prepd. in 80–99% yield by reaction of RCO_2H with R^1H in the presence of $(BuO)_4M$ (M = Ti or Zr).

B2.2. 96629f Isonicotinic hydrazide. Seefluth, Horst; Moll, Karl K.; Baltz, Hans; Bruesehaber, Ludwig; Schrattenholz, Gisela Ger. (East) 63,493 (Cl. C 07d), 05 Sep 1968, Appl. 27 Dec 1967; 3 pp. An improved method for the prepn. of the title compd. (I) from isonicotinonitrile (II) and hydrazine hydrate (III) is described. Heating (100°) II in aq. soln. (10–50%) in the presence of an alk. catalyst such as the oxide, hydroxide, or carbonate of an alkali metal and addg. III dropwise results in improved yields of I and without the formation of insol. by-products.
E. Tobler

ISONIAZID

Miscellaneous

B2.3. 89: 204222w Pharmaceutical preparation specific for nodular thelitis. Laboratoire TECHNA Fr. Demande 2,361,117 (Cl. A61K47/00), 10 Mar 1978, Appl. 76/24,840, 09 Aug 1976; 6 pp. A topical prepn. for treating nodular thelitis in ruminants contains *kanamycin monosulfate* [25389-94-0], *hexamidine isethionate* [659-40-5], *isoniazid* [54-85-3], and *diaminodiphenyl sulfone* [80-08-0] in an oil-in-water emulsion. The preferred vehicle is 10 parts DMSO to 80 parts of a lanolin, lanette N, and propylene glycol mixt. After several weeks of treatment with the prepn. the nodules become soft and cease being painful. In most cases, the nodules eventually disappear.

B2.4. 98: 49669n Technetium-99m-labeled isonicotinic acid hydrazide and a pharmaceutical agent containing this compound. Yamada, Norihisa; Koizumi, Kiyoshi; Hisada, Kinichi (Ikeda Mohando Co., Ltd.) Ger. Offen. DE 3,216,026 (Cl. C07D213/86), 11 Nov 1982, JP Appl. 81/65,981, 30 Apr 1981; 20 pp. ^{99m}Tc-labeled isonicotinic acid hydrazide was prepd. by reacting $Na^{99m}TcO_4$ with isonicotinic acid hydrazide in the presence of a reducing agent. ^{99m}Tc-labeled isonicotinic acid hydrazide was useful in diagnosing tumors (Yoshida sarcomas in rats and Ehrlich ascites tumors in mice).

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B3

LIDOCAINE.HCL

PATENTS

1967-1985

APPENDIX P16

ANALYSIS OF THE ABSTRACTS OF PATENTS

The only patent abstracted concerns a process in which 2,6-xylidine reacts with diethyl diethylaminomalonate.

ABSTRACTS OF PATENTS

B3

LIDOCAINE.HCL

Preparation

B3.1. 101111g ω-Diethylamino-2,6-dimethylacetanilide. Nitta, Yoshihiro; Takamura, Keiichi; Asada, Takaaki (Chugai Pharmaceutical Co., Ltd.) Japan. 72 24,547 (Cl. C 07c), 06 Jul 1972, Appl. 66 28,041, 04 May 1966; 3 pp. 2,6-Xylidine (1 mole) was made to react with >10 (preferably, 12–18) moles diethyl diethylaminomalonate, the reaction mixt. treated with an inorg. acid, bis(2,6-dimethylanilide) diethylaminomalonate salt removed, and the residual 2,6-dimethylanilide monoethyl diethylaminomalonate heated in the presence of an inorg. acid to give the title product, useful as a local anesthetic.

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B4

NIACIN

PATENTS

1967-1985

APPENDIX P17

ANALYSIS OF THE ABSTRACTS OF PATENTS

42 Synthesis patents reflect significant research activity in this field.

Hydrolysis of cyanopyridine is claimed in the following patents: B4.13., B4.14. and B4.17..

Oxidation of ß-picoline is claimed in the following patents: B4.5., B4.7., B4.9., B4.11., B4.20. - B4.22., B4.24. - B4.27., B4.29., B4.30., B4.33., B4.35., B4.37., B4.39. and B4.42.. In B4.25. a yield of 98.3% is indicated with 97.4% purity. The yield in B4.42. is 92%..

Oxidation of 5-ethyl-2-methylpyridine is claimed in the following patents: B4.7., B4.8., B4.11., B4.12., B4.15., B4.18. B4.19., B4.20., B4.23., B4.32., B4.35., B4.38. and B4.40.In B4.8. a yield of 91% is indicated with a purity of 99.8%, in B4.32. 84-95% yield and 99.6% purity are given.

The use of complex hydrides for synthesis of niacin is described in B4.6..

Patents B4.43. - B4.47. describe processes for the purification of niacin, in B4.48. - B4.50. processes for removal of isonicotinic acid and recovery from mother liquors are described.

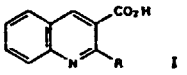
ABSTRACTS OF PATENTS

B4

NIACIN

Preparation

B4.1. 102: 113321y **Oxidation of alkyl groups to carboxyl groups under basic conditions.** American Cyanamid Co. Jpn. Kokai Tokkyo Koho JP 59,'99,637 [84,199,637] (Cl. C07B3/00), 12 Nov 1984, US Appl. 485,769, 18 Apr 1983; 6 pp. Alkyl groups were



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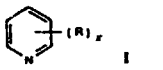
oxidized by M_nO_n (M = Cu, Co, Ag; m = 1, 2; n = 2–6) at 25–95° under basic conditions. Thus, 20 mL 15% NaOCl was added to a soln. of CuO 3.8, H_2O 7.5, 50% aq. NaOH 3, and quinoline deriv. (I; R = Me) 1.0 g at 70° and stirred 18 h to give 92% dicarboxylic acid I (R = HO_2C).

B4.2. 102: 102453s **Electrochemical oxidation of pyridine bases.** Toomey, Joseph E., Jr. (Reilly Tar and Chemical Corp.) U.S. US 4,462,439 (Cl. 204–78; C25B3/02), 13 Nov 1984, Appl. 597,014, 05 Apr 1984; 7 pp. Improved electrochem. oxidns. of I were carried out



I

in a membrane cell on a PbO_2 anode. In I, x = 1–3 and R = $-CH_3$, a C_{2-6} primary or secondary alkyl, a C_{3-6} cycloalkyl, an aralkyl of the formula [$-(CH_2)_n$–aryl], where n = 1–3, $-(CH_2)_mCOR^1$ or $-(CH_2)_mCHOHR^1$, where m = 0–5 and R^1 = H, or a C_{1-6} cycloalkyl, aryl or aralkyl group having C_{2-6} and wherein 2 adjacent R groups on the ring may be a fused cycloaklyl or a fused aryl group. Thus, 2-picoline was oxidized to picolinic acid at c.d. 20 mA/cm² to give a product yield of 80% and a current efficiency of 67%. Using c.d. 80 mA/cm², current efficiencies of ~90% were obtained in subsequent expts.

B4.3. 99: 139754m **Aromatic or heteroaromatic carboxylated compounds.** Fon, Marco; Bencini, Elena (Montedison S.p.A.) Eur. Pat. Appl. EP 81,384 (Cl. C07C51/10), 15 Jun 1983, IT Appl. 81/25,502, 09 Dec 1981; 31 pp. RCO_2R^1 (R = arom., heteroarom.; R^1 = H, alkyl, cation) were prepd. by treating an arom. or heteroarom. halide with CO in the presence of a Co carbonyl, an org. halide, and an acid acceptor. Thus, 2-naphthoic acid was prepd. in 91% yield by carbonylating 2-chloronaphthalene in the presence of $Co(CO)_8$, K_2CO_3, and $ClCH_2CO_2Me$ in MeOH, followed by sapon.
Hughes, Leslie Richard (Imperial

B4.4. 97: 51017g **Nicotinic acid.** Kuliev, A. M.; Dzhafarov, E. D.; Kulieva, D. M.; Shakhgel'diev, M. A. (Institute of the Chemistry of Additives, Academy of Sciences, Azerbaidzhan S.S.R.) U.S.S.R. SU 910,617 (Cl. C07D213/80), 07 Mar 1982, Appl. 2,851,447, 18 Apr 1980. From *Otkrytiya, Izobret., Prom. Obraztsy, Tovarnye Znaki* 1982, (9), 83. *Nicotinic acid* [59-67-6] is produced from 3-alkylpyridine by fermn. with *Bacillus* species.

B4.5. 90: 87294d **Highly selective oxidation for manufacturing pyridine carboxylic acids.** Stoppani, Luigi, S.p.A. Belg. 868,261 (Cl. C07D), 16 Oct 1978, Ital. Appl. 77/25,812, 18 Jul 1977; 13 pp. The alkali dichromate oxidn. of alkylpyridines at 150–300° and pH 4.5–8.5 yielded the resp. pyridinecarboxylic acids. β-Picoline was heated with $Na_2Cr_2O_7$ in water at 250° and ≤38 kg/cm² to give nicotinic acid.

B4.6. 87: 135089c Nicotinic acid from pyridine. Kawamata, Motoo; Fujikake, Shiro; Tanabe, Hidenori (Mitsui Toatsu Chemicals, Inc.) Japan. Kokai 77 36,670 (Cl. C07D213/80), 22 Mar 1977, Appl. 75/110,875, 16 Sep 1975; 3 pp. Nicotinic acid was prepd. by treating pyridine with CO_2 in the presence of a metal hydride. Thus, 420 mmol pyridine and 105 mmol $LiAlH_4$ in 100 mL THF was heated for 1 h and treated with 100 mL/min CO_2 at 0–5° for 3 h to give 62% nicotinic acid based on $LiAlH_4$. The yield was raised to 80–90% with dioxane or $BuOCH_2CH_2OBu$ as the solvent or with 20 kg/cm² CO_2 at 10°. NaH, LiH, $NaBH_4$, or $LiAlH(OCMe_3)_3$ instead of $LiAlH_4$ gave 24–58% yields. I. Matsumoto

B4.7. 87: 135084x Niacin. Lundin, Sten Tore; Jaraas, Sven Gunnar (Aktiebolag Bofors) Ger. Offen. 2,647,712 (Cl. C07D213/80), 18 May 1977, Swed. Appl. 75/11,816, 22 Oct 1975; 24 pp. Niacin was prepd. (up to 68% selectivity) by the oxidn. of 3-picoline or 2-methyl-5-ethylpyridine in the gas phase in the presence of a V_2O_5 catalyst with TiO_2 promoter.

B4.8. 86: 139875h Nicotinic acid. Masuda, Keiji; Kizawa, Hidenori; Otaki, Yasuhiko (Nippon Soda Co., Ltd.) U.S. 4,001,257 (Cl. 260-295.5R; C07D213/55), 04 Jan 1977, Appl. 303,028, 02 Dec 1972; 7 pp. Nicotinic acid was produced in ~91% yield with 99.8% purity by oxidizing 2-methyl-5-ethylpyridine with 100-8% of the stoichiometric amt. of HNO_3 at 225-35°, 30-45 kg/cm² and pH 2.1-2.4 for 12-16 min.

B4.9. 86: 121171r Nicotinic or isonicotinic acid from 3- or 4-picolines. Trzeczanowicz, Edward; Lipka, Barbara; Burzynska, Barbara; Musierowicz, Jerzy; Stefaniak, Lech; Wawer, Antoni; Grzybowsk., Maria (Instytut Chemii Przemysłowej) Pol. 75,601 (Cl. C07D31/38), 20 Dec 1975, Appl. 155,466, 19 May 1972; 4 pp. The known prep. methods of the title acids were simplified. Thus, ammoxidn. of 3- or 4 picoline in the presence of 15-55% by wt. H_2O gave 3- or 4 cyanopyridine, which was sepd. by sublimation at 10-14° and hydrolyzed in NH_4OH. The ammonium salts of the acids were thermally decompd. to give high purity title acids. K. Butkiewicz

B4.10. 85: 123773s Nicotinic acid. Suvorov, B. V.; Kagarlitskii, A. D.; Emel'yanov, V. L. (Institute of Chemical Sciences, Academy of Sciences, Kazakh S.S.R.) U.S.S.R. 289,731 (Cl. C07D31/34), 05 Mar 1976, Appl. 1,367,607, 04 Sep 1969. From *Otkrytiya, Izobret., Prom. Obraztsy, Tovarnye Znaki* 1976, 53(9), 210. Nicotinic acid prepn. by ammoxidn. of pyridine derivs. and hydrolysis and decarboxylation of the intermediate isocinchomeronic dinitrile was improved by using substituted 2- or 5-alkenylpyridines as the starting materials.

B4.11. 85: 94233h Nicotinic acid from β-alkylpyridines. Inoue, Toshio; Hara, Tadanori (Nippon Steel Chemical Co., Ltd.) Japan. Kokai 76 29,483 (Cl. C07D213/80), 12 Mar 1976, Appl. 74/100,952, 04 Sep 1974; 3 pp. Nicotinic acid was prepd. by gas-phase oxidn. of β-alkylpyridines with a V_2O_5-B_2O_3 catalyst on TiO_2. Thus, an aq. soln. of vanadyl oxalate and H_3BO_3 was kneaded with TiO_2, pelletized, and calcined at 500° to give a 4:1 molar V_2O_5-B_2O_3 catalyst (10% V_2O_5 based on TiO_2). The catalyst (500 ml) was packed into a tubular reactor and treated with 800 hr⁻¹ air, 30 g 2-methyl-5-ethylpyridine (I)/m³ air, and 35 g steam/g I at 285° 15 days to give 66% nicotinic acid, 98% pure. I. Matsumoto

B4.12. 84: 121660h Nicotinic acid. Suvorov, B. V.; Kagarlitskii, A. D.; Lebedeva, O. B.; Pavlov, B. A.; Kutzhanov, R. T. (Institute of Chemical Sciences, Academy of Sciences, Kazakh S.S.R.) U.S.S.R. 236,473 (Cl. C07d), 25 Dec 1975, Appl. 1,172,555, 17 Jul 1967. From *Otkrytiya, Izobret., Prom. Obraztsy, Tovarnye Znaki* 1975, 52(47), 169. Nicotinic acid prepn. by ammoxidn. of alkylpyridines was improved by using 2-methyl-5-ethylpyridine; the latter was prepd. from isocinchomeronic acid dinitrile by sapon. with aq. NH_3 and decarboxylation of the intermediate ammonium salt in an autoclave at 250–80° and 40–65 atm.

B4.13. 84: 90016w Pyridine nitriles and carboxylic acids. Gelbein, Abraham P.; Sze, Morgan C.; Paustian, John E. (Lummus Co.) U.S. 3,929,811 (Cl. 260-295.5R; C07D), 30 Dec 1975, Appl. 415,991, 15 Nov 1973; 8 pp. Nicotinonitrile (I) was prepd. by reaction of 2,3-lutidine or 2-methyl-5-ethylpyridine with NH_3 in the absence of O and in the presence of V_2O_5 catalyst; I was hydrolyzed by heating with aq. NH_3 to give an aq. soln. of NH_4 nicotinate, which was stripped with steam or steam–N at elevated temp. to give nicotinic acid. A flow diagram of the app. was given.

B4.14. 178572q Catalytic acid hydrolysis of aromatic or heterocyclic nitriles to their corresponding acids. Norton, Richard V. (Sun Ventures, Inc.) Ger. Offen. 2,438,263 (Cl. C07C), 17 Apr 1975, US Appl. 404,966, 10 Oct 1973; 8 pp. Arom. nitriles, e.g., p-$C_6H_4(CN)_2$, were hydrolyzed to the corresponding carboxylic acids by refluxing the aq. nitrile soln. with an acid catalyst, e.g., AcOH or $EtCO_2H$, at ~250°, followed by distn. to remove the acid catalyst in the form of the amide. Hydrolysis of m-$C_6H_4(CN)_2$ under these conditions gave 86% m-$C_6H_4(CO_2H)_2$; 2,6-$C_{10}H_6(CN)_2$ and nicotinonitrile were also hydrolyzed.

B4.15. 164003t Pyridinecarboxylic acids. Yasui, Hirochi; Inoue, Toshio; Hara, Tadanori (Nippon Steel Chemical Industry Co., Ltd.) Japan. Kokai 75 46,670 (Cl. C07D. B01J), 25 Apr 1975, Appl. 73 92,409, 20 Aug 1973; 4 pp. Pyridinecarboxylic acids were prepd. by vapor phase contact oxidn. of alkylpyridines or quinoline (I) in the presence of catalysts contg. V_2O_5, Fe_2O_3, and SnO_2. Thus, a mixt. of vanadyl oxalate, $Fe(NO_3)_3$, $Sn(NO_3)_4$, and TiO_2 in H_2O was molded, dried, and calcined at 500° to form a catalyst (100:15:100 molar V_2O_5-Fe_2O_3-SnO_2; 1:10 V_2O_5-TiO_2 by wt.). A mixt. of 2-methyl-5-ethylpyridine (II), air, and steam was passed on the catalyst at 290° and 1000 hr^{-1} space velocity to give 60.8 wt.% nicotinic acid (III). Selectivity coeff. for III was 60.6 mole%. I and 3-ethylpyridine were also used in place of II. K. Sempuku

B4.16. 97037s Pyridine derivatives. Gelbein, Abraham P.; Sze, Morgan C.; Paustian, John E. (Lummus Co.) Ger. Offen. 2,403,121 (Cl. C07D), 22 May 1975, US Appl. 415,991, 15 Nov 1973; 18 pp. Nicotinonitrile was prepd. in 10 mole % yield by treating 2,3-dimethylpyridine with NH_3 on a 40% V_2O_5 on SiO_2-Al_2O_3 (87:13) catalyst with a pore vol. 0.75 cm^3/g, surface area 200 m^2/g and particle size 60μ at 371° and a linear spatial velocity of 600 hr^{-1}.

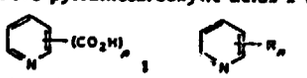
B4.17. 97036r Pyridine mononitrile. Sze, Morgan C.; Gelbein, Abraham P.; Paustian, John E. (Lummus Co.) Ger. Offen. 2,435,134 (Cl. C07D), 22 May 1975, US Appl. 415,991, 15 Nov 1973; 30 pp. Nicotinonitrile was manufd. continuously by treating 2,3-lutidine or 2-methyl-5-ethylpyridine with NH_3 on a catalyst contg. 40% V_2O_5 on SiO_2-Al_2O_3(87:13) with pore vol. 0.75 cm^3/g, surface area 200 m^2/g, and particle size 60μ at 440°. The nitrile was hydrolyzed to a nicotinic acid.

B4.18. 43205b Nicotinic acid. Masuda, Keiji; Kizawa, Hidenori; Otaki, Yasuhiko (Nippon Soda Co., Ltd.) Brit. 1,385,920 (Cl. C07D), 05 Mar 1975, Appl. 18,896/73, 19 Apr 1973; 7 pp. Addn. to Brit. 1,385,919. Isocinchomeronic acid-free nicotinic acid (I) was prepd. from dialkylpyridine mixts. by successive HNO_3 oxidn., concn. of the reaction mixt., and cooling. Thus, I was prepd. continuously by treating a mixt. of 2-methyl-5-butylpydine 60, 2-propyl-5-ethylpyridine 30, and 2-methyl-5-ethylpyridine (II) 10 wt % with the quantity of HNO_3 theor. required for the oxidn. at 230° and 35 kg/cm² for 10 min. The reaction-terminated soln., pH 2.2, was concd. and the pH adjusted to 3.2 by adding II; subsequent cooling to 0-5° gave 73.3 wt. % of 99% pure I. The mother liquor was recycled.

B4.19. 28116e Nicotinic acid. Nippon Soda Co., Ltd. Fr. Demande 2,228,776 (Cl. C07d), 06 Dec 1974, Appl. 72 40,742, 16 Nov 1972; 5 pp. Addn. to Fr. 2,165,850 (See Ger. Offen. 2,256,508 CA 79:31894e). Nicotinic acid was manufd. in 68.5% yield with 96.4% conversion by oxidizing a mixt. of 2-methyl-5-ethylpyridine, 2-propyl-5-ethylpyridine, and 2-methy-5-butylpyridine (1:3:6) with the stoichiometric amt. of 28% HNO_3 at 230° and 35 kg/cm² for 10 min.

B4.20. 120493g Pyridinecarboxylic acids from alkylpyridines. Nakajima, Kazuhisa; Sato, Tsuneo (Japan Synthetic Chemical Industry Co., Ltd.) Japan. Kokai 74 61,173 (Cl. 16 E431), 13 Jun 1974, Appl. 72 102,566, 12 Oct 1972; 4 pp. Alkylpyridines, e.g., β-picoline, γ-picoline, or collidines, are oxidized to pyridinecarboxylic acids in the gas phase with O-contg. gas in the presence of a V oxide catalyst contg. Ti, Al, and (or) Ni oxides. Thus, 118 g V_2O_5 and 246 g $TiCl_4$ in concd. HCl was dild. with H_2O, adjusted to pH 7.0, and the solid heated to 500° and pelletized. The catalyst (40 ml) of 1.07:1 V-Ti atomic ratio was treated at 335° with 172 g 6.08% aq. β-picoline and 70.5 l. air over 1 hr to give 81.2% nicotinic acid, together with 3.91 g unchanged β-picoline. Similarly, γ-picoline and 5-ethyl-2-picoline were oxidized to isonicotinic and nicotinic (sic) acids, resp.

B4.21. 120789n Pyridinecarboxylic acids. Hanotier, Jacques D. V.; Hanotier-Bridoux, Monique G. S. (Labofina S. A.) Ger. Offen. 2,242,386 (Cl. C 07d), 07 Feb 1974, Fr. Appl. 72 26,867, 26 Jul 1972; 9 pp. Five pyridinecarboxylic acids I (n = 1, 2, or 3)



were manufd. by air-oxidn. of the appropriate alkylpyridine derivs. II (R_n = 2, 3, or 4-Me, 3,4-Me_2, 4-Et, or 2,4,6-Me_3) over a Co(III) carboxylate catalyst with maintaining a definite Co(III) ion concn., i.e. >0.1 g/l., by addn. of regenerating AcH. Thus, 100 l. air/hr was passed into 0.120M II (R_n = 2-Me) and 0.240M Co(III) acetate in HOAc 6 hr at 60°, 10 kg/cm² air, and >0.1 g/l. Co(III) ion concn. (maintained by addn. of 35% AcH in HOAc at 5 g./hr) to give, at 100% selectivity, 95% I (R_n = 2-CO_2H).

B4.22. 146416t Pyridinecarboxylic acids. Yokoyama, Ryoichi; Sawada, Katsumi (Teijin Chemicals Ltd.) Brit. 1,330,135 (Cl. C 07d, B 01j), 12 Sep 1973, Appl. 47,743/70, 07 Oct 1970; 8 pp. Pure 3- and 4-pyridinecarboxylic acids were prepd. in high yield by air or O oxidn. of β- or γ-picoline at 250-450° in the presence of steam and a V oxide-Cr oxide catalyst contg. a metal oxide promotor, e.g. Sn and Sb oxide. Thus, 0.8 g Sb_2O_3 and 4 g $SnCl_4.3.5H_2O$ sep. dissolved in HCl were added to 25 g NH_4VO_3 and 25 g $(NH_4)_2CrO_4$ in 1 l. H_2O. The suspension was poured onto 100 ml SiC carrier sp. surface area 1.2 m²/g and av. particle diam. 2.0 mm and the impregnated product presintered at 400-50° and calcined 2 hr at 700°. γ-Picoline at a concn. of 25.0 g/Nm³ of air was continuously passed 3 hr with 195 ml H_2O/g of γ-picoline/hr and 200 l./hr air through a reactor tube contg. 40 ml catalyst at 350°. The air was divided into 2 portions; one portion was passed through a H_2O-evaporator and the other through a γ-picoline-evaporator. The portions were mixed and fed into the reactor via a preheater. Crude isonicotinic acid, 106.0 wt. % of 96.1% purity, was sepd. from the discharged vapor by air- and water-coolers.

B4.23. 31894e Nicotinic acid. Masuda, Keiji; Kizawa, Hidenori; Otaki, Yasuhiko (Nippon Soda Co., Ltd.) Ger. Offen. 2,256,508 (Cl. C 07*d*), 24 May 1973, Japan. Appl. 71 92,142, 17 Nov 1971; 23 pp. Nicotinic acid was prepd. in 85–90% yield by continuously oxidizing 2-methyl-5-ethylpyridine with 100–117% of the stoichiometric amt. of HNO_3 at 205–25° and 30–45 kg/cm² with residence times of 7–45 min.

B4.24. 29627f Catalytic manufacture of pyridinecarboxylic acids. Teijin Chemicals Ltd. Fr. 2,110,607 (Cl. C 07*d*, B 01*j*), 07 Jul 1972, Appl. 70 38,300, 23 Oct 1970; 17 pp. Oxidn. catalysts for picolines contain V and Cr (in the ratio 1:0.5–1), Sb_2O_3 and $SnCl_4$, Ge_2O_3, $NbCl_5$, $TaCl_5$, Ga_2O_3, or $ZrCl_4$, and are calcined at >560°. Thus, a catalyst was prepd. by treating 25 g NH_4VO_3 and 25 g $(NH_4)_2CrO_4$ in 1 l. H_2O with 0.8 g Sb_2O_3 and 4 g $SnCl_4.3:5H_2O$, pouring over 100 ml SiC, prefritting at 400–50°, and calcining for 2 hr at 700°. γ-Picoline was quant. oxidized over the catalyst to 96.1% pure isonicotinic acid.

B4.25. 139828j Nicotinic acid from β-picoline. Yokoyama, Ryoichi; Sawada, Katsumi (Teijin Chemical Industry Co., Ltd.) Japan. 72 27,515 (Cl. C 07*d*, B 01*j*), 22 Jul 1972, Appl. 68 30,390, 07 May 1968; 3 pp. Addn. of water to O in the catalytic vapor-phase oxidn. of β-picoline (I) increased the yield of nicotinic acid (II) by 20–40 wt. %. E.g., O (200 l./hr) contg. 25 g I/m³ O and 133 ml H_2O/g I/hr were fed to 100:15:4:1 V-Cr-Sm-Sb catalyst on silicon carbide carrier at 365–75° to give 98.3% II (purity 97.4%).
K. Sempuku

B4.26. 126435d Pyridinecarboxylic acids. Kubo, Masayoshi; Horikawa, Takeshi (Daicell Co., Ltd.) Ger. Offen. 2,165,035 (Cl. C 07*d*), 13 Jul 1972, Japan. Appl. 70 122,247, 30 Dec 1970; 11 pp. Nicotinic acid (I) and isonicotinic acid were prepd. by oxidn. of β- or γ-picoline, resp., with O in the presence of Zr salts, Co acetate, Mn acetate, and NH_4Br. Thus, 20 l. air/hr was passed into 186 parts β-picoline, $ZrO(OAc)_2$, Co acetate, Mn acetate, and NH_4Br (each 1.86 parts) in 559 parts HOAc at 200° and 20 kg/cm². After 2 hr, 80% I was obtained.

B4.27. 61822f Pyridinecarboxylic acids. Dieterich, Dieter (Farbenfabriken Bayer A.-G.) Ger. Offen. 2,055,102 (Cl. C 07*d*), 18 May 1972, Appl. P 20 55 102.4, 10 Nov 1970; 24 pp. Se loss in the oxidn. of alkylpyridines to dinicotinic acid is reduced by using oleum contg. ≥60% SO_3 at 270-300°. Thus 138 g pyridine stock contg. 84.5% 3,5-dimethyl-, 7.3% 3-ethyl-5-methyl-, and 1.4% 3-methylpyridine in 1.5 kg 65% oleum was added during 2–3 hr at 270–90° to 400 g H_2SO_4, 100 g 65% oleum, and 4 g Se, preheated to 225°, to give 76% dinicotinic acid. Nicotinic and isonicotinic acids were similarly prepd. The dinicotinic acid was also recovered as the di-Me, di-Et, di-Pr, and diisopropyl esters.

B4.28. 85713b Continuous manufacture of isocinchomeronic acid and nicotinic acid. Avedikian, Souren Z. Ger. Offen. 2,125,653 (Cl. C 07*d*), 09 Dec 1971, US Appl. 28 May 1970; 17 pp. A continuous process is described by which Cu isocinchomeronate (prepd. according to U.S. 3,081,307) is converted to niacin by treating it with NaOH, sepg. the CuO, and treating the Na isocinchomeronate with H_2SO_4 to give the free acid, which is continuously decarboxylated under pressure.

B4.29. 143488a Pyridine carboxylic acids. Costea, Teodor; Camarasu, Constantin (Institutul de Cercetari Chimico-Farmaceutice) Rom. 53,589 (Cl. C 07*d*), 25 Aug 1971, Appl. 05 Feb 1968; 2 pp. High yields of the titl. compds. were obtained by continuously refluxing an alkylpyridine sulfate, NH_4 vanadate, and counterflow HNO_3 vapors at atm. pressure, and the resulting mother liquor mixed with alkylpyridine up to the initial concn. and recycled.
C. T. Papadopol Calimah

B4.30. 110193w Nicotinic acid. Tyupalo, N. F.; Yakobi, V. A.; Kozorez, L. A.; Gangrskii, P. A.; Nikiforov, A. A. (Lenin, V. I., Polytechnic Institute, Kharkov) U.S.S.R. 306,848 (Cl. A 61k, C 07d), 21 Jun 1971, Appl. 02 Jul 1969; no pp. given. From *Otkrytiya, Izobret., Prom. Obraztsy, Tovarnye Znaki* 1971, 48(20), 15–16. Nicotinic acid was prepd. by the oxidn. of 3-methylpyridine by an O_2–air mixt. in H_2SO_4 contg. a mixt. of salts of variable valence metals, such as Mn and Cr.

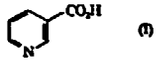
B4.31. 98452v Nicotinic acid. Skryabin, G. K.; Golovleva, L. A. (Institute of Biochemistry and Physiology of Microorganisms, Academy of Sciences, U.S.S.R.) U.S.S.R. 302,341 (Cl. C 07d), 28 Apr 1971, Appl. 30 Dec 1969; From *Otkrytiya, Izobret., Prom. Obraztsy, Tovarnye Znaki* 1971, 48(15), 80. Nicotinic acid was prepd. by the oxidn. of 3-methylpyridine using *Nocardia* microorganisms.

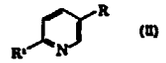
B4.32. 48924e Nicotinic acid. Stocker, August; Marti, Othmar; Pfammatter, Theodul; Schreiner, Gerhart; Brander, Stephan Lonza Ltd.) Ger. Offen. 2,046,556 (Cl. C 07d), 22 Apr 1971, Swiss Appl. 24 Sep 1969; 11 pp. Nicotinic acid (I) (99.6% pure) was manufd. in 84–95% total yield by oxidn. of 2-methyl-5-ethylpyridine with 33% HNO_3 at 330°, 290 atm gage, 5.5 sec residence time, and 95% conversion in a tubular flow reactor, crystn. of I·HNO_3 salt at 0°, and crystn. of I liberated at 95° and pH 3.3.

B4.33. 48914b Catalytic manufacture of pyridinecarboxylic acids. Yokoyama, Ryoichi; Sawada, Katsumi (Teijin Ltd.) Ger. Offen. 1,940,320 (Cl. C 07d, A 61k), 25 Feb 1971, Appl. 07 Aug 1969; 22 pp. β-Picoline or γ-picoline (I) yields 64–79 mole % β-picolinic or 68–94.5 mole % γ-picolinic acids (II), resp., when it is oxidized at 320–450° in the vapor phase with air contg. H_2O. The oxidn. is catalyzed by a mixt. of V and Cr oxides, contg. 1–15% Sn and Sb or Ge, In, Nb, W, Ga, Zr oxides. The catalyst was calcined at 560–850°. Thus, 25 g ammonium vanadate and 25 g ammonium chromate were dissolved in 1 l. H_2O, and 0.8 g Sb_2O_3 dissolved into a little amt. of HCl and 4 g $SnCl_4.3.5H_2O$ were added. This suspension was poured onto 100 ml. silicon carbide granules. The soaked granules were sintered at 400–450° and calcined 2 hr at 700°. An air stream contg. I and H_2O was passed over the catalyst at 350° 3 hr to give 80 mole % yield of 96.1% pure II.

B4.34. 64213g Nicotinic acid. Kimura, Goro; Takada, Minoru; Yamamoto, Kosuke (Mitsui Toatsu Chemicals Co., Ltd.) Japan. 70 31,179 (Cl. C 07d), 08 Oct 1970, Appl. 09 Jan 1967; 2 pp. An oligomer (I) obtained as a side product in a reductive dimerization of acrylonitrile with NaHg is hydrogenated, dehydrogenated, and the resulting 3-substituted-pyridine is oxidized. Thus 100 g I in 150 ml MeOH is subjected to catalytic redn. with 10 g Raney Co in an autoclave with 100 atm H at 120° 4 hr, the resulting piperidine deriv. heated 5 hr at 220° in an H stream with 20 g 10% Pd/C, the resulting pyridine deriv. gradually added to 2 kg concd. H_2SO_4 (d = 1.42), and the mixt. heated 2–3 hr to give 73 g nicotinic acid. Hiroshi Kataoka

B4.35. 45352q Nicotinic acid by oxidation of pyridines with nitric acid. Stocker, August; Marti, Othmar; Pfammatter, Theodul; Schreiner, Gerhart (Lonza Ltd.) Ger. Offen. 1,956,117 (Cl. C 07d), 11 Jun 1970, Swiss Appl. 08 Nov 1968-19 Sep 1969; 11 pp. The title compd. (I) was prepd. by oxidn. of II (R = Me or Et, R^1 = H or Me) or quinolin with 40–400% excess HNO_3 at


(I)


(II)

230–330° and 50–300 atm to give I.HNO_3 (Ia) and subsequent crystn. of I by adjusting aq. Ia to the isoelec. point of I with the starting pyridines. Thus, a mixt. contg. 6.3% II (R = Et, R^1 = Me) (IIa) and 28.1% HNO_3 was passed through a reactor tube 35 min at 239° and 56 atm, subsequently concd. by evapn. and cooled at 5° to give 354.2 g Ia. Ia was dissolved in H_2O, heated at 60°, adjusted to pH 3.3 by addn. of IIa, and heated at 90° to give 66.9% I. The combined mother liquors contg. 77.8 g I and 244.81 g IIa were mixed with IIa and HNO_3 to get the starting concns. and were recycled. KSPG

B4.36. 43476p Nicotinic and isonicotinic acid. Eilhauer, Dieter; Hoefling, Wilhelm; Reckling, Gerhard; Meinicke, Karl H.; Fahrig, Peter Ger. (East) 68,229 (Cl. C 07d), 05 Aug 1969; Appl. 15 Jul 1968; 2 pp. Crude pyridine base mixts. (b. 140–50°) are treated with aq. HCHO soln. to give a distillate free of hydroxymethyl derivs. and a residue contg. methylolated compds. Oxidn. of these fractions yields nicotinic (I) and isonicotinic acid (II), resp. Thus, 815 kg picoline mixt., contg. 24% 4-picoline, 42% 3-picoline (III), 6% 2-picoline (IV), 18% 2,6-lutidine (V), and 8% 2-ethylpyridine (VI), was refluxed 40 hr with 835 kg 37% aq. HCHO soln. After steam distn., 700 kg hydroxymethyl-4-picoline mixt., contg. 40% H_2O, remained. This was added to 2800 kg 30 wt.% boiling aq. HNO_3 in 30 hr, and 1400 kg H_2O was distd. to give a distillate contg. <1% HNO_3. The reaction mixt. was dild. with 400 kg H_2O and the pH was adjusted to 3.5 with 10% NaOH to give 80% II. The steam distillate (1500 kg), representing a 36% aq. soln., composed of 58% III, 6% IV, 29% V, and 7% VI, was distd. to give a first fraction (500 kg) contg. 39% base, consisting of 17% III, 14% IV, 52% V, and 17% VI, and a second fraction (900 kg) contg. 39% base, consisting of 94% III, 5% V, and 1% VI. The latter mixt. (900 kg) was oxidized with 1450 kg $KMnO_4$ at 50–70° to give 180 kg I.

B4.37. 49785q Nicotinic acid. Suvorov, B. V.; et al. (Institute of Chemical Sciences, Academy of Sciences, Kazakh S.S.R. and Karaganda Metallurgical Plant) U.S.S.R. 235,764 (Cl. C 07d), 24 Jan 1969, Appl. 04 Nov 1966; From *Otkrytiya, Izobret., Prom. Obraztsy, Tovarnye Znaki* 1969, 46(6), 27. The title compd. is prepd. by oxidative ammonolysis of 3-picoline in the presence of a V oxide catalyst modified with Sn oxides, or promoted with W oxides followed by hydrolysis of the nicotinamide and nicotinonitrile. MCCL

B4.38. 68170f Nicotinic acid. Zundel, Jean Fr. 1,509,120 (Cl. C 07d), 12 Jan 1968, Appl. 28 Nov 1966, 3 pp. 5-Ethyl-2-methylpyridine (I) (350 g.), 1350 g. 60% HNO_3, and 700 ml. H_2O reacted in the autoclave at 160–80° and satd. with air under pressure until the oxidn. step was terminated, at 24 bars and 200°, the mixt. satd. with air and steam, cooled, and neutralized with Na_2CO_3 gave 237 g. nicotinic acid (II) [contg. 0.5–1% isocinchomeronic acid (III)]. Mother liquors contain 28 g. I, 29 g. II, and 17 g. III. A tech. procedure is also described.

B4.39. 37656s Nicotinic acid and isonicotinic acid. Ruetgerswerke und Teerverwertung A.-G. Brit. 1,132,746 (Cl. C 07*d*), 06 Nov 1968, Ger. Appl. 24 Jun 1965; 4 pp. Nicotinic acid or isonicotinic acid is prepd. by oxidn. of a substituted pyridine (3-alkylpyridine or 4-alkylpyridine) in an org. solvent which remains chem. unchanged, and the resulting soln. heated in the presence of SeO_2 to 130–200° with introduction of NO_2 into the soln. Thus, 94 g. 3-methylpyridine of 98% purity was dissolved in 750 g. 1,2,4-trichlorobenzene, 1 g. SeO_2 added, and at 130°, 0.5 g. NO_2/min. introduced to a total amt. 65 g. NO_2. The mixt. was heated to 150°, with continuation of addn. of NO_2 to an addnl. amt. of 70 g., cooled, and worked up to give 90 g. crude acid. The acid was dissolved in 400 ml. water and 40 ml. concd. HCl and adjusted to the isoelec. point with NaOH. The mother liquor was concd. to give a total of 79 g. nicotinic acid, m. 235–7°. From the trichlorobenzene soln., 11.7 g. and from the water mixt. 9.36 g. methylpyridine was obtained to give a total yield of nicotinic acid of approx. 85%. Similarly, an 87.8% yield of isonicotinic acid was obtained from 4-methylpyridine, and com. mixts. of 4-methylpyridine, 3-methylpyridine, and small amts. of 2,6- and 2,4-dimethylpyridine, 2-ethylpyridine, and 2-methylpyridine were converted to mixt. of isonicotinic and nicotinic acids. BRPN

B4.40. 37657r Nicotinic and isonicotinic acids. Aries, Robert Fr. 1,509,049 (Cl. C 07*d*), 12 Jan 1968, Appl. 28 Nov 1966; 3 pp. Alkyl- and dialkylpyridines are treated with reduced amts. of HNO_3 to give the title acids. Thus, a mixt. of 1.4 kg. 5-ethyl-2-methylpyridine, 5.4 kg. 60% HNO_3, and 2.8 l. water is agitated at 160°/18 atm., air introduced at 3500 l./hr. at up to 180°, air then introduced at 1000 l./hr., and steam introduced at 3000 l./hr. The mixt. is heated to 200°, the pressure increased to 24 atm., and the introduction of the air-steam mixt. continued (until CO_2 evolution stops) to give 1070 g. nicotinic acid. Similarly prepd. is isonicotinic acid. BDPF

B4.41. 104997a Nicotinic acid. Eastern Scientific-Research Coal-Chemical Institute (by N. D. Rus'yanova, N. V. Malysheva, L. P. Yurkina, and V. K. Kondratov). U.S.S.R. 191,562 (Cl. C 07*d*), Jan. 26, 1967, Appl. Oct. 12, 1965. The title compd. is prepd. by oxidn. of quinoline or its derivs., e.g. 8-hydroxyquinoline, with ozonized O. The process is simplified and yield increased by conducting the oxidn. in dil. AcOH at the b.p. of the reaction mixt. From *Izobret., Prom. Obraztsy, Tovarnye Znaki* 44(4), 37(1967). MGCL

B4.42. 90685n Preparation of nicotinic acid. Robert D. Lekberg, Raymond A. Jensen, and William Buiter (to Chemlek Laboratories, Inc.). U.S. 3,313,821 (Cl. 260-295.5), April 11, 1967, Appl. Aug. 3, 1964; 4 pp. Compds. contg. a pyridine nucleus are converted to the salts and oxidized with $Na_2Cr_2O_7$ to prep. nicotinic acid (I) in high yields. Thus, 3-picoline 186, H_2SO_4 124, and water 786 g. is mixed, 596 g. $Na_2Cr_2O_7 \cdot 2H_2O$ added, cond., in a sealed autoclave capable of withstanding 600 psi., the mixt. was heated at 450° for 42 hrs. I (92%, yield) was isolated as described in U.S. 2,415,147 (CA 41: 2756g). I was also prepd. from 3-picoline·HCl and the H_2SO_4 salts of 3-picoline, 2-methyl-5-ethylpyridine, and quinoline. CNPX

NIACIN

Purification

B4.43. **170701q Purification of pyridinecarboxylic acids.** Inoue, Toshio (Nippon Steel Chemical Industry Co., Ltd.) Japan. Kokai 74,124,070 (Cl. 16 E431), 27 Nov 1974, Appl. 73 35,590, 30 Mar 1973; 3 pp. Pyridinecarboxylic acids (I) were purified by passing gases contg. I through layers of adsorbent particles below the pptn. temp. of I. Thus, 30 g nicotinic acid (II) (purity 97%) in N was sublimed at 230° and 610 mm Hg and gaseous II passed at 230° over 339 g electrically fused Al_2O_3 (contg. 86% Al_2O_3; preheated 5 hr at 250°) to give 94.7% II (purity >99%). Porcelain Al_2O_3, SiO_2–Al_2O_3 (87:13), active terra alba, silicon carbide, and kieselguhr brick were also used. K. Sempuku

B4.44. **170685n Recrystallization of pyridine derivatives having polar substituents.** Kato, Satoru; Inoue, Toshio; Hara, Tadanori (Nippon Steel Chemical Industry Co., Ltd.) Japan. Kokai 74 100,087 (Cl. 16 E431), 20 Sep 1974, Appl. 73 11,194, 29 Jan 1973; 3 pp. Pyridine derivs. with polar substituents are recrystd. from a solvent contg. H_2O and alcs. Thus, 15 g nicotinic acid of 98.7% purity, prepd. by gas-phase oxidn. of alkylpyridines, was recrystd. from 193 g 7:3 MeOH–H_2O with C to recover 82.3% colorless acid, >99.8% pure. Recrystn. from MeOH or H_2O alone gave a colored product. $MeOCH_2CH_2OH$–H_2O (7:3) was also a good solvent. Similarly, nicotinamide was recrystd. from 1:1 aq. EtOH. I. Matsumoto

B4.45. **170684m Pyridinecarboxylic acid purification.** Inoue, Toshio (Nippon Steel Chemical Industry Co., Ltd.) Japan. Kokai 74 100,086 (Cl. 16 E431), 20 Sep 1974, Appl. 73 11,193, 29 Jan 1973; 2 pp. Crude pyridinecarboxylic acids are recrystd. first from alcs. and then from H_2O. Thus, 15 g nicotinic acid of 99.1% purity, prepd. by gas-phase oxidn. of alkylpyridines and sublimed, was recrystd. first from 135 g EtOH and then from 135 g H_2O with C to recover 66.7% pure acid, which was less colored than the control (the solvent order reversed). I. Matsumoto

B4.46. **135981p Purification of pyridinecarboxylic acids.** Inoue, Toshio; Yasui, Hiroshi; Kato, Satoru; Hara, Tadanori (Nippon Steel Chemical Industry Co., Ltd.) Japan. Kokai 74 49,966 (Cl. 16 E431), 15 May 1974, Appl. 72 92,939, 18 Sep 1972; 3 pp. Pyridinecarboxylic acids (I) were purified after heating crude I. Activated clay may be added to crude I before heating. E.g., 300 g nicotinic acid (II) (purity 96.6 wt. %) was heated with 5 wt. % activated clay for 10 hr at 220° in the air, treated with activated C in H_2O, to give 68.3% II (purity 99.9 wt. %). K. Sempuku

B4.47. **120503v Pharmaceutical grade nicotinic acid.** Fahrig, Peter; Angermann, Werner; Meinicke, Karl H. Ger. (East) 72,525 (Cl. C 07d), 20 Apr 1970, Appl. 18 Dec 1968; 2 pp. Tech. nicotinic acid prepd. by $KMnO_4$ oxidn. of 3-picoline contains mineral salts and dipicolinic acid which are difficult to remove by the customary recrystn. from H_2O. The title process is characterized by the use of $FeSO_4$ as a complexing agent for the quant. elimination of dipicolinic acid. Tech. nicotinic acid (75 kg cor tg. 3% K_2SO_4 and 2% dipicolinic acid) and 1.9 kg $FeSO_4.7H_2O$ in 600 l. tapwater stirred 2 hr under reflux and cooled to 20° gave 45 kg pharmaceutical grade homogeneous white nicotinic acid. The deep red combined mother-liquors and filtrates was concd. and the crystal mash filtered off, returned to a new batch of tech. nicotinic acid, and again treated with $FeSO_4.7H_2O$. C. R. Addinall

NIACIN

Separation

B4.48. 43469p Separation of a eutectic mixture of nicotinic and isonicotinic acids. Bialek, Jerzy; Porada, Slawomira (Instytut Chemii Ogolnej) Pol. 57,343 (Cl. C 07*d*), 30 Jun 1969, Appl. 29 Dec 1966; 2 pp. An efficient method is described for the sepn. of nicotinic acid (I) and isonicotinic acid I (II) from their eutectic mixt. by crystn. Thus, 15 g of a eutectic mixt. contg. I 75 and II 25%, was dissolved in 310 ml H_2O, the pH of the soln. was brought with gaseous NH_3 to 4.5, and the soln. was evapd. to 170 ml and left to crystallize; 8 g of I, contg. <5% II was obtained and after recrystn. pure I was obtained, m. 235.5–7°. Crystn. mother liquors were evapd. to dryness and the ammonium salts of the pyridinecarboxylic acids were decompd. at 120–30°. The residue, contg. 86.5% of I and II in the ratio 6:4 was sepd. by conventional method, e.g. according to Pol. 50,079. Cf. Pol. 34,921 and 35,452; U.S. 2,748,136; Austrian 242,699.
Karol Butkiewicz

B4.49. 3842g Separation of nicotinic and isonicotinic acid. Hoelling, Wilhelm; Eilhauer, Hans D.; Krautschik, Gerd; Mohrhauer, Rolf Ger. (East) 58,090 (Cl. C 07*d*), 05 Oct 1967, Appl. 26 Jan 1967; 2 pp. Mixts. of nicotinic acid (I) and isonicotinic acid (II) were sepd. by an extn. with substituted pyridines (III) at 50–120° followed by an extn. with HNO_3 at 0–30°. Thus, 1 kg. I and 1 kg. II in 3 kg. III (b. 115–250°) was stirred 2 hrs. at 97°, the suspension filtered, the filter-cake washed with 1 l. MeOH, and dried to yield 770 g. II (purity 94.1%). The filtrate was evapd. to dryness, the residue (1205 g.) treated with 1690 g. 64% aq. HNO_3 at 50°, the reaction product filtered off and dried to give 1.4 kg. nitrate of I (purity 93%). For further purification, the nitrate was stirred with 1120 g. 20% aq. HNO_3 2 hrs. at 20–25°, filtered off, and dried to give 1315 g. nitrate (purity 95.5%). This substance was suspended in 2630 g. distd. water, aq. KOH added to ppt. I at pH 3.5, the ppt. filtered off, washed with MeOH, and dried to yield 855 g. I (purity 97%). The washings and the mother liquor were worked up in a similar manner to give 285 g. of a mixt. of 28.5% I and 71.5% II which was used for the next extn. process.
A. Roders

B4.50. 40629p Recovery of nicotinic and isonicotinic acid. Eilhauer, Hans D.; Krautschick, Gerd; Kurtschinkski, Gerhard Ger. (East) 61,544 (Cl. C 07*d*), 05 May 1968, Appl. 28 Aug 1967; 3 pp. The title compds. (I) are recovered from mother liquors contg. 2–5% I by continuous countercurrent extn. at 0–100° with an org. base satd. with H_2O, followed by extn. with concd. (till 50%) aq. NaOH at 0–120°. A description of a pilot-plant is given and a table contg. results with various bases, % recovery etc.
H. Pouwels

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Miscellaneous

B4.51. 135975q Catalysts for oxidation of alkylpyridines. Morita, Masamichi; Inoue, Toshio; Hara, Tadanori (Nippon Steel Chemical Co., Ltd.) Japan. Kokai 74 39,591 (Cl. 23(9)G112, 13(9)G113, 16 E431), 13 Apr 1974, Appl. 72 82,849, 21 Aug 1972; 4 pp. V, Sn, Ti, Bi, Sb, and W compds. were used as catalysts for the air oxidn. of β- or γ-alkylpyridines. E.g., 1 l. 2-methyl-5-ethylpyridine vapor was air-oxidized in the presence of a catalyst contg. 1 kg TiO_2, 117 g NH_4VO_3, 175 g $SnCl_4.5H_2O$, 100 g $Bi(NO_3)_3.6H_2O$, and 850 ml H_2O to give 61.2% nicotinic acid.

B4.52. 99516b Catalyst composition for gas phase catalytic oxidation of picoline. Yokoyama, Ryoichi; Sawada, Katsumi (Teijin Chemical Industry Co., Ltd.) Japan. 72 00,805 (Cl. C 07c, B 01j), 11 Jan 1972, Appl. 04 Mar 1968; 2 pp. A mixt. of V_2O_5 and Cr_2O_3 (V:Cr = 1:0.5 to 1:1) was calcined preferably at 650–780° in the presence of O to give a desired catalyst. E.g., a mixt. of V, Cr, Sn, and Sb (100:75:4:1) carried on SiC (8–10 mesh) was heated at 650° in the presence of O to give a catalyst. β-Picoline was oxidized using the resulting catalyst at 390° with 200 l./hr air to give 86.8% 3-pyridinecarboxylic acid of 98% purity.
Hiroshi Kataoka

B4.53. 101: 191699w T-Butylphenoxyalkylene esters of benzoic and nicotinic acids, compositions containing them and their anti-histaminic method of use. Berger, Frank M.; De Graw, Joseph I., Jr.; Johnson, Howard L. U.S. US 4,451,474 (Cl. 424-266; C07D213/55), 29 May 1984, US Appl. 114,183, 22 Jan 1980; 15 pp. Cont.-in-part of U.S. Ser. No. 114,183, abandoned. 3,4-$RR^1C_6H_3O(CH_2)_m(CR^2_2)_n(CH_2)_pOR^3$ (I, R = H; R^1 = alkyl; RR^1 = alkylene; R^2 = H, alkyl; R^3 = H, acyl; m, n, p = 0–10) were prepd. and 4-$Me_3CC_6H_4O(CH_2)_qOR^4$ (II, R^4 = nicotinoyl, q = 3, 4; R^4 = Bz, q = 4) were claimed. Thus, 4-$Me_3CC_6H_4OH$ was treated with $Cl(CH_2)_4OAc$ to give II (R^4 = Ac, q = 4) which was sapond. to give II (R^4 = H, III). III was esterified with nicotinoyl chloride to give II (R^4 = nicotinoyl, q = 4, IV). The histamine release–inhibiting activity of III and IV relative to that of chlorphenesin was 10.0 and 20.0, resp.
101: 191700q 1,4-Dihydropyridine esters and drugs contining these esters. Sunkel Letelier, Carlos; Pau de Casa-Juana Munoz, Miguel; Statkov, Peter R.; Straumann, Danielle (Cermol S. A.)

B4.54. 101: 97664j Antidepressants containing L-tryptophan and a monoamine oxidase inhibitor. Coppen, Alec James Brit. UK Pat. Appl. GB 2,129,299 (Cl. A61K45/06), 16 May 1984, Appl. 82/31,975, 09 Nov 1982; 3 pp. Antidepressants contain *L-tryptophan* [73-22-3] at lower doses when combined with a *monoamine oxidase* [9001-66-5] inhibitor, e.g., *phenelzine* [51-71-8] or *tranylcypromine* [155-09-9]. The antidepressant action of the compn. is greater than either compd. alone in their usual dosages. The compns. may also contain *folic acid* [59-30-3], *ascorbic acid* [50-81-7], *pyridoxine* [65-23-6], *thiamine* [59-43-8], *riboflavin* [83-88-5], *nicotinic acid* [59-67-6] or *nicotinamide* [98-92-0].

B4.55. 101: 92147h **Latent curing agents for epoxy resins.** Takeuchi, Koji; Abe, Masahiro; Ito, Nobuo; Hirai, Kiyomiki (Ajinomoto Co., Inc.) Eur. Pat. Appl. EP 104,837 (Cl. C08G59/56), 04 Apr 1984, JP Appl. 82/164,557, 21 Sep 1982; 32 pp. The curing agents, useful in formulating novel stable 1-package heat-curable epoxy resin-based compns., are prepd. by treating a polyfunctional epoxy compd. and a compd. having a tertiary group and ≥1 OH, SH, COOH, and $CONHNH_2$ groups, and by treating the 2 above components and an org. compd. having ≥2 active H atoms (excluding compds. having epoxy or tertiary amine groups). Thus, a mixt. contg. *Epon 828* (I) [25068-38-6] 100, ZnO 3, TiO_2 2, and curing agent, prepd. by treating I with *1-(2-hydroxy-3-phenoxypropyl)-2-phenylimidazole* (II) [91454-81-8] 20 parts, had onset temp. 90°, peak temp. 135°, curing temp. and time 120° and 60 min, resp., and storage stability at 30° >1 mo, compared with 60°, 170°, 100°, 60 min, and <1 day, resp. for a similar compn. contg. unreacted II.

B4.56. 101: 53697t **Supplementary food containing vitamins and/or minerals and optionally further components.** Van der Eijnden, Cornelis Maria Joseph (Van Melle Nederland B. V.) Eur. Pat. Appl. EP 102,663 (Cl. A23L1/30), 14 Mar 1984, NL Appl. 82/3,150, 10 Aug 1982; 12 pp. A food product is prepd. from water, carbohydrates, and vegetable oils, and fortified with vitamins and minerals. The product may be used to supplement food in areas of malnutrition. Thus, a mixt. of *sucrose* [57-50-1] 42, glucose syrup 42, hydrogenated cocoa fat 8, *gum arabic* [9000-01-5] 1, and water 7% was boiled at 123° to 7% residual moisture, cooled to 70°, and treated with 4.5 g of a mixt. of *vitamin A* [11103-57-4], *vitamin D_3* [67-97-0], *vitamin E* [1406-18-4], *vitamin C* [50-81-7], *vitamin B_1* [59-43-8], *vitamin B_2* [83-88-5], *vitamin B_6* [8059-24-3], *vitamin B_{12}* [68-19-9], *folic acid* [59-30-3], *niacin* [59-67-6], and *pantothenic acid* [79-83-4]. The mass was mixed, cooled, formed into blocks, and packaged.

B4.57. 98: 3538r **Concentrated GTF chromium complex brewers yeast.** Szalay, Andrew U.S. US 4,343,905 (Cl. 435-256; C12N1/16), 10 Aug 1982, Appl. 166,454, 07 Jul 1980; 5 pp. Brewers' yeast contg. ~2000 μg Cr/mg, >80% of which is present as glucose tolerance factor (GTF)-active org. Cr complex, is prepd. by culturing the yeast in a medium contg. Cr oxide ~23, nicotinic acid 29-32, glucine 17-20, L-glutamic acid 17-20, and L-cysteine-HCl 19.3%, based on wt. of solids. The yeast nutrient was prepd. by dissolving nicotinic acid, glycine, and L-glutamic acid in H_2O at 90° with const. agitation; a soln. of Cr oxide in H_2O was added slowly, followed by L-cysteine-HCl. The soln. was stirred for 1 h at 90°, and allowed to settle and cool for 48 h. A suspension of brewers' yeast in H_2O at 35° was added, and the mixt. agitated for 24 h at 35°, and heated to 90° for 3 h. The killed yeast was spray dried, hydrolyzed with a proteolytic enzyme, the cell fragments were removed by centrifuging, and the sol. material was spray dried and assayed. The org. Cr content was 80% of the total Cr. When administered to normal subjects with abnormal glucose control, mature diabetics, and juvenile diabetics at 200 μg Cr/day for 4 mo, blood cholesterol and triglyceride levels decreased, and high-d. lipoproteins increased. Glycosylated Hb levels in diabetics were normalized.

B4.58. 94: 69228p **Charge for melting vanadium ferroalloy.** Bairamov, B. I.; Zaiko, V. P.; Ryss, M. A.; Shcherbakov, S. S.; Pigasov, V. F.; Sibilev, Yu. P. (Chelyabinsk Electrometallurgical Combine) U.S.S.R. 765,384 (Cl. C22C33/04), 23 Sep 1980, Appl. 2,598,527, 03 Apr 1978. From *Otkrytiya, Izobret., Prom. Obraztsy, Tovarnye Znaki* 1980, (35), 170. The loss of metal by slag is decreased and the sepn. of slag from metal in a solid form improved by adding 10-25% sludge from manuf. of *nicotinic acid* [59-67-6] (MnO_2 50-60, NaOH 0.7-1.2, Pb 0.01-0.1%, balance H_2O) to the title charge contg. V material 30-40, Si-contg. reducing agent 8-15, C-contg. reducing agent 2-5%, balance Ca-contg. flux.

B4.59. 105298d Trapping nicotinic acid. Hara, Tadanori; Inoue, Toshio (Nippon Steel Chemical Industry Co., Ltd.) Japan. Kokai 74 62,475 (Cl. 16 E431), 17 Jun 1974, Appl. 72 104,440, 20 Oct 1972; 3 pp. Nicotinic acid (I) was trapped by introducing I-contg. gases at 100–200° onto the layers bearing fillers of inactive particles of 0.5–10 mm in diam. E.g., 13.5 g crude I (purity 97%) was sublimed 8 hr under 30 l./hr N current at 235° and 610 mm. The sublimed vapor (220°) was passed over 100 ml fused Al_2O_3 (1–1.4 mm in diam.; inlet temp. 180°, outlet temp. 140°) to trap 13 g I (purity >99%, 0.5–1 mm in diam.).
K. Sempuku

B4.60. 43287b Nicotinic acid esters. Azerbaev, I. N.; Erzhanov, K. B.; Kasymkhanona, U. F. (Institute of Chemical Sciences, Academy of Sciences, Kazakh S.S.R.) U.S.S.R. 351,849 (Cl. C 07*d*), 21 Sep 1972, Appl. 13 Aug 1970. From *Otkrytiya, Izobret., Prom. Obraztsy, Tovarnye Znaki* 1972, 49(28), 72. Heating nicotinoyl chloride hydrochloride with acetylenic glycols in the presence of a tertiary amine afforded the corresponding title esters.

B4.61. 123706v Microbiological production of protein–vitamin concentrates. Dikanskaya, E. M.; Balabanova, A. A. (All-Union Scientific-Research Institute of Protein Biosynthesis) Brit. 1,226,477 (Cl. C 07*d*), 31 Mar 1971, Appl. 28 May 1969; 3 pp. Protein–vitamin concs. fortified with riboflavine are produced by *Eremothecium ashbyii* in a yeast medium produced from petroleum hydrocarbons. Thus, yeast produced on a mixt. of petroleum *n*-paraffins was dild. to a concn. of 6 wt. %, sterilized in 500 ml rocking flasks, and inoculated with a 2% 2-day culture of *E. ashybii* grown on similar yeast medium. The culture was grown under different aeration conditions for 6 days. With aeration of 0.4, 2.2, and 3.5 g O/hr, 280, 1330, and 1730 mg of riboflavine/kg of dry prepn. were formed after 2 days; 10,330, 11,600, and 10,980 mg/kg were formed after 6 days. The fungus was then grown in a 500 ml fermentation tank with 300 ml of yeast medium prepd. as above. Biomycin antibiotic, 200 units/ml, was added and the medium was inoculated with 10 vol. % of flask culture of *E. ashbyii*. Fermentation was carried out with aeration and mixing; oleic acid was added to control foaming. The temp. was kept at 30°. In 24 hr the medium turned yellow due to riboflavine. In 48 hr the vitamin B_2 content was 500 μg/ml and in 70 hr it was 880 μg/ml, which corresponded to 9000 mg/kg of dry prepn. After 70 hr the culture mass was dried at 100°. The dry powder contained crude protein 40%, riboflavine 9000, pantothenic acid 540, pyridoxine 20, nicotinic acid 500, thiamine 10, and biotin 0.2 mg/kg.
S. P. Marino

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B5

NIKETHAMIDE

PATENTS

1967-1985

APPENDIX P18

ANALYSIS OF THE ABSTRACTS OF PATENTS

The patents B5.1. - B5.6. are held by the same firm and describe syntheses starting from nicotinic acid by reaction with diethylamine, phosgene and similar compounds. In B5.7. nicotinic acid reacts with diethylacetamide and in B5.8. a gasphase reaction of nicotinic acid with diethylamine on silicagel is described.

ABSTRACTS OF PATENTS

B5

NIKETHAMIDE

Preparation

B5.1. 85: 32655p N,N-Disubstituted carboxylic amides Grega, Erzsebet; Gribovszky, Pal; Marosvolgyi, Sandor; Pinter, Zoltan; Szilagyi, Gyula; Szita, Istvan; Tarr, Csaba; Tasi, Laszlo (Eszakmagyarorszagi Vegyimuvek) U.S. 3,941,783 (Cl. 260-247.7V; C07D), 02 Mar 1976, Appl. 421,642, 04 Dec 1973; 6 pp. Nineteen $RCONR^1R^2$ [R = $Me(CH_2)_{14}$, $ClCH_2$, Ph, substituted phenyl, 3-pyridyl, Ph_2CH; R^1,R^2 = same or different C_{1-4} alkyl or Ph; or NR^1R^2 = morpholino] were prepd. by reaction of RCO_2H with $ClCONR^1R^2$ at 110–220°.

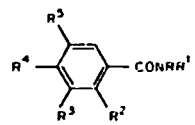
B5.2. 84: 179901d N,N-Disubstituted carboxylic acid amides. Eszakmagyarorszagi Vegyimuvek Neth. Appl. 73 17,053 (Cl. C07C), 16 Jun 1975, Appl. 73 17,053, 12 Dec 1973; 19 pp. $RCONR^1R^2$ (I; R = C_{1-18} alkyl or haloalkyl, Ph, or substituted phenyl; R^1, R^2 = the same or different C_{1-14} alkyl or substituted alkyl, Ph, or substituted phenyl, or R^1R^2N = a N heterocycle) were prepd. by reacting RCO_2H with R^1R^2NH or with $ClCONR^1R^2$, with elimination of HCl and CO_2. Thus, $Me(CH_2)_{14}CO_2H$ with Bu_2NH gave 75% I (R = n-$C_{15}H_{31}$, R^1 = R^2 = Bu), and BzOH with $ClCONPhCHMe_2$ gave 78% $BzNPhCHMe_2$. Eighteen other I were prepd.

B5.3. 84: 58967w N,N-Disubstituted aromatic and aliphatic carboxylic amides. Gribovski, Erzsebet P.; Marosvolgyi, Sandor; Pinter, Zoltan; Szilagyi, Gyula; Szita, Istvan; Tarr, Csaba; Tasi, Laszlo (Eszakmagyarorszagi Vegyimovek) Fr. Demande 2,253,735 (Cl. C07CD), 04 Jul 1975, Appl. 73 43,898, 10 Dec 1973; 22 pp. Amidation of benzoic acids or Ph_2CHCO_2H with amine–phosgene mixts. and with carbonyl chlorides gave twelve $RCONR^1R^2$ (I; R = Ph, substituted phenyl, $CHPh_2$; R^1 = C_{1-4} alkyl; R^2 = Ph, C_{1-4} alkyl; NR^1R^2 = morpholino). Similarly prepd. were seven I (R = pentadecyl, $ClCH_2$; R^1 = Bu, $CHMe_2$, Ph, alkoxymethyl; R^2 = Bu, Ph, dialkylphenyl). I are useful as herbicides and analeptics and in the treatment of arteriosclerosis.

B5.4. 84: 4690g N,N-Disubstituted carboxylic acid amides. Grega, Erzsebet; Gribovszki, Pal; Marosvolgyi, Sandor; Pinter, Zoltan; Szilagyi, Gyula; Szita, Istvan; Tarr, Csaba; Tasi, Laszlo Austrian 323,123 (Cl. C07C), 15 Sep 1974, Appl. 10,088/73, 03 Dec 1973; 10 pp. The title amides were prepd. in high yield in 1 step by treating the acid with the secondary amine and $COCl_2$ or the carbamoyl chloride. Thus $Me(CH_2)_{14}CONBu_2$ was obtained in 75% yield by treating $Me(CH_2)_{14}CO_2H$ with $COCl_2$ and $NHBu_2$, or in 74.8% yield by treating $Me(CH_2)_{14}CO_2H$ with Bu_2NCOCl. Other amides similarly prepd. include $BzNPhCHMe_2$, $ClCH_2CONPh_2$, *N,N*-diethylnicotinamide, and *N*-benzoylmorpholine.

B5.5. 163852g N,N-Disubstituted carboxylic acid amides. Grega, Erzsebet; Gribovszki, Pal; Marosvolgyi, Sandor; Pinter, Zoltan; Szilagyi, Gyula; Szita, Istvan; Tarr, Csaba; Tasi, Laszlo (Eszakmagyarorszagi Vegyimuvek) Ger. Offen. 2,365,451 (Cl. C07C), 31 Jul 1975, Appl. P 23 65 451.5-42, 11 Dec 1973; 28 pp. Division of Ger. Offen. 2,361,604. $RCONR^1R^2$ (R, R^1, R^2 = alkyl, Ph; NR^1R^2 = morpholino) were prepd. by heating a carboxylic acid with a disubstituted carbamoyl chloride at 110-180° without a solvent. Thus, $3,5-(O_2N)_2C_6H_3CO_2H$ was heated with Bu_2NCOCl at 140-60° to give 74% $3,5-(O_2N)_2C_6H_3CONBu_2$.

B5.6. 96777w N,N-Disubstituted benzamides. Grega, Erzsebet; Gribovszki, Pal; Marosvolgyi, Sandor; Pinter, Zoltan; Szilagyi, Gyula; Szita, Istvan; Tarr, Csaba; Tasi, Laszlo (Eszakmagyarorszagi Vegyimuvek) S. African 74 00,572 (Cl. C07c), 24 Oct 1974, Appl. 74 0572, 29 Jan 1974; 24 pp. Benzoic acids reacted with amine-phosgene mixts., or carbamoyl chlorides, to give eleven benzamides [I; R and R^1 (same or different) are $CHMe_2$, Ph, Bu, Et, CH_2CHMe_2, CHMeEt, and NRR^1 = 4-morpholinyl; R^2 = H, Cl; R^3 = H, Cl, NO_2, OMe; R^4 = H, Cl, OMe; R^5 = H, NO_2.



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OMe]. Similarly prepd. were six $RCONR^1R^2$ [II; R = pentadecyl, CH_2Cl, $CHPh_2$; R^1 and R^2 (same or different) are Bu, $CHMe_2$, Ph, Me]. I and II are useful in the treatment of arteriosclerosis and as tranquilizers, analeptics, and herbicides.

B5.7. 112819w N,N-Diethylnicotinamide. Moulin, Francois (Lonza Ltd.) Swiss 473,123 (Cl. C 07d), 15 Jul 1969, Appl. 22 Feb 1966; 2 pp. Through a mixt. of 30 g. nicotinic acid (I) and 36 g. $AcNEt_2$ (II) was passed 120 ml./hr. N and the flask heated so that, at a vapor temp. of 130-50°, 5 ml. of mixt. AcOH-II distd./hr. In 9 hrs., 43.5 ml. distillate was collected and 40 ml. II added to the mixt. After cooling 6.9 g. I crystd. and the residue distd. to give II and 89.7% title compd., b_{10} 155-7°.
Gerben Sipma

B5.8. 100567e N,N-Diethylamide of nicotinic acid. Dormidontova, N. V.; Ustavshchikov, B. F.; Farberov, M. I. (Yaroslavl Technological Institute) U.S.S.R. 218,185 (Cl. C 07d), 17 May 1968, Appl. 6 Dec 1966; From *Izobret., Prom. Obraztsy, Tovarnye Znaki* 1968, 45(17), 26. Title compd. is prepd. from nicotinic acid and Et_2NH in the vapor phase in the presence of a silica gel catalyst.
N.N.C.L.

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C1

METRONIDAZOLE

PATENTS

1967-1985

APPENDIX P19

ANALYSIS OF THE ABSTRACTS OF PATENTS

There are two main groups of patents both starting from 2-methyl-5-nitroimidazole. In Cl.1., Cl.2. and Cl.8. this compound reacts with ethylenoxide and in Cl.3. - Cl.6. it reacts with chloroethanol. In Cl.5. a yield of 71.8% is given.

Other processes Cl.7. - Cl.9. at a first analysis do not reveal significant advantages compared to the standard processes.

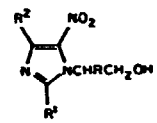
ABSTRACTS OF PATENTS

C1

METRONIDAZOLE

Preparation

C1.1. 147480d 1-Hydroxyalkyl-5-nitroimidazoles. Frank, Anton; Karn, Helmut; Spaenig, Hermann (BASF A.-G.) Ger. Offen. 2,359,625 (Cl. C07D), 05 Jun 1975, Appl. P 23 59 625.0, 30 Nov 1973; 11 pp. 1-Hydroxyalkyl-5-nitroimidazoles (I, R = R^2



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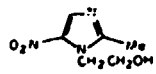
= H, R^1 = Me, H, Et, $CHMe_2$; R = R^1 = Me, R^2 = H; R = R^1 = H, R^2 = Me; R = R^2 = Me, R^1 = H) were obtained in 53.6-78.4% yields by treatment of a 5-nitroimidazole with ethylene or propylene oxide in a mixt. of $(HCO)_2O$ and Ac_2O and 25-30°. I are polymn. catalysts and condensation catalysts.

C1.2. 97648p 1-(2-Hydroxyethyl)-2-methyl-5-nitroimidazole. Muhlbrod, Jan (Starogardzkie Zaklady Farmaceutyczne "Polfa") Brit. 1,301,225 (Cl. C 07*d*), 29 Dec 1972, Pol. Appl. 138,-251, 19 Jan 1970; 3 pp. The title compd. (I) was prepd. in 80% yield from 2-methyl-5-nitroimidazole sulfate and ethylene oxide in mixts. of H_2SO_4 and a satd. aliph. compd. having an O-contg. functional group or an O heterocycle. Thus, 200 g 2-methyl-5-nitroimidazole (II) was poured and 158 g H_2SO_4 added dropwise to 140 ml Me_2CO and 23 ml ethylene glycol below 40°. A total of 320 g ethylene oxide and 66 g H_2SO_4 were alternatively added in portions over 100 min to the reaction mixt. at 45-50°. After pptn. of unreacted II by soln. with 450 ml H_2O the mixt. with 35% NaOH at 35° pptd. 205 g crude product which gave 141 g I.

C1.3. 101618c 2-Substituted-1-(hydroxyethyl)-5-nitroimidazoles. Klosa, Josef; Thomas, Gottfried; Friese, Johannes Ger. (East) 88,028 (Cl. C 07*d*), 20 Feb 1972, Appl. WP 12p/145,335, 05 Feb 1970; 3 pp. The imidazole (I) was obtained in 71.8-



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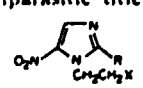
4.5% yield of 18.3-19.2% conversion by hydroxyethylating methylnitroimidazole with ethylene chlorohydrin, satd. with HCl(g) at 125-7° for 9.5-10.5 hr.

C1.4. 101609a Antiparasitic 1-substituted 5-nitroimidazoles. Valles, Paolo (CRC Compagnia di Richerche Chimiche S. A.) Swiss 520,090 (Cl. C 07*c*), 28 Apr 1972, Appl. 3211/67, 06 Mar 1967; 5 pp. The antiparasitic title compds. (I) were prepd.



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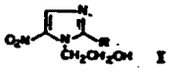
from alkylene dihalide and 1*H*-imidazoles in the presence of HCO_2H, HOAc, or $EtCO_2H$. Thus, 6.3 g 2-methyl-5-nitroimidazole, 84.6 g $Br(CH_2)_2Br$, and 21 g HOAc was heated 48 hr at 110-14° to give 1.4 g I (R = Me, X = Br). Similarly prepd. were I (R = Me, X = I and OH). H. J. Nitzschke

C1.5. 110314m 1-(β-Hydroxyethyl)-2-alkyl-5-nitroimidazoles. Klosa, Josef Ger. Offen. 2,001,432 (Cl. C 07d), 15 Jul 1971, Appl. 08 Jan 1970; 7 pp. The title imidazoles (I) are prepd. by



I

treatment of 2-alkyl-5-nitroimidazoles with $HOCH_2CH_2Cl$ in the presence of HCl at a raised temp. Thus, 2-methyl-5-nitroimidazole (m. 252–4°) in $HOCH_2CH_2Cl$ satd. with dry HCl stirred 10.5 hr at 125–7° gave in the basic residue 2-methyl-4(5)-nitroimidazole. The filtrate made alk. with NaOH to pH 10 and the H_2O- and iso-PrOH-washed ppt. dried yielded 71.8% I (R = Me), m. 158.5–60.5°. Similarly was obtained I (R = Et), m. 87–9°.
C. R. Addinall

C1.6. 22129s Chemotherapeutic nitroimidazoles. Toth, Joszef; Fekete, Gyorgy; Gorog, Sandor; Gorgenyi, Katalin; Szporny, Laszlo; Boor, Anna; Holly, Sandor (Richter, Gedeon, Vegyeszeti Gyar R. T.) Austrian 269,135 (Cl. C 07d), 10 Mar 1969, Hung. Appl. 26 Nov 1966; 8 pp. I and II, wherein R is H or low alkyl were prepd. Thus, 20.5 g. 2-methylimidazole is refluxed 3 hrs. in 60 ml. $ClCH_2CH_2OH$ giving 40 g. light yellow oil,

(I, 4-NO_2) (II, 5-NO_2)

$b_{0.1-0}$ 140–240° which yielded 12.44 g. 1-(2-hydroxyethyl)-2-methylimidazole, m. 63–5° (AcOEt); hydrochloride m. 125–7°; picrate m. 154–6°; nitrate (III)-HCl, m. 108–15°, nitrate picrate m. 160–2°. III was stirred at 20–30° while 78 ml. HNO_3 was added dropwise. P_2O_5 (16.6 g.) was added and after 10–15 hrs. at 20–75° worked up to give 41:59 I–II (R = H) m. 128–30° and m. 157–9°, resp.; nitrates m. 98–100° and 69–70°, resp. Also prep. were I (R = Ac) m. 142–4° and II (R = Ac), m. 70–3°. The new compds. are of therapeutical value as chemotherapeutics against trichomonas infections. Friedrich Epstein

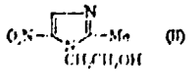
C1.7. 87814k 1-(2-Hydroxyethyl)-2-methyl-5-nitroimidazole. K R K A Tovarna Zdravil Brit. 1,138,805 (Cl. C 07d), 01 Jan 1969, Yugoslavia Appl. 20 Jun 1966; 2 pp. A mixt. of 11.7 g. 1-(2-bromoethyl)-2-methyl-5-nitroimidazole, 39 ml. $HCONH_2$, 1.8 ml. water, and 0.3 ml. 98–100% HCO_2H is heated 3 hrs. at 110–15°, 27–8 ml. $HCONH_2$ distd. at 0.7–0.8 mm., and the residue worked up to give 69% 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole, m. 160–2°. BDPN

C1.8. 77973x 1β-(Hydroxyethyl)-2-methyl-5-nitroimidazole. Aldea, Vasilichia; Banulescu, Virginia; Cilianu, Stefan B.; Peloni, Viorica (Romania, Institute for Chemical-Pharmaceutical Research) Rom. 51,308 (Cl. C 07d), 16 Sep 1968, Appl. 11 Oct 1967; 2 pp. The title product (I) had pharmacol. activity. Thus, 13 HCO_2H, 1.4 crude 2-methyl-5-nitroimidazole and 2.8 kg. ethylene oxide was treated at 25–30° for 90 min., kept 75 min. at this temp. and worked up to give 75–6% I, 153–9°.
Marcel M. Gregorian

C1.9. 26918z **Imidazole derivatives.** Toth, Jozef; Fekete, Gyorgy; Boor, Mrs. Lajos; Szporny, Laszlo; Gregenyi, Mrs. Akos; Gorog, Sandor; Holly, Sandor (Richter, Gedeon, Vegyeszeti Gyar R. T.) Hung. 154,716 (Cl. C 07*d*), 30 Apr 1968, Appl. 26 Nov 1966; 33 pp. Ethylolation of 2-methylimidazole (I) with $ClCH_2CH_2OH$, $(CH_2)_2O$, or $(CH_2O)_2CO$ affords 1-(2-hydroxyethyl)-2-methylimidazole (II), which is then esterified, the nitrate (III) and acetate esters are nitrated, and the 4- and 5-nitro derivs. are sepd., followed by hydrolysis of the ester group. The ratio of 4- and 5-nitro derivs. varied depending on the reaction conditions. Thus, a mixt. of 20.5 g. I and 60 ml. $ClCH_2CH_2OH$ was refluxed 2 hrs., concd. in vacuo and fractionated, the fraction $b_{0.1}$ 140–240° taken up in EtOH, the HCl content neutralized with KOH, and the soln. filtered and concd. in vacuo, to yield II, m. 63–5° (EtOAc); hydrochloride m. 125–7°; picrate m. 154–6°. II (25.2 g.) was added with stirring to 100 ml. 96% HNO_3 at 0° and the mixt. stirred at room temp. 2 hrs., poured onto ice and extd. with $CHCl_3$ at pH 10 (NaOH) to yield 92% III, a pale yellow oil; hydrochloride m. 108–15°; picrate m. 160–2°. II (12.6 g.) was dissolved in 42.7 ml. Ac_2O at 0°, the soln. kept at 110–20° 3 hrs., and concd. in vacuo, the oily residue added in portions to 12.6 ml. concd. HNO_3 and 15.7 g. P_2O_5 at 0–20°, and kept 5 hrs., 4.2 ml. concd. HNO_3 added at room temp., and the whole kept at room temp. 15 hrs., dild. with 100 ml. H_2O at 0°, and neutralized with 115 ml. 40% KOH soln. with cooling to pH 10 to deposit 7.8 g. 1-(2-acetoxyethyl)-2-methyl-4-nitroimidazole, m. 142–4° (H_2O). The mother liquor was extd. with CH_2Cl_2 and worked up to yield 1-(2-acetoxyethyl)-2-methyl-5-nitroimidazole, m. 70–3° (iso-Pr_2O). The acetyl group was removed by heating in *N* HCl at 90° several hrs. to give 1-(2-hydroxyethyl)-2-methyl-4-nitroimidazole (IV), m. 128–30°, 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole (V), m. 158–60°. A mixt. of 200 g. I, 268 g. $(CH_2O)_2CO$, 20 g. K_2CO_3, and 500 ml. $HCONMe_2$ was stirred at 140–5° 3 hrs., filtered at 60°, and concd. in vacuo, the residue added in portions with stirring to 1060 ml. concd. HNO_3 at 0–10°, the mixt. stirred at room temp. 1 hr., 356 g. P_2O_5 added at 0–10°, the whole stirred at room temp. 18 hrs., added to 1600 g. ice, extd. with CH_2Cl_2, and made alk. with 2550 ml. 50% NaOH (pH 10), the alk. soln. was extd. with CH_2Cl_2, and the org. phase worked up to yield 214.6 g. 1-(2-hydroxyethyl)-2-methyl-4-nitroimidazole and 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole nitrate esters (VI and VII, resp.) in a ratio of 40:60. A soln. of a mixt. of 42:58 VI and VII in 98 ml. 5*N* H_2SO_4 was kept at 100° 2 hrs., dild. with 100 ml. H_2O, and neutralized to pH 5 with 70 ml. 40% NaOH soln. to deposit 19.3 g. V. The mother liquor was extd. with EtOAc at pH 9 and worked up to yield IV. T. Mohacsi

C1.10. 19156b **1-(β-Hydroxyethyl)-2-methyl-5-nitroimidazole.** Kraft, M. Ya.; Kochergin, P. M.; Tsyganova, A. M.; Shlikhunova, V. S.; Ordzhonikidze, S. (All-Union Scientific-Research Chemical-Pharmaceutical Institute) U.S.S.R. 201,416 (Cl. C 07*d*), 08 Sep 1967, Appl. 14 Jan 1966. From *Izobret., Prom. Obraztsy, Tovarnye Znaki* 1967, 44(18), 38. The title compd. is prepd. by treating 2-methyl-4(5)-nitroimidazole with Et_2O in the presence of org. acids. The process is conducted in a mixt. of H_3PO_4 and AcOH. MGCL

C1.11. 21910v **1-(2-Hydroxyethyl)-2-methyl-5-nitroimidazole.** C.R.C. Compagnia di Ricerca Chimica S.A. Neth. Appl. 6,608,513 (Cl. C 07*d*), Dec. 22, 1966; Swiss Appl. June 21, 1965; 6 pp. A suspension of 20 g. MeCH:NCH:$CHNO_2$ in 500 ml. dry dioxane is heated with stirring at 50° until complete soln. and, after cooling to 10°, 20 g. HON:$CHCH_2OAc$ is added. The mixt. is heated 20 hrs. at 90°, dioxane is removed in vacuo, the residue is acidified with $(CO_2H)_2$, and kept 10 hrs. at −10° to give 4 g. $AcOCH_2CH$:$NCH(NO_2)CH(OH)N$:CHMe (I), m. 128–32° (AcOEt). To a soln. of 4 g. I in 300 ml. dioxane at −10° is added slowly 10 g. P_2O_5, keeping the temp. <5°. After 10 hrs. at 5° the mixt. is neutralized with 10% NaOH, kept 10 hrs. at 90°, and concd. in vacuo. The residue is suspended in 400 ml. H_2O, the pH adjusted to 9–10, and the product extd. with



(II)

EtOAc to give 1.9 g. 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole (II), m. 157–9° (EtOAc). II has antimicrobial activity. G. Boshuizen

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C2

SULFAMETHOXAZOLE

PATENTS

1967-1985

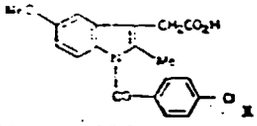
APPENDIX P20

ANALYSIS OF THE ABSTRACTS OF PATENTS

There are only two new synthesis patents. C2.1. mainly deals with the approach to the isoxazolamine, whereas C2.2. describes an interesting alternative to protect the amine group of p-aminosulfonyl-chloride.

ABSTRACTS OF PATENTS

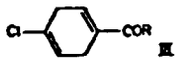
A6.86. 57305m Antiinflammatory indomethacin preparations for external use. Umemura, Koshiro, Shomura, Tomoko (Meiji Confectionary Co., Ltd.) Ger. 1,617,653 (Cl. A 61k), 18 Jun 1970, Appl. 08 Sep 1970; 5 pp. Indomethacin (I) is dissolved



in a dicarboxylic acid ester which penetrates the skin easily and from which I is readily absorbed by the organism. I is dissolved in malonic, succinic, glutaric, adipic, pimelic, suberic, azelaic, or sebacic diesters and used as a soln. of transformed into a suspension or cream with the usual pharmaceutical agents. The equiv. of the normal oral dose of 25–50 mg/day is absorbed by the organism when 1–2 g of the prepn. contg. 5–10% I is used externally. A. Mangels

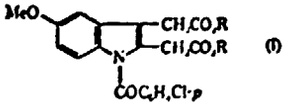
A6.87. 85: 177045z N-(p-Chlorobenzoyl)-N-(p-methoxyphenyl)-hydrazine hydrochloride. Fisnerova, Ludmila; Nemecek, Oldrich Czech. 162,229 (Cl. C09C109/10), 15 Feb 1976, Appl. 72/6,622, 29 Sep 1972; 2 pp. p-$MeOC_6H_4NHNH_2$ was reacted with p-ClC_6H_4COCl in chilled CH_2Cl_2 in the presence of Et_3N to give 69% N-(p-chlorobenzoyl)-N-(p-methoxyphenyl)hydrazine, an intermediate for the prepn. of indomethacin. L. J. Urbanek

A6.88. 34333r 1-(4-Chloro-1,4-cyclohexadien-1-ylcarbonyl)-2-methyl-5-methoxy-3-indoleacetic acid. Levine, Seymour David; Diassi, Patrick A.; Vogt, Berthold R.; Weisenborn, Frank L. (Squibb, E. R., and Sons, Inc.) Ger. Offen. 2,151,798 (Cl. C 07dc, A 61k), 27 Apr 1972, US Appl. 82,512, 20 Oct 1970; 60 pp.



The title compd. (I), useful as antiinflammatory, antipyretic, and analgesic agent and as intermediate in the prepn. of 1-(p-chlorobenzoyl)-5-methoxy-2-methyl-3-indoleacetic acid (II), was prepd. Thus, reaction of 2.4 g III (R = Cl) with 2 g $MeCH{:}NNHC_6H_4OMe$-p in dioxane contg. pyridine 5 hr at 6° gave 1.25 g III [R = $N(C_6H_4OMe$-$p)N{:}CHMe$] (IV). Treatment of 1.25 g IV with HCl(g) in MeOH/EtOAc 20 min on an ice bath gave 1.01 g III [R = $N(C_6H_4OMe$-$p)NH_2.HCl$] (V). Heating 1.75 g V and 0.76 g levulinic acid in HOAc 3 hr at 80° gave 1.8 g I. Redn. of I with H over Pd-C or with S gave II.

A6.89. 101708h 1-(p-Chlorobenzoyl)-2,3-bis(carboxymethyl)-5-methoxyindole and esters. Chemerda, John M.; Sletzinger, Meyer (Merck and Co., Inc.) U.S. 3,454,594 (Cl. 260-326.13; C 07d), 08 Jul 1969, Appl. 26 Jul 1967; 3 pp. The di-Me ester (I, R = R¹ = Me) (Ia) [useful intermediate in the prepn. of 1-(p-chlorobenzoyl)-2-methylindole-3-acetic acid, of the title compd. (I, R = R¹ = H) (Ib)] was prepd. Thus, to 0.01 mole 1-(p-chlorobenzoyl)-5-methoxyindole in 100 ml. tetrahydrofuran (THF) was added 0.021 mole Me diazoacetate in 25 ml. THF over 15 min., and the mixt. irradiated at 20–5° to give Ia. Simi-



(I)

larly prepd. was I (R = H, R¹ = Me) (II). A mixt. of 0.01 mole II, 8.5 g. anhyd. LiI, and 200 ml. 2,6-lutidine was refluxed 8 hrs. under N to give Ib, also prepd. from Ia by this procedure. II was prepd. in a 3-stage reaction from di-Me 3-oxo-4-br noadipate. F. J. Sprules

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A7

MEBENDAZOLE

PATENTS

1967-1985

APPENDIX P7

ANALYSIS OF THE ABSTRACTS OF PATENTS

Patents of the compound mebendazole are still valid !

Apart from the standard process (A7.6.) other interesting syntretic alternatives are described in patents A7.1. to A7.5. among which A7.3. amd A7.4. seem particularly interesting because of the use of calcium cyanamide.

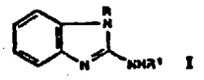
ABSTRACTS OF PATENTS

A7

MEBENDAZOLE

Preparation

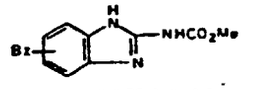
A7.1. 99: 38464m N-Acylaminoazoles. Martin, Dieter; Graubaum, Heinz; Schumann, Hiltraud (Akademie der Wissenschaften der DDR) Ger. (East) DD 156,388 (Cl. C07D235/32), 12 Jan 1983, Appl. 220,703, 25 Apr 1980; 11 pp. 2-Aminoazoles were transacylated



I

by heating in an inert solvent with an *N*-acylazole to give *N*-acyl-2-amino(or imino)azoles, which underwent rearrangement to give 2-(acylamino)azoles. Thus, benzimidazole I (R = R¹ = H) (II) was heated 15 min in THF with 1-(ethoxycarbonyl)imidazole to give 87% I (R = CO_2Et, R¹ = H). II was heated in PhMe with 1-(isopropoxycarbonyl)imidazole to give 70% I (R = H, R¹ = CO_2CHMe_2).

A7.2. 25669k Methyl 5(6)-benzoylbenzimidazol-2-ylcarbamate. Barker, Alan Charles; Foster, Richard Gregory (Imperial Chemical Industries Ltd.) Brit. 1,350,277 (Cl. C 07d), 18 Apr 1974, Appl. 44,203/71, 22 Sep 1971; 5 pp. The title compd.

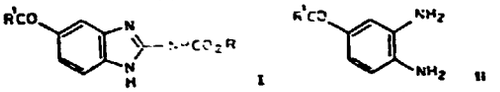


I

(I) was prepd. by decompn. of 1*H*-2,1,4-benzothiadiazine derivs. with acid or Ph_3P. E.g., decompn. of Me 7-benzoyl-1*H*-2,1,4-benzothiazin-3-ylcarbamate (II) in MeOH with 2*N* HCl gave 52% I. II was prepd. in 2 stages from 4-benzoyl-2-nitroaniline.

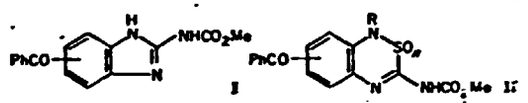
A7.3. 3936t Preparation of alkyl 5(6)-acylbenzimidazolyl carbamates. Harsanyi, Kalman; Roth, Geza; Simay, Antal; Gonczi, Csaba; Takacs, Kalman; Ajzert, Ilona K. (Chinoin Gyogyszer es Vegyeszeti Termekek Gyara Rt.) Brit. 1,348,460 (Cl. C 07d), 20 Mar 1974, Hung. Appl. 14,618, 06 Oct 1971; 5 pp. The title compds. were prepd. by reaction of (alkoxycarbonyl)-cyanamides with acyl-*o*-phenylenediamines. Thus, $NCNHCO_2$-Me reacted with 4-benzoyl-*o*-phenylenediamine at 90-5° for 45 min with pH kept at 3.5-4.0 by addn. of HCl to give 81.5% Me 5(6)-benzoyl-2-benzimidazolylcarbamate. $NCNHCO_2Me$ had been prepd. by reaction of Ca cyanamide (in tech. Ca_3N_2) with $ClCO_2Me$.

A7.4. 78801n 5(6)-Acylbenzimidazolyl alkyl carbamates. Harsanyi, Kalman; Toth, Geza; Simay, Antal; Gonczi, Csaba; Takacs, Kalman; Ajtert, Irma K. (Chinoin Gyogyszer es Vegyeszeti Termekek Gyara Rt.) Hung. Teljes 5809 (Cl. C 07d), 28 Feb 1973, Appl. Ci-1172, 05 Oct 1971; 14 pp. I



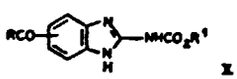
(R = Me, Et; R^1 = Me, Ph, *p*-tolyl, *p*-ClC_6H_4) were prepd. by treating II with $NCNHCO_2R$ in aq. medium at 30–10° and pH 3.0–4.5. Thus, CuNCN was treated with $ClCO_2Me$ in aq. EtOH at 30–40°, and the mixt. heated 45 min at 90–5° with II (R^1 = Ph) at pH 3.5–4 (HCl) to give 83% I (R = Me, R^1 = Ph). T. Mohacsi

A7.5. 5341c Methyl [5(6)-benzoyl-2-benzimidazolyl]carbamate. Barker, Alan Charles; Foster, Richard G. (Imperial Chemical Industries Ltd.) Ger. Offen. 2,246,605 (Cl. C 07d), 29 Mar 1973, Brit. Appl. 44,203/71, 22 Sep 1971; 16 pp. The title compd. (I),



useful as anthelmintic, was prepd. from the benzothiadiazines II (PhCO connected in position 6 or 7; *n* = 0 or 1; R = H, Ac, or Bz). Thus, II (PhCO connected in position 7, *n* = 0, R = H), prepd. from 4,2-$PhCO(O_2N)C_6H_3NH_2$ and $SCNCO_2Me$ via 4,2-$PhCO(O_2N)C_6H_3NHCSNHCO_2Me$, was refluxed in 2*N* HCl and MeOH for 17 hr to give 52% I.

A7.6. 100047s Anthelmintic alkyl N-[5(6)-acyl-2-benzimidazolyl] carbamates. Van Gelder, Josephus L. H.; Raeymaekers, Alfons H. M.; Roevens, Leopold F. C. (Janssen Pharmaceutica N.V.) Ger. Offen. 2,029,637 (Cl. C 07d), 18 Feb 1971, US Appl. 20 Jun 1969; 28 pp. The title compds. (I), active against e.g.



Syphacia muris, *Trichostrongylus*, were prepd. according to U.S. 3,010,968 from 3,4-$(H_2N)_2C_6H_3COR$ (II) and $H_2N(MeS)C{:}NCO_2R^1$. II were prepd. from PhF and RCOCl in the presence of $AlCl_3$ via *p*-FC_6H_4COR, nitration and ammonolysis to give 4,3-$H_2N(O_2N)C_6H_3COR$, which were hydrogenated over Pd/C. Among 14 compds. prepd. were I (R and R^1 given): Ph, Me (III); Et, Me; cyclopropyl, Me; *p*-$MeOC_6H_4$, Me; 2-thienyl, Me; Ph, Et. III had LD_{50} >80 mg/kg in sheep and >40 mg/kg in mice, rats, chicks, and chickens on oral administration. KRPG

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A8

NALIDIXIC ACID

PATENTS

1967-1985

ANALYSIS OF THE ABSTRACTS OF PATENTS

Among the patents cited A8.25. seems to be an interesting alternative to the standard process. In this process ethylamino-methyl-pyridine is used so that the ethylation step of the standard process can be omitted. Also patents A8.8., A8.10. and A8.17. are similar to the standard process. (in A8.8. there is an obvious misprint in the first reaction step.)

The process given in A8.18 seems to be of particular interest because it makes use of relatively cheap starting materials (acetoacetic ester and orthoformic acid).

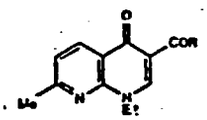
In A8.21. different alkylation procedures for 1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridin-3-carboxylicester and subsequent hydrolysis to nalidixid acid are described.

ABSTRACTS OF PATENTS

NALIDIXIC ACID

Preparation

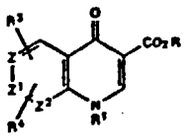
A8.1. 101: 130678w 1-Ethyl-4-oxo-1,4-dihydro-7-methyl-1,8-naphthyridine derivatives. Garemszegi, Ferenc; Leboczky, Gabor; Somfai, Eva; Ban, Karoly; Hernadi, Gyula, Mrs. (Chinoin Gyogyszer es Vegyeszeti Termekek Gyara Rt.) Hung. Teljes HU 30,014 (C.. C07D471/04), 28 Feb 1984, Appl. 80/2,818, 26 Nov 1980; 14 pp. The title compds. I (R = C_{1-2} alkyl or allyl) were



I

prepd. Thus, 75 kg I (R = H) was ethylated with 90 kg Et_2PO_4 in the presence of 23 kg K_2CO_3 in 30 kg ligroine for 1 h at 140–160°; the azeotrope was distd. simultaneously and the mixt. was heated at 210° to give 76 kg I (R = Et). The latter was sapond. to give nalidixic acid.

A8.2. 92: 76479h 1-Substituted-1,4-dihydro-4-oxo-3-pyridinecarboxylic acid derivatives. Agui, Hideo; Saji, Ikutaro; Nakashita, Mitsuo (Sumitomo Chemical Co., Ltd.) Jpn. Kokai Tokkyo Koho 79,112,877 (Cl. C07D215/48), 04 Sep 1979. Appl. 78/18,794, 20 Feb 1978; 5 pp. Fifty-one title derivs. I [R^2 = alkyl, OH- or halo-substituted alkyl, alkenyl; R^3, R^4 = H, halo, NO_2, alkyl, alkenyl, aryl, R^5R^6N (R^5, R^6 = H, alkyl; R^5R^6N may form a ring); Z, Z^1, Z^2 = CH, N] were prepd. by e.g.,

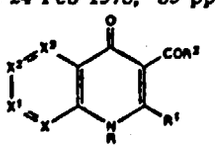


I, R=R^2, R^7=H
II, R=H, R^7=R^7

alkylation of II (R^7 = H, alkyl) in the presence of quaternary ammonium salts or KF followed by hydrolysis. Thus, 11.65 g II (R^3R^4 = 6,7-OCH_2O, R^7 = H, Z = Z^1 = Z^2 = CH) was stirred in H_2O 30 min at 20–5°, 0.59 g Bu_4N^+ Br^- added, 27 g Et_2SO_4 added, 55 g 20% aq. KOH added over 30 min, the mixt. heated 1 h at 40–5°, 68 g 20% H_2SO_4 added, and the mixt. heated 2 h at 90–5° to give 12.8 g I (R^2 = Et, R^3R^4 = 6,7-OCH_2O, Z = Z^1 = Z^2 = CH).

K. Sempuku

A8.3. 92: 41916w 4-Pyridinone-3-carboxylic acids and/or their derivatives. Grobe, Klaus; Zeiler, Hans Joachim; Metzger, Karl (Bayer A.-G.) Ger. Offen. 2,808,070 (Cl. C07D471/04), 30 Aug 1979, Appl. 24 Feb 1978; 39 pp. The title compds. I

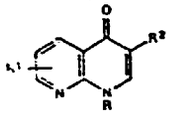


I

(1–3 of X–X^3 = N, the rest optionally substituted CH; R = *tert*-alkyl, cycloalkyl, optionally substituted NH_2, heterocyclyl; R^1 = H, alkyl, aryl, aralkyl; R^2 = OH, ester or amide group) were prepd. for use as bactericides and feed additives (no data). Thus, 2-chloro-6-methylnicotinoyl chloride reacted with MeN=HCMe:$CHCO_2H$ in dioxane in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene to give 54% I (X = N, X^1 = CMe, X^2 = X^3 = CH, R = R^1 = Me, R^2 = OMe).

A8.4.

85: [illegible] 1-Alkyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acids. Otaka, Hiroshi; Mikata, Susumu; Nagai, Kunio (Kanebo, Ltd.) Japan. Kokai 76 32,594 (Cl. C07D [illegible]), 19 Mar 1976, Appl. 74/105,204, 11 Sep 1974; 3 pp. Naphthyridines I (R = alkyl; R¹ = H, alkyl, alkoxy,



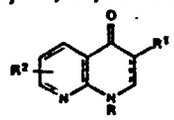
I, R¹=H
II, R¹=CO₂H

nitrofurylvinyl, OCH_2O) were treated with $COCl_2$ or its derivs. and hydrolyzed to give title carboxylic acids II. Thus, 1.2 g I [R = Et, R¹ = CH(MeO)₂] in THF was stirred with 1.2 ml $ClCO_2Et$ at room temp. 0.5 hr and hydrolyzed with N NaOH to give 0.4 g corresponding II. Among 7 more II prepd. were (R, R¹ given): Et, 7-[illegible]; Me, 7-Me; Et, 7-Et; Et, 7-nitrofurylvinyl.

I. Matsumoto

A8.5.

85: 94340r 1-Alkyl-1,4-dihydro-4-oxo-1,8-naphthyridines. Tayama, Tatsuya; Nagai, Kunio; Iizuka, Yasuhiro (Kanebo, Ltd.) Japan. Kokai 76 32,593 (Cl. C07D471/04), 19 Mar 1976, Appl. 74/104,526, 10 Sep 1974; 3 pp. Tetrahydrona-

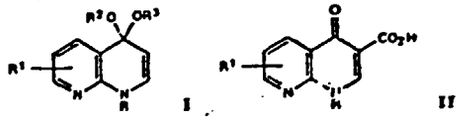


I, 2,3-satd.
II, 2,3-unsatd.

phthyridines I (R = alkyl; R¹ = alkyl, hydroxyalkyl, carboxy, substituted carboxy; R² = H, alkyl, alkoxy, alkylthio, alkylsulfinyl, amino, nitro, alkylamino, hydrazino, carboxyacylamino, nitrofurylvinyl, pyrrolidino, piperazino) were dehydrogenated to give 1,4-dihydro-4-oxonaphthyridines II. Thus, 2 g I (R = Et, R¹ = CO_2H, R² = 7-Me) was refluxed with 6 g 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in C_6H_6 1.5 hr to give 1.71 g corresponding II. Also prepd. were II (R¹ = CO_2H, R² = 7-Me, R = Me, Bu). Chloranil was also the dehydrogenating agent. I. Matsumoto

A8.6.

85: 94339x 1-Alkyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acids. Aikawa, Norio; Teyama, Tatsuya; Otaka, Hiroshi (Kanebo, Ltd.) Japan. Kokai 76 32,592 (Cl. C07D471/04), 19 Mar 1976, Appl. 74/104,525, 10 Sep 1974; 3 pp. Naphthyridine ketals I (R = alkyl; R¹ = H, alkyl, alkoxy,



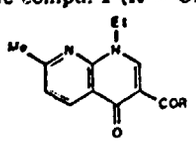
I II

alkylthio, alkylsulfinyl, amino, nitro, alkylamino, hydrazino, carboxyacylamino, pyrrolidino, piperazino; R², R³ = alkyl, R²R³ = alkylene) were carboxylated with $COCl_2$ or its derivs. and the ketals hydrolyzed to give title carboxylic acids II. Thus, 1 g I (R = Et, R¹ = 7-Me, R²R³ = CH_2CH_2) in $CHCl_3$ was treated with 1 g $COCl_2$ at 0°, kept at room temp. 3 hr, and hydrolyzed with p-toluenesulfonic acid in Me_2CO to give 0.4 g II (R = Et, R¹ = 7-Me). Also prepd. was II (R = Me, R¹ = 7-Me). The carboxylation was also effected with $ClCO_2Et$ in DMF.

I. Matsumoto

A8.7.

85: 5609v 1-Ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid. Chinoin Gyogyszer- es Vegyeszeti Termekek Gyara Rt. Neth. Appl. 74 16,927 (Cl. C07D, A61K), 01 Jul 1975, Hung. Appl. CL-1430, 29 Dec 1973; 7 pp. The title compd. I (R = OH) was prepd. in 97.2%



I

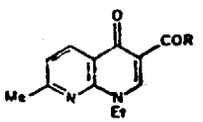
yield by the alk. hydrolysis of I (R = $CH_2N^+Z.I^-$, where N^+Z = pyridinium, α-picolinium, quinolinium, or isoquinolinium).

A8

84: 121798i 3-Acetyl-1,4-dihydro-4-oxo-1,8-naphthyridines. Lesher, George Y.; Brundage, Ruth P. (Sterling Drug, Inc.) U.S. 3,925,398 (Cl. 260-295N; C07D), 09 Dec 1975, Appl. 333,541, 20 Feb 1973; 9 pp. Division of U.S. 3,875,172. 2-Amino-6-methylpyridine was treated with EtOCH:C(CO$_2$Et)COMe and the α-(6-methyl-2-pyridylaminomethylene)acetoacetate cyclized to give 3-acetyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine which was ethylated followed by treatment with NaOH and Br to give 1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid. The naphthyridines were bactericidal (no data).

A8.9.

84: 59431d 1,8-Naphthyridine derivatives. Chinoin Gyogyszer-es Vegyeszeti Termekek Gyara Rt. Neth. Appl. 74 15,825 (Cl. C07D, A61K), 01 Jul 1975. Hung. Appl. CL-1436, 29 Dec 1973; pp. The bactericidal (no data) acid I (R = CO$_2$H) was

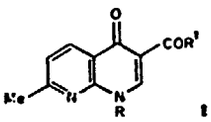


I

prepd. by treating I (R = CHMe$_2$, CH$_2$R^1, R^1 = Me, Et, Pr, Ph, CH$_2$Ph, cyclohexyl, cyclohexylmethyl) with pyridine, picoline, isoquinoline, quinoline, or NMe$_3$ and iodine to give the quaternary iodides I (R = quaternary ammoniomethyl) and hydrolyzing with base.

A8.10.

179028d 3-Acetyl-1-alkyl-1,4-dihydro-4-oxo-1,8-naphthyridines and intermediates. Lesher, George Y.; Brundage, Ruth P. (Sterling Drug, Inc.) U.S. 3,895,017 (Cl. 260-295R; C07D), 15 Jul 1975, Appl. 333,541, 20 Feb 1973; 9 pp. Division of U.S. 3,875,172. 2-Amino-6-methylpyridine was treated with

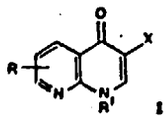


I

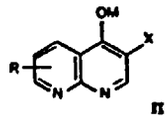
EtOCH:C(CO$_2$Et)COMe and the α-(6-methyl-2-pyridylaminomethylene)acetoacetate, cyclized to the naphthyridine I (R = H, R^1 = Me), which was ethylated and the I (R = Et, R^1 = Me) brominated in NaOH to give I (R = Et, R^1 = OH).

A8.11.

131562w 1-Alkyl-3-substituted-4-oxo-1,8-naphthyridine derivatives. Morita, Yoshiharu; Wagatsuma, Kazuo (Mitsubishi Chemical Industries Co., Ltd.) Japan. Kokai 75 24,292 (Cl. 16E612), 15 Mar 1975, Appl. 73 74,658, 02 Jul 1973; 6 pp.



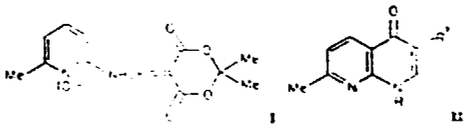
I



II

1-Alkyl-3-substituted-4-oxo-1,8-naphthyridines I (R = H, alkyl, alkoxy; R^1 = alkyl; X = alkoxycarbonyl, carboxylic acid alkali metal salts) were prepd. by reaction of 3-substituted-4-hydroxy-1,8-naphthyridine alkali metal salts II (M = alkali metals) with alkyl trifluoromethanesulfonates followed by hydrolysis of the resulting complexes. Thus, 2 g 3-ethoxycarbonyl-4-hydroxy-7-methyl-1,8-naphthyridine (III) was added to a mixt. of PhMe, EtOH, and 0.37 g K and the whole refluxed 2 hr to give 2.45 g III K salt. Reflux of a mixt of III K salt and 3.5 g Et trifluoromethanesulfonate in Et$_2$O 2 hr and hydrolysis with 5% aq. NaOH 2 hr with reflux gave 87.2% 1-ethyl-3-carboxy-4-oxo-7-methyl-1,8-naphthyridine (nalidixic acid) (IV). Also, 3-ethoxycarbonyl-1-ethyl-4-oxo-7-methyl-1,8-naphthyridine was prepd. IV was antibacterial. K. Sempuku

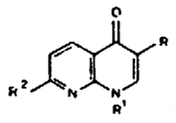
...-oxo-1,8-naphthyl... cyclic alkyl... ...ylaminomethylene)malonates. ... Robert K. (Ste... Drug, Inc.) U.S. 3,856,800 ... C07d), 24 De... Appl. 335,733, 26 Feb ... 9 pp.



I II

The isopropylidenyl methylenemalonate I (n = 0) was oxidized and the resulting I (n = 1) was cyclized by heat and hydrogenated to give the naphthyridine II (R = R^1 = H), which was hydroxymethylated and the resulting II (R = H, R^1 = $HOCH_2$) alkylated with EtI and oxidized with $KMnO_4$ to give II (R = Et, R^1 = CO_2H). Correction of *CA* 82: 140101b.

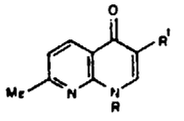
A8.13. **97252h 1-Alkyl-1,4-dihydro-7-substituted-4-oxo-1,8-naphthyridine-3-carboxylic acids via the 3-aminomethyl analogs.** Lesher, George Y.; Gruett, Monte D. (Sterling Drug, Inc.) U.S. 3,882,132 (Cl. 260-295.5B; C07d), 06 May 1975, Appl. 339,090, 08 Mar 1973; 11 pp. The naphthyridines I (R =



I

Et_2NCH_2, H, CO_2H; R^1 = H, Et; R^2 = H, Me) were prepd. Thus I (R = R^1 = H, R^2 = Me) was treated with Et_2NH and HCHO and the resulting I (R = Et_2NCH_2) ethylated to give I (R = Et_2NCH_2, R^1 = Et, R^2 = Me), which was oxidized with $KMnO_4$ to give I (R = CO_2H).

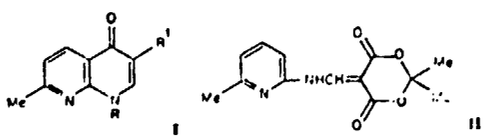
A8.14. **97250f 1-Alkyl-1,4-dihydro-7-substituted-4-oxo-1,8-naphthyridine-3-carboxylic acids via the 3-carboxaldehyde analogs.** Lesher, George Y.; Gruett, Monte D. (Sterling Drug, Inc.) U.S. 3,873,554 (Cl. 260-295.5B; C07d), 25 Mar 1975, Appl. 338,613, 06 Mar 1973; 10 pp. 1,8-Naphthyridine-3-carboxylic



I, R = CO_2H, R^1 = Et
II, R = R^1 = H
III, R = H, R^1 = CHO
IV, R = Et, R^1 = CHO

acid (I), useful as a bactericide (no data) was prepd. by formylating naphthyridine II, ethylating the formyl deriv. III, and oxidizing IV. Thus, 3.8 g III, obtained by formylation of II, was heated with 3.8 g EtI in DMF contg. K_2CO_3 for 90 min to give IV, which was oxidized ($KMnO_4$) to give I.

A8.15. **79218x 1-Alkyl-1,4-dihydro-7-substituted-4-oxo-1,8-naphthyridine-3-carboxylic acids via the 3-hydroxymethyl analogs.** Lesher, George Y.; Gruett, Monte D. (Sterling Drug, Inc.) U.S. 3,869,464 (Cl. 260-295.5B; C07d), 04 Mar 1975, Appl. 335,734, 26 Feb 1973; 10 pp. 1,8-Naphthyridine-3-carboxylic

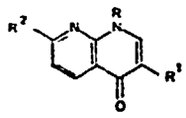


I II

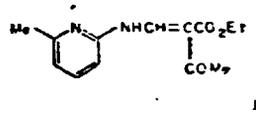
acid (I, R = Et, R^1 = CO_2H), useful as a bactericide (no data), was prepd. from cyclic isopropylidenyl malonate II via cyclization, hydroxymethylation, ethylation, and oxidn. Thus, I (R = R^1 = H) obtained by cyclization of II, was hydroxymethylated with HCHO to give I (R = H, R^1 = CH_2OH), which was ethylated (EtI) to I (R = Et, R^1 = CH_2OH). Oxidn. of the latter with $KMnO_4$ gave I (R = Et, R^1 = CO_2H).

A8.16. 557[illegible] 3-(Dialkylaminomethyl)-1,4-dihydro-4-oxo-1,8-naphthyridines. Lesher, George Y.; Gruett, Monte D. (Sterling Drug, Inc.) U.S. 3,876,650 (Cl. 260-295N; C07d), 08 Apr 1975, Appl. [illegible], 06 Mar 1973; 11 pp. Aminomethylation of 1,4-dihydro-4-oxo-1,8-naphthyridines followed by alkylation and oxidn. gave 1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acids, useful as bactericides (no data). Thus, 1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine was refluxed with Et2N in aq. CH2O to give the 3-(diethylaminomethyl) deriv. which was alkylated with EtI and then oxidized with KMnO4 in aq. pyridine to yield 1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid.

A8.17. 557[illegible] 1-Alkyl-1,4-dihydro-7-substituted-4-oxo-1,8-naphthyridine-3-carboxylic acids via the 3-acetyl analogs. Lesher, George Y.; Brundage, R. Pauline (Sterling Drug, Inc.) U.S. 3,875,172 (Cl. 260-295.5B; C07d), 01 Apr 1975, Appl. 333,541, 20 Feb 1973; 10 pp. Antibacterial (no data)



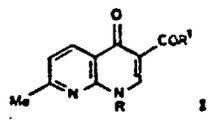
I



III

naphthyridinecarboxylate I (R = Et, R1 = CO2H, R2 = Me) (II) was prepd. from acetoacetate III. Thus, heating a mixt. of III and mineral oil for 30 sec at 300° gave I (R = H, R1 = Ac, R2 = Me) (IV). To a suspension of IV and DMF was added EtI to give I (R = Et, R1 = Ac, R2 = Me) (V). The addn. of V to a cooled soln. of NaOH-H2O-Br gave II. The condensation of 6-methyl-2-pyridinamine with EtOCH:CAcCO2Et gave III.

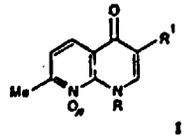
A8.18. 43292c 1,4-Dihydro-1,8-naphthyridin-4-ones. Meszaros, Zoltan; Hermecz, Istvan; Vasvari, Lelle; Horvath, Agnes; Rittli, Peter; Mandi, Atilla (Chinoin Gyogyszer es Vegyeszeti Termekek Gyara Rt.) Ger. Offen. 2,432,730 (Cl. C 07d), 06 Feb 1975, Hung. Appl. CI-1397, 17 Jul 1973; 16 pp.



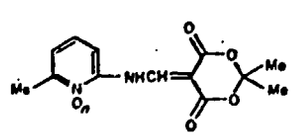
I

Four naphthyridinones I (R = H, Et; R1 = Me, CF3, OH), useful as bactericides (no data), were prepd. from 2-amino-6-methylpyridine (II). Thus, II, MeCOCH2CO2Et, and HC(OEt)3 were heated in the presence of AlCl3 to give 82% Et 2-[[(6-methyl-2-pyridyl)amino]methylene]acetoacetate, which was heated in paraffin oil to give 79.5% I (R = H, R1 = Me) (III). III was ethylated with EtI and K2CO3 in DMF to give 95.7% I (R = Et, R1 = Me), which on treatment with Br in aq. NaOH and dioxane at 5-10° gave 65% I (R = Et, R1 = OH).

A8.19. 170864v 1,4-Dihydro-4-oxo-1,8-naphthyridine-3-carboxaldehydes. Lesher, George Y.; Gruett, Monte D. (Sterling Drug, Inc.) U.S. 3,857,851 (Cl. 260-295N; C 07d), 31 Dec 1974, Appl. 338,613, 06 Mar 1973; 10 pp. The title carboxaldehyde I



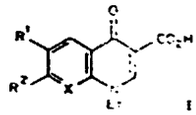
I



II

(R = H, R1 = CHO, n = 0) was prepd., ethylated to I (R = Et), and oxidized to I (R = Et, R1 = CO2H, n = 0). Thus, II (n = 0) was oxidized to II (n = 1) with m-ClC6H4CO3OH, the product cyclized to I (R = R1 = H, n = 1) (III) at 275° in di-Et phthalate and III hydrogenated to give I (R = R1 = H, n = 0) (IV). Formylation of IV (DMF, POCl3) gave I (R = H, R1 = CHO, n = 0). This was ethylated to I (R = Et, R1 = CHO, n = 0) with EtI and the product oxidized with KMnO4 to give I (R = Et, R1 = CO2H, n = 0).

A8.20. [illegible]-Oxo-1,4-dihydro-[illegible]carboxylic acids and their derivatives. Budesinsky, Zdenek; Roubinek, Frantisek (Czech. 154,546 (Cl. C 07d), 15 Aug 1974, Appl. 7365/72, 01 Nov 1973, 5 pp. The title compds. I, R^1R^2 = OCH_2O, X = CH; R^1

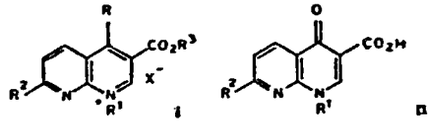


I

= H, R^2 = Me, X = N) were prepd. in 94.2% and 60% yields, resp., by reaction of the corresponding 3-acetyl-6,7-dihydroquinoline or 3-acetyl-1,8-naphthyridine with NaOCl or NaOBr in aq. NaOH-dioxane. Many are antibacterial (no data). L. J. Urbanek

A8.21. 49665k 1-Ethyl-1,4-dihydro-4-oxo-7-methyl-1,8-naphthyridine-3-carboxylic acid (nalidixic acid). Veza, Lucia M.; Badea, Veronica; Radulescu, Nora; Ambrus, Ivan P. (Institutul de Cercetari Chimico-Farmaceutice) Rom. 56,228 (Cl. C 07d), 08 Nov 1973, Appl. 63,979, 20 Jul 1970; 2 pp. Nalidixic acid was prepd. by ethylation of Et 1,4 dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylate with Et_2SO_4, $MeC_6H_4SO_2Et$, $PhSO_2Et$ (1:1.5–3 molar). The product was hydrolyzed without sepn. of the intermediate. The ethylation was conducted either without a solvent or in the presence of hydrocarbons inert to the alkylating agents, preferably xylene. Reaction time was 0.5–5 hrs. Lola Brodfeld

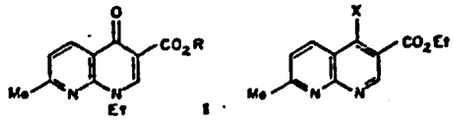
A8.22. 133409p 1-Ethyl-1,4-dihydro-7-methyl-1,8-naphthyridine-3-carboxylic acid. Domori, Renzo; Yoshimura, Ryuichi (Daiichi Seiyaku Co., Ltd.) Japan. Kokai 73 80,597 (Cl. 16 E812), 29 Oct 1973, Appl. 72 12,411, 03 Feb 1972; 3 pp. 1-Substituted



I II

1,8-naphthyridinium salts I, (R^1 and R^2 = lower alkyl; R^3 = H or lower alkyl; X = halogen; R = NH_2 or substituted amino) were hydrolyzed to give the naphthyridines II. II are bactericides. Thus, 2.31 g Et 4-R^4-7-methyl-1,8-naphthyridine-3-carboxylate (III) (R^4 = NH_2) and EtI was refluxed in EtOH for 12 hr to give 2 g I (R = NH_2, R^2 = Me, R^1 = Et, X = I), which (3.87 g) was heated 1 hr at 100° in 5% NaOH to give 81.2% II (R^1 = Et, R^2 = Me) (IV). III (R^4 = piperidino) and Me_2SO_4 was similarly treated to give IV. Hiroshi Kataoka

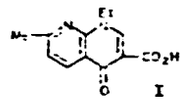
A8.23. 3486a 1-Ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid and ester. Nakagome, Takenari; Agui, Hideo; Mitani, Toru; Nakashita, Mitsuo (Sumitomo Chemical Co., Ltd.) Ger. Offen. 2,166,375 (Cl. C 07d), 18 Oct 1973, Japan. Appl. 70 7895, 28 Jan 1970; 25 pp. Division of Ger. Offen. 2,103,805 (*CA* 75: 98458b). The 1-substituted



I II, X = OEt
III, X = Cl

oxonaphthyridine (I, R = Et or H), useful as antibacterial or central nervous system-stimulating drug, was prepd. from the ethoxy deriv. II with Et group migration either by heating without solvent at 155–60° in an oil bath, or in the presence of EtI on a water bath, or in the presence of EtBr in a closed tube at 130°, optionally followed by sapon. II was prepd. by treating III with EtONa.

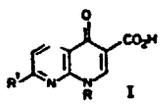
A8.[illegible]. 3830a 1-Ethyl-7-methyl-1,4-dihydro-1,8-naphthyridin-4-one-3-carboxylic acid. Kovacs, Gabor; Meszaros, Zoltan; Bodnar, Janos; Kadas, Istvan (Chinoin Gyogyszer es Vegyeszeti Termekek Gyara Rt.) Ger. Offen. 2,110,066 (Cl. C 07d), 23 Sep 1971, Hung. Appl. 11 Mar 1970; 10 pp. Title compd. (I),



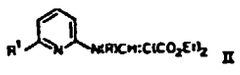
I

useful as a bactericide for gram-neg. bacteria, was prepd. from Et 4-chloro-7-methyl-1,8-naphthyridine-3-carboxylate (II). Thus, II was refluxed 1 hr with $(EtO)_3PO$ and 7–8 hr with addnl. aq. NaOH to give 80% I.

A8.25. 3829g 1-Alkyl-1,8-naphthyridine-3-carboxylic acid derivatives. Wada, Yasuo; Watanabe, Nanao (Koei Chemical Co., Ltd.) Ger. Offen. 2,168,046 (Cl. C 07d), 07 Oct 1971, Japan. Appl. 20 Feb 1970; 14 pp. Title compds. (I), useful against



I



II

gram-neg. bacteria, were prepd. by cyclization of aminomethyl enemalonates (II) prepd. by condensing corresponding 5-alkyl-2-(alkylamino)pyridines with $EtOCH:C(CO_2Et)_2$ (III) in polyphosphoric acid (IV). Thus, a mixt. contg. 102 g II (R = R^1 = Me) prepd. by heating 85 g 6-methyl-2-(methylamino)pyridine (V) and 151 g III at 100–10° and 88 g IV was heated 10 min at 200–30°. After cooling the mixt. was made alk. with 20% NaOH, extd. with Et_2O, and HOAc was added to give 42 g I (R = R^1 = Me). V was recovered from the ether phase. Similarly prepd. were 8 other I, e.g. (R and R^1 given): Et, Me; Pr, Me; Bu, Me; pentyl, Me; Et, Et.

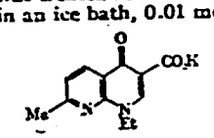
A8.26. 87933f 1-Ethyl-7-methyl-1,4-dihydro-1,8-naphthyridin-4-one-3-carboxylic acid. Kovacs, Gabor; Meszaros, Zoltan; Bodnar, Janos; Kadas, Istvan (Chinoin Gyogyszer es Vegyeszeti Termekek Gyara Rt.) Hung. Teljes 1161 (Cl. C 07d), 24 Oct 1970, Appl. 11 Mar 1970; 8 pp. The title compd. (I) was prepd. by alkylation of Et 4-chloro-7-methyl-1,8-naphthyridine-3-carboxylate (II) with Et_3PO_4 and subsequent alk. hydrolysis. Thus, a soln. of 2.5 g II in 10 ml Et_3PO_4 was refluxed 1 hr, 25 ml 10% NaOH soln. added at 100°, the mixt. refluxed until homogeneous (6–7 hr), and acidified with HCl to pH 2 to ppt 80% I, m. 225–8° (DMF–MeOH). T. Mohacsi

A8.27. 64379w 1-Ethyl-7-methyl-1,8-naphthyridin-4-one-3-carboxylic acid. Chinoin Gyogyszer es Vegyeszeti Termekek Gyara Rt. (by Zoltan Meszaros, Gabor Kovacs, Peter Szentmiklosi, and Iren Czibula). Hung. 153,292 (Cl. C 07d), Nov. 22, 1966, Appl. June 23, 1965; 3 pp. Et 4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylate (m. 272–3°, 116 g.) was heated with stirring in 273 g. Et_3PO_4 to 210° in about 1 hr., the mixt. was kept at 210–15° for 30–40 min., allowed to cool with stirring to 50–60° and 300 g. NaOH in 2000 ml. H_2O added. The soln. was heated with stirring and refluxed for 2 hrs., acidified with dil. HCl to pH 3–4 at room temp., the ppt. collected, washed, suspended in 1000 ml. H_2O, and treated with 20% NaOH (pH 9), decolorized, and acidified again, to yield 100 g. title product, m. 225–6° (AcOH or $HCONMe_2$). T. Mohacsi

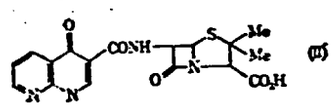
NALIDIXIC ACID

Use

A8.28. 111464k 6-(Nalidixamido)penicillanic acid. Uglesic, Ana; Seiwerth, Rativoj (Pliva Pharmazeutische und Chemische Fabrik) Ger. Offen. 1,940,511 (Cl. C 07*d*), 26 Mar 1970, Yugoslavia Appl. 08 Aug 1968; 6 pp. Nalidixic acid (I) (0.01 mole) dispersed in a 1:3 Me_2CO-dioxane mixt. and 2.0 ml Et_3N was treated 15 min with 0.01 mole iso-BuO_2CCl in 10 ml dioxane in an ice bath, 0.01 mole 6-aminopenicillanic acid and 2 ml Et_3N



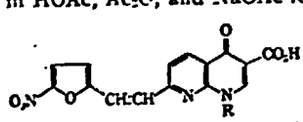
(I)



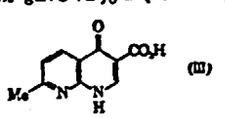
(II)

in 20 ml H_2O added, and the mixt. stirred 1 hr and acidified with 1*M* HCl to pH 3.5 to give 59% antimicrobial title compd. (II). KHPG

A8.29. 66551u Bactericidal 1-ethyl-7-[β-(5-nitro-2-furyl)vinyl]-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid. Kovacs, Gabor; Meszaros, Zoltan; Szentmiklosi, Peter; Bodnar, Janos; Simonidesz, Vilmos (Chinoin Gyogyszer es Vegyeszeti Termekek Gyara Rt.) Ger. Offen. 1,933,463 (Cl. C 07*d*, A 61*k*), 30 Jul 1970, Hung. Appl. 15 Jul 1968; 17 pp. The bactericidal title compd. (I, R = Et) was prepd. by reaction of 5-nitrofurfural (II) and III and subsequent ethylation. Thus, refluxing II and III in HOAc, Ac_2O, and NaOAc for 4 hr gave 72% I (R = H),



(I)



(III)

which was treated with $(EtO)_2PO$ to give 87.5% I (R = Et) (IV). IV was active against bacteria. KSPG

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A9

NICOTINAMIDE

PATENTS

1967-1985

APPENDIX P9

ANALYSIS OF THE ABSTRACTS OF PATENTS

15 Synthetic patents were analysed, 11 of which proceed from the nitrile (A9.1., A9.4. - A9.13.).

Hydration is frequently carried out in presence of metal oxide catalysts In A9.9. a copper catalyst leads to 99.9% yield.

In patent A9.13. the reaction is carried out in absence of a catalyst only using water at 150-200°C and 5-20 bar pressure.

The use of an ion exchanger is claimed in two patents: A9.4. describes hydration with DOWEX 1X4 in OH form, A9.6. describes the use of strongly basic ion exchanger, e.g. WOFATIT SBW in OH form.

In A9.3. nicotinamide is synthesized from 3-pyridylmethanol and ammonia, in A9.2. from pyridine-3-aldehyde, ammonia and oxygen.

The process nicotinic acid and ammonia is not described.

In A9.19. a catalyst is given, which allows transformation of a nitril to the amide with 100% selectivity in the case of acrylamide.

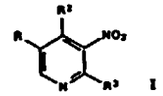
ABSTRACTS OF PATENTS

A9

NICOTINAMIDE

Preparation

A9.1. 100: 120889b Nicotinic acid derivatives. Simonovitch, Chaim (ABIC Ltd.) Israeli IL 56,965 (Cl. C07D213/64), 31 Dec 1982, Appl. 28 Mar 1979; 13 pp. The title compds. I (R = cyano, $CONH_2$,



I

CO_2R^1; R^1 = alkyl; R^2 = halo; R^3 = Cl; R ≠ CO_2R^2, R^2,R^3 = OH, R^2 = NH_2] were prepd. Thus, chlorination of II by $POCl_3$ at 5° followed by overnight refluxing gave the dichloro deriv. I (R = CO_2Me, R^2 = R^3 = Cl) which was converted into the nitrile followed by hydrolysis to give the amide.

A9.2. 94: 65475u Carboxylic acid amides. Asahi Chemical Industry Co., L'd. Jpn. Kokai Tokkyo Koho 80 69,518 (Cl. C07B29/00). 26 May 1980, Appl. 78/141,216, 17 Nov 1978; 3 pp. Carboxylic acid amides were prepd. by reaction of aldehydes with NH_3 or Me_2NH in the presence of O-contg. gases and Pd or Pt catalysts. Thus, a mixt. of pyridine-3-carboxaldehyde 2, 28% aq. NH_3 50, and 5% Pd/C 2 g was kept 2 h at 40° with introduction of 10 L/h O to give 57% nicotinic acid amide. $PhCONH_2$, nicotinic acid dimethylamide, and DMF were similarly prepd. K. Sempuku

A9.3. 93: 113984n Carboxylic acid amides. Tamura, Watahiko; Fukuoka, Yohei; Nishikido, Joji; Yamamatsu, Setsuo; Suzuki, Yoshio (Asahi Chemical Industry Co., Ltd.) Jpn. Kokai Tokkyo Koho 80 22,611 (Cl. C07C102/00), 18 Feb 1980, Appl. 78/94,135, 03 Aug 1978; 3 pp. The amides were prepd. by treating primary alcs. with O and NH_3 (o primary and secondary amines) in the presence of Pd or Pt catalysts. Thus, treating aq. Me_2NH in MeOH with 5% Pd-C and air 2 h at 40° gave 78% DMF with 92% conversion of Me_2NH. Similarly prepd. were nicotinamide [from 3-(hydroxymethyl)pyridine and NH_3] and $AcONMe_2$ (from Me_2NH and EtOH).

A9.4. 90: 186814e Nicotinamide. Suverkropp, Geertrudes; Hofman, Johannes H. A. (Stamicarbon B. V.) Neth. Appl. 77 06,612 (Cl. C07D213/80), 19 Dec 1978, Appl. 77/6,612, 16 Jun 1977; 8 pp. Nicotinamide (I) was prepd. with 94% selectivity at 62% conversion by hydrolyzing aq. 3-cyanopyridine on Dowex 1X4 in the OH- form and extg. I with PhMe.

A9.5. 89: 179552u Hydrolysis of nitriles. Feldman, Julian; Smith, David W. (National Distillers and Chemical Corp.) U.S. 4,096,149 (Cl. 260-295.5A; C07D213/57), 20 Jun 1978, Appl. 521,014, 05 Nov 1974; 7 pp. The catalytic hydrolysis of nicotinonitrile or RCN (R = substituted or unsubstituted C_{1-20} alkyl, alkenyl, cycloalkyl, aryl, or alkaryl) to the corresponding amides was improved by using reaction product of $RhCl_3$ and a trialkyl trithiophosphate on a solid support such as C, Al_2O_3, SiO_2, mol. sieve, or a ligand functionalized polymer. Thus, heating $RhCl_3$, trilauryl trithiophosphite, pyridine, H_2O, and H_2C:CHCN at 120° and 225 psig initial N pressure for 18 h gave H_2C:$CHCONH_2$. Benzamide was similarly prepd.

A9.6. 85: 192568r Preparation of nicotinic acid amide from 3-cyanopyridine. Zieborak, Kazimierz; Ratajczak, Wlodzimierz; Treszczanowicz, Edward; Teichert, Andrzej; Musierowicz, Jerzy; Stefaniak, Lech (Instytut Chemii Przemyrlowej) Pol. 78,808 (Cl. C07D31/44), 31 Dec 1975, Appl. 149,254, 06 Jul 1971; 4 pp. Nicotinamide (I) was obtained by incomplete hydrolysis of 3-cyanopyridine (II) by using strongly basic anion exchangers as catalysts. Thus, a mixt. contg. II 24, H_2O 33.2, and MeOH 42.8 g was passed at 50° through a column filled with Wofatit SBW in the OH^- form; 79% I was crystd. from the eluate.

A9.7. 85: 62938a Nicotinic acid amide from 3-cyanopyridine. Treszczanowicz, Edward; Teichert, Andrzej; Ratajczak, Wlodzimierz; Musierowicz, Jerzy; Zieborak, Kazimierz; Misiewicz, Leonard; Stefaniak, Lech; Bellen, Natalia (Instytut Chemii Przemyslowej) Pol. 77,202 (Cl. C07D), 31 Jul 1975, Appl. 162,442, 09 May 1973; 3 pp. An aq. 45–60% soln. of 3-cyanopyridine was treated at 90–105° with NaOH (the rate of NaOH addn. was increased continuously), the mixt. was heated at 105° for 30 min, and the hydrolysis product was purified and crystd. to give nicotinamide (I) suitable for fodder. Then the product was dissolved in H_2O, the soln. was passed through an anionite, and crystd. to give I suitable for pharmaceutical purposes. K. Butkiewicz

A9.8. 85: 21134s Nicotinic acid amide and isonicotinic acid amide. Ishioka, Ryoji; Kametaka, Norio; Marumo, Kuniomi (Showa Denko K. K.) Ger. Offen. 2,539,435 (Cl. C07D), 08 Apr 1976, Japan. Appl. 74 103,789, 11 Sep 1974; 19 pp. Nicotinamide was manufd. with selectivity of 97.9% and 3-cyanopyridine (I) conversion of 98.6% by hydrating I over Fe oxide–Ni oxide catalyst, prepd. by treating 291 g $Ni(NO_3)_2.6H_2O$ and 81 g $Fe(NO_3)_2.9H_2O$ with 219 g $(NH_4)_2CO_3$ and calcining the ppt. Isonicotinamide was similarly obtained with a selectivity of 97.2%.

A9.9. 84: 135478s Nicotinamide from 3-cyanopyridine. Okano, Takeshi; Tamaru, Akio; Umeno, Koichi (Mitsubishi Chemical Industries Co., Ltd.) Japan. Kokai 75 111,077 (Cl. C07D, B01J), 01 Sep 1975, Appl. 74 18,851, 16 Feb 1974; 6 pp. Nicotinamide (I) was prepd. by catalytic hydration of 3-cyanopyridine (II) with a Cu catalyst, prepd. by decompn. of Cu hydride. Cu hydride was decompd. in the presence of an acid amide or a compd. contg. Cr, V, Si, Fe, Ru, Ti or Zr. Thus, 398 g Na hypophosphite and 38 g H_2SO_4 in H_2O was treated at 50° with 627 g $CuSO_4.5H_2O$ and 5 g $Cr(NO_3)_3.9H_2O$ in H_2O, and 25% aq. AcOH added at 50° to give a Cu catalyst. The catalyst (1 g) was heated with 0.5 g II in H_2O at 95° for 0.5 hr to give 99.9% I. Similarly, Cu catalysts were prepd. from Cu hydride in the presence of Na_2SiO_3, NH_4VO_3, $Ti(SO_4)_2$, acrylamide or $BzNH_2$. I. Matsumoto

A9.10. 192601c Acid amides and catalyst for use in preparing them. Watanabe, Yoshihiro; Yamahara, Takeshi; Inokuma, Shun; Tokumaru, Tooru (Sumitomo Chemical Co., Ltd.) Ger. Offen. 2,429,269 (Cl. C07C, B01J), 20 Mar 1975, Japan. Appl. 73 69,555, 19 Jun 1973; 26 pp. A catalyst for hydrolyzing nitriles to amides was prepd. by polymg. 4-vinylpyridine with divinylbenzene or styrene and treating the polymer with a Cu salt, such as $Cu(O_2CH)_2.4H_2O$. Acrylonitrile was 78.8% hydrolyzed by the catalyst in 5 hr at 100° with 99.1% selectivity for acrylamide. $AcNH_2$, $H_2NCO(CH_2)_4CONH_2$, $NC(CH_2)_4CONH_2$, $BzNH_2$, $C_6H_4(CONH_2)_2$-o, o-$NCC_6H_4CONH_2$, $HOCMe_2CONH_2$, $H_2N(CH_2)_5CONH_2$, $HCONH_2$, $H_2NCOCONH_2$, and nicotinamide were similarly prepd.

A9.11.

28110y Pyridinecarboxamides from cyanopyridines. Watabiki, Yukio; Sugimoto, Nobutaka; Miyoshi, Masamitsu; Uehara, Yoshihiro; Sakai, Koji (Yuki Gosei Kogyo Co., Ltd.) Japan. Kokai 74,127,976 (Cl. 16 E431), 07 Dec 1974, Appl. 73 43,624, 19 Apr 1973; 3 pp. Cyanopyridines were hydrated to pyridinecarboxamides with a Cr oxide catalyst contg. Ni, Cu, Zn, Co, Fe, Sn, and (or) Ce oxides. Thus, 250 g $(NH_4)_2Cr_2O_7$ was mixed with 110 g basic Cu carbonate and heated at 250° for 2 hr. The catalyst (0.5 g) was heated with 50 g 3-cyanopyridine in 200 ml H_2O at 96° for 8 hr to give 99.87% nicotinamide and 0.13% nicotinic acid. 2- And 4-cyanopyridines were similarly hydrated to pyridinecarboxamides in high yields. I. Matsumoto

A9.12.

170694q Amides. Asano, Shiro; Yoshimura, Kiyotaka; Hashimoto, Masao (Mitsui Toatsu Chemicals, Inc.) Ger. Offen. 2,427,204 (Cl. C 07*cd*), 19 Dec 1974, Japan. Appl. 73 62,510, 05 Jun 1973; 18 pp. Five amides were prepd. in high conversion from RCN (R = CH_2:CH, CH_2:CMe, Ph, Et, or 3-pyridyl) by treatment with H_2O in the presence of long active Cu catalysts contg. Na, Ca, Zn, or Fe nitrates as promoters. Thus, aq. CH_2:CHCN was freed from O and then heated with Raney Cu and 20 ppm $NaNO_3$ at 120° to give CH_2:$CHCONH_2$ and ≤0.5% by-products at 68% conversion rate.

A9.13.

147816q Nicotinamide. Sugihara, Akira; Kakei, Minoru; Mitsuno, Shinya (Fujisawa Pharmaceutical Co., Ltd.) Japan. 73 03,625 (Cl. C 07*d*), 01 Feb 1973, Appl. 70 127,208, 29 Dec 1970; 2 pp. Nicotinamide was prepd. in 35.5–62.7% yield by treating 3-pyridinecarbonitrile with H_2O at 5–20 kg/cm² and 150–200° in the absence of a catalyst. S. Morita

A9.14.

81206n Nicotinamide. Wendler, Norman L.; Taub, David; Kuo, Chan Hwa (Merck and Co., Inc.) U.S. 3,450,706 (Cl. 260-295.5; C 07*d*), 17 Jun 1969, Appl. 03 Jun 1966; 4 pp. The title compd. was prepd. from 1-acyl-3-cyano-4-oxohexahydropyridine by (*1*) a Ritter reaction to give a *tert*-butyl amide, (*2*) redn. to a 4-OH compd., (*3*) acylation, (*4*) aromatization with loss of the 1- and 4-substituents, and (*5*) hydrolysis. Thus, to a soln. of 13.2 g. 1-acetyl-3-cyano-4-oxohexahydropyridine in 350 ml. AcOH was added 37 ml. concd. H_2SO_4 at 20°; iso-C_4H_8 was bubbled in to give *N-tert*-butyl-1-acetyl-4-oxohexahydronicotinamide (I), m. 96–8°. I (2.2 g.) in 40 ml. H_2O was reduced with 0.5 g. $NaBH_4$ in 20 ml. H_2O contg. 2 drops 2.5*N* NaOH to give *trans*-*N*-*tert*-butyl-1-acetyl-4-hydroxyhexahydronicotinamide (II), m. 167–8°. II (1 g.) mixed with 2.5 ml. Ac_2O and 5 ml. C_5H_5N gave *trans-N-tert*-butyl-1-acetyl-4-acetoxyhexahydronicotinamide (III), m. 165–6°. A mixt. of 0.8 g. III, 0.8 g. 30% Pd/C, and 50 ml. Decalin was refluxed to give *N-tert*-butylnicotinamide, m. 85–6°, which, on hydrolysis, gave nicotinamide. Also prepd. were 1-acetyl-3-cyano-4-amino-1,2,5,6-tetrahydropyridine, m. 177–8°, *cis-N-tert*-butyl-1-acetyl-4-acetoxyhexahydronicotinamide, m. 184–7°, and 1-acetylhexahydronicotinamide, m. 141–2°. Carl Osuch

A9.15: 81191d 1-Acetylhydronicotinamides. Wendler, Norman L.; Taub, David; Kuo, Chan Hwa (Merck and Co., Inc.) U.S. 3,441,568 (Cl. 260–294.9; C 07*d*), 29 Apr 1969, Appl. 03 Jun 1966; 5 pp. Nicotinamide (I) is prepd. from 3-cyano-4-amino-1,2,5,6-tetrahydropyridine (II). Thus, 150 ml. Ac_2O is added to 32.0 g. II in 300 ml. C_5H_5N at 30° to give 1-acetyl-4-amino-3-cyano-1,2,5,6-tetrahydropyridine (III), m. 177–8°. III (1.0 g.), 10 ml. C_5H_5N, and 5 ml. Ac_2O is heated 16 hrs. at 100° under N to give 1-acetyl-4-acetamido-3-cyano-1,2,5,6-tetrahydropyridine, m. 163–5°. The 4-propionamido analog was prepd. from

III and $(EtCO)_2O$. III (5.1 g.) is added portionwise to 30 ml. concd. H_2SO_4 at 10–15° over 30 min. After 2 hrs. the mixt. is added dropwise to 250 ml. H_2O at 0–5° and worked up to give 1-acetyl-4-oxohexahydronicotinamide (IV), m. 155–7°. 4-Amino-3-cyano-1,2,5,6-tetrahydropyridine is similarly converted into 4-oxohexahydronicotinamide. IV (2.0 g.) in 35 ml. MeOH is hydrogenated in 20 ml. MeOH over 500 mg. PtO_2 to give *cis*-1-acetyl-4-hydroxyhexahydronicotinamide (V), m. 135–40 and 150–5°. V is acetylated to give *cis*-4-acetoxy-1-acetylhexahydronicotinamide (VI), m. 154–8°. IV (1 g.) in 10 ml. H_2O is reduced with 350 mg. $NaBH_4$ in 7 ml. H_2O contg. 1 drop 2*N* NaOH to give *trans*-1-acetyl-4-hydroxyhexahydronicotinamide (VII), m. 190–2°. VII is acetylated to give the di-Ac deriv. (VIII), m. 204–5°. VI (160 mg.) and 100 mg. 30% Pd/C is heated under 1 atm. N 2 hrs. at 235–40°, during which cryst. I (m. 124–6°) sublimes from the mixt. VIII (250 mg.) and 200 mg. 30% Pd/C is refluxed in 7 ml. Decalin 18 hrs. to give I. VIII (456 mg.) in 8 ml. *tert*-BuOH under N is treated with 2.00 ml. 1.09*N* *tert*-BuOK in *tert*-BuOH. After 18 hrs. at 25° the soln. is worked up to give 1-acetyl-1,2,5,6-tetrahydronicotinamide (IX), m. 153–5°, which with Pd/C gives I. VI (600 mg.) and 450 mg. 30% Pd/C at 200° 2 hrs. under N give 1-acetyl-1,4,5,6-tetrahydronicotinamide, m. 201–3°. VIII (500 mg.) and 400 mg. 30% Pd/C is kept 2 hrs. at 200° under N in a sublimation app. The pot residue is extd. with Me_2CO to give 1-acetyl-1,2-dihydronicotinamide, m. 175–80°, dehydrogenated to I. IV (1.00 g.) in 30 ml. 10% NH_3 in EtOH is kept in a sealed vessel 6 hrs. at 80° to give *cis*-4-hydroxyhexahydronicotinamide. All of the above reactions can also be performed starting from other lower acylates of II. Diana B. Rosen

NICOTINAMIDE

Miscellaneous

A9.16. 133056w Carbonyl and sulfonyl chlorides. Keil, Guenther (Farbwerke Hoechst A.-G.) Ger. Offen. 2,240,883 (C.. C 07*d*), 28 Feb 1974, Appl. P 22 40 883.9, 19 Aug 1972; 15 pp. Ten carbonyl and sulfonyl chlorides, e.g. BzCl, 4-$MeC_6H_4SO_2Cl$, cyclohexanecarbonyl chloride, adipoyl chloride, or nicotinoyl chloride, were manufd. by reaction of the *N*-methylpyrrolidinone (I) or $AcNMe_2$ adduct of the appropriate acids with $COCl_2$ in MeCN. Some of the chlorides were converted in situ into amides or esters. Thus, 60 parts $COCl_2$ was passed into 61 parts BzOH, 49.5 parts I, and 200 parts by vol. MeCN within ~30 min at −15 to −10° and the temp. raised within 2 hr to ~20° to give 85% BzCl.

A9.17. 49785q Nicotinic acid. Suvorov, B. V.; et al. (Institute of Chemical Sciences, Academy of Sciences, Kazakh S.S.R. and Karaganda Metallurgical Plant) U.S.S.R. 235,764 (Cl. C 07*d*), 24 Jan 1969, Appl. 04 Nov 1966; From *Otkrytiya, Izobret., Prom. Obraztsy, Tovarnye Znaki* 1969, 46(6), 27. The title compd. is prepd. by oxidative ammonolysis of 3-picoline in the presence of a V oxide catalyst modified with Sn oxides, or promoted with W oxides followed by hydrolysis of the nicotinamide and nicotinonitrile. MGCL

A9.18. 16037p Separating an acid from an amide via an anion-exchange resin mechanism. Finkelstein, Ehud (Merck and Co., Inc.) U.S. 3,678,060 (Cl. 260/295.5A; C 07*d*), 18 Jul 1972, Appl. 60,057, 03 Aug 1970; 3 pp. The use of $CO_3^{=}$ in place of OH^- on strong anion exchange resins seps. acidic substances from others equally well and without hydrolysis of compds. such as niacinamide. D. E. Nettleton, Jr.

A9.19. 87: 185236u Catalyst for the manufacture of acid amides. Nakamura, Shinji; Inokuma, Shun; Tanaka, Shin; Hirose, Kenichi; Deguchi, Takashi (Sumitomo Chemical Co., Ltd.) Ger. Offen. 2,702,014 (Cl. C07C103/133), 21 Jul 1977, Japan. Appl. 76/5,289, 19 Jan 1976; 31 pp. A vanadate is treated with a cupric salt, Cu and a cupric salt, Cu and a cuprous salt, or a cupric salt and a cuprous salt to prep. catalyst for the hydration of nitriles to amides, e.g., of *acrylonitrile* (I) [107-13-1] to *acrylamide* (II) [79-06-1]. Thus, $CuCl_2$ 2.25, Na orthovanadate 1.5, and Cu 2.25 mmol. were mixed with 20 mL water, mixed with 1.2 g I, and heated at 80° for 1 h to give 85% conversion to II. The selectivity was 100%.

NICOTINAMIDE

Use

A9.20. 101: 116583a Vitamin-containing composition for hair regeneration and hair care. Agoston, Laszlo Hung. Teljes HU 31,556 (Cl. A61K7/06), 28 May 1984, Appl. 81/2,985, 15 Oct 1981; 10 pp. A hair prepn. contains an aq. ext. of wheat germ or bran and the usual vitamins. Thus, *vitamin A* [11103-57-4] 2,000,000, *vitamin E* [67-97-0] 10,000, and *vitamin D_2* [50-14-6] 12,000 IU, *vitamin C* [50-81-7] 2900, *vitamin B_{12}* [68-19-9] 0.25, *vitamin B_6* [8059-24-3] 225, *testosterone propionate* [57-85-2] 25, *vitamin B_1* [59-43-8] 37.5, *vitamin B_2* [83-88-5]50, and *vitamin E* [1406-18-4] 50 mg, 125 ng *vitamin K* [12001-79-5], 750 mg *nicotinamide* [98-92-0] and 5000 mg *choline iodide* [17773-16-3] in 200 mL water was added to 1 L wheat bran ext., to give a hair prepn active in controlling dandruff and preventing baldness.

A9.21. 101: 97664j Antidepressants containing L-tryptophan and a monoamine oxidase inhibitor. Coppen, Alec James Brit. UK Pat. Appl. GB 2,129,299 (Cl. A61K45/06), 16 May 1984, Appl. 82/31,975, 09 Nov 1982; 3 pp. Antidepressants contain *L-tryptophan* [73-22-3] at lower doses when combined with a *monoamine oxidase* [9001-66-5] inhibitor, e.g., *phenelzine* [51-71-8] or *tranylcypromine* [155-09-9]. The antidepressant action of the compn. is greater than either compd. alone in their usual dosages. The compns. may also contain *folic acid* [59-30-3], *ascorbic acid* [50-81-7], *pyridoxine* [65-23-6], *thiamine* [59-43-8], *riboflavin* [83-88-5], *nicotinic acid* [59-67-6] or *nicotinamide* [98-92-0].

A9.22. 96: 35094t Preparation of pyridine. Organic Chemicals Co., Inc. Jpn. Kokai Tokkyo Koho JP 81 86,161 (Cl. C07D213/127), 13 Jul 1981, Appl. 79/163,942, 17 Dec 1979; 4 pp. Pyridine was prepd. from pyridinecarboxamides or cyanopyridines. E.g., treating 61 g nicotinamide with 3.14 g $Cu(OAc)_2.H_2O$ in H_2O at 310° in an autoclave gave 37.4 g pyridine.

A9.23. 91: 62750g Synthesis of a glucose tolerance factor. Silio, Fernando (Consejo Superior de Investigaciones Cientificas) Span. 472,034 (Cl. A61K), 16 Feb 1979, Appl. 26 Jul 1978; 8 pp. A synthetic glucose tolerance factor was prepd. by complexing nicotinamide with Co^{2+} and treating the resulting 2:1 complex with reduced glutathione. The product had hypoglycemic activity of 4×10^{-8} M in vitro.

A9.24. 90: 29008c Polymer of formaldehyde and carbohydrates. Blaszczak, Joseph W. Ger. Offen. 2,707,069 (Cl. C07D487/04), 24 Aug 1978, Appl. 18 Feb 1977; 18 pp. Addn. to Ger. Offen. 1,568,121. Liq., resinous or cryst. reaction products of riboflavin, nicotinamide, vitamin B_1, ribose and HCOH, and optionally contg. pyridoxine, citric acid, adenine or metal salts are prepd. by mixing the starting materials, suspending the mixt. in H_2O, and polymg. it by heating to ≤350° and/or exposing it to UV light optionally in the presence of a peroxide catalyst. These produced are useful in compns. for prevention and treatment of abnormal cell metab., including neoplasia. For example, a mixt. of riboflavin 300, ribose 25, thiamine 75, adenine 10, pyridoxine 10, Co glycinate, K carbonate 25, Mg perchlorate 10, Ca lactate 25, K permanganate 5, ferrous sulfate 25, manganese dioxide 5, ascorbic acid 50, citric acid 25, 95% paraformaldehyde 600 and nicotinamide 50 g was mixed into 2000 mL warm H_2O and then adding an O donor substance. The exothermic reaction bubbled and developed a temp. of ~80° and gave a pasty orange product. The reaction mixt. was polymd. under UV light for 3 days, held at -20° to promote stronger bonding, and then heated until it reached 150°. The cryst. polymn. product was dissolved in hot H_2O, treated with Bz_2O_2 for 1 h, cooled, heated to 100° for 1 h, and then heated to 350° to give a heat-stable, H_2O-sol. cryst. polymer product. The product formed dark cherry-red aq. solns.

A9.25. 89: 48915s Pharmaceuticals containing minerals and vitamins. Liesche Pharmaceutical Corp. Japan. Kokai 78 38,630 (Cl. A61K31/315), 08 Apr 1978, US Appl. 724,311, 17 Sep 1976; 5 pp. Mineral and vitamin complex compns. contain, e.g., $MgSO_4$ 14.47, *zinc gluconate* [4468-02-4] (as base) 23.15, $MnCl_2$ 1.16, *pyridoxine* [65-23-6] 7.23, *nicotinamide* [98-92-0] 14.47, *vitamin A* [11103-57-4] 0.87, *vitamin E* [1406-18-4] 9.69, *vitamin C* [50-81-7] 28.93, and *biotin* [58-85-5] 0.03%.

A9.26. 90046r Stable, aqueous, multivitamin preparations. Maekawa, Hideyuki; Egawa, Shohei (Shionogi and Co., Ltd.) U.S. 3,626,065 (Cl. 424/255; A 61k), 07 Dec 1971, Japan. Appl. 25 May 1967; 4 pp. Stable aq. multivitamin prepns. are obtained by formulating 2 liqs., one contg. vitamin A palmitate, niacinamide, and ascorbic acid, the other contg. thiamine. The liqs. contain the usual stabilizing and flavoring agents and are filled into sep. chambers of a partitioned container. The two liqs. are admixed just prior to use. Robert F. Doerge

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A10

OXYPHENBUTAZONE

PATENTS

1967-1985

APPENDIX P10

ANALYSIS OF THE ABSTRACTS OF PATENTS

Only 1 patent for synthesis is given which comes from a Hungarian group. In the first step 4-hydroxyazobenzene is tosylated to protect the hydroxy function. There are obviously 2 mistakes in the abstract: tosylation with toluenesulfonic acid at pH 8.5-9 will probably not succeed and butylmalonicacidchloride has to be reacted with compound III and not II.

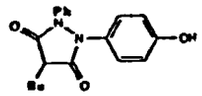
ABSTRACTS OF PATENTS

A10

OXYPHENBUTAZONE

Preparation

A10.1. 97: 38934y 1-Phenyl-2-(4-hydroxyphenyl)-3,5-dioxo-4-n-= butylpyrazolidine. Urogdi, Laszlo; Kisfaludy, Lajos; Gyuran, Janos; Patthy, Mrs. Andras; Trischler, Ferenc; Illes, Sandor (Richter, Gedeon, Vegyeszeti Gyar Rt.) Hung. Te!jes HU 21,369 (Cl. C07D231/34), 28 Nov 1981, Appl. 78/Ri695, 29 Dec 1978; 13 pp. The title compd. (I) was prepd. from



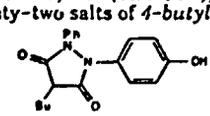
I

4-(tosyloxy)azobenzene (II) by redn. with Na_2S/AcOH, Zn/NaOH, Zn/NH_4OH, or Zn/HCl, treatment with $BuCH(COCl)_2$ or $BuCH(CO_2H)_2$, and alk. deprotection. Thus, a mixt. of *p*-HO=C_6H_4N:NPh and *p*-$MeC_6H_4SO_3H$ in Me_2CO was stirred at pH 8.5–9 and dild. with H_2O to give 96–9% II. The latter in Me_2CO was added to aq. Na_2S and stirred 30 min with AcOH to give 99.5% 4-(tosyloxy)hydrazobenzene (III). A mixt. of $BuCH(COCl)_2$, II, and pyridine in THF stirred 2 h at room temp. gave 85% product, which was stirred with NaOH in MeOH 3 h at room temp. to give 85% I. T. Mohacsi

OXYPHENBUTAZONE

Salts

A10.2. 86: 95992n Antiinflammatory compounds. Laboratorios Miquel S. A. Span. 423,379 (Cl. A61K), 16 May 1976, 19 Feb 1974; 12 pp. Twenty-two salts of *4-butyl-2-(p-hydroxyphenyl*=



I

)-1-phenyl-3,5-pyrazolidinedione (I) [129-20-4] were prepd. by the reaction of I with the appropriate basic compd., e.g. 1-benzyl-3-(3-dimethylaminopropoxy)-1*H*-indazole, *N,N*-di= ethylaminoethanol, and pyrrolidine. These derivs. showed a greater antiinflammatory activity and lower gastric toxicity than I.

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A11

PARACETAMOL

PATENTS

1967-1985

APPENDIX P11

ANALYSIS OF THE ABSTRACTS OF PATENTS

The standard process is claimed in patents A10.2., A10.5., A10.8., A10.9., A10.11., A10.14. and A11.16..

Reduction is carried out chemically or catalytically, in most cases a one pot reaction is carried out, in A11.2. and A11.16. a yield of 90% is given.

In the following patents p-nitrosophenol is used with the reduction in one case (A11.14.) carried out electrolytically, in other cases the method of reduction not being indicated: A11.1., A11.4., A11.6., A11.14. - A11.16.. In most cases one pot reaction is carried out, the yield in A11.16. being 88%.

A11.10. and A11.12. start from p-aminophenol.

In the patents A11.17. - A11.20. purification methods are described.

ABSTRACTS OF PATENTS

A11

PARACETAMOL

Preparation

A11.1. 101: 130331q N-Acetyl-p-aminophenol. Benzaria, Jacques Raphael Fr. Demande FR 2,533,559 (Cl. C07C103/38), 30 Mar 1984, Appl. 82/16,227, 27 Sep 1982; 8 pp. 4-Nitrosophenol underwent simultaneous redn. and *N*-acetylation to yield 4-AcNHC$_6$H$_4$OH. Thus, H was introduced into a mixt. of 4-ONC$_6$H$_4$OH, Pd/C, Me$_2$CHOAc, HOAc, and Ac$_2$O to give 4-AcNHC$_6$H$_4$OH.

A11.2. 101: 110547v N-Acetyl-p-aminophenol. Monsanto Co. Jpn. Kokai Tokkyo Koho JP 59 98,048 [84 98,048] (Cl. C07C103/38), 06 Jun 1984, US Appl. 439,244, 04 Nov 1982; 7 pp. 4-HOC$_6$H$_4$NHAc (I) was prepd. by simultaneous redn. and acetylation of 4-HOC$_6$H$_4$NO$_2$ (II). Thus, a mixt. of 220 g II, 80 g Me$_2$CHOH, 140 g H$_2$O, and 0.1 wt. % (based on II) 3% Pd/C was autoclaved at H 585 kPa and 110° for 8 min, 180 g Ac$_2$O was added in 59 min (at the rate of H consumption), and the mixt. was kept at H 585 kPa and 110° for another 53 min to give 90% I.

A11.3. 101: 6815v Hydroxylation of phenol and aniline derivatives by hydrogen peroxide in a superacidic medium. Morellet, Guy; Jacquesy, Jean Claude; Jouannetaud, Marie Paule (Produits Chimiques Ugine Kuhlmann) Eur. Pat. Appl. EP 97,564 (Cl. C07C69/157), 04 Jan 1984, FR Appl. 82/10,644, 18 Jun 1982; 25 pp. Phenol and aniline derivs. were treated with H$_2$O$_2$ in superacids at between −80° and 0° to yield hydroxylated isomers contg. significant amts. of the meta isomers. Thus, PhOAc and H$_2$O$_2$ were introduced into a HF-SbF$_5$ mixt. at −40°, and the mixt. was worked up after 30 min to give hydroxylated product contg. 3-HOC$_6$H$_4$OAc 51, 4-HOC$_6$H$_4$OAc 43, and 2-HOC$_6$H$_4$OAc 6%.

A11.4. 100: 191599t Purification of N-acetyl-p-aminophenol. Horyna, Jaroslav; Sadlo, Lubos Czech. CS 203,692 (Cl. C07C85/26), 15 Nov 1983, Appl. 79/6,680, 03 Oct 1979; 2 pp. The crude mixt. from redn. of *p*-ONC$_6$H$_4$OH and subsequent acetylation of *p*-H$_2$NC$_6$H$_4$OH was aerated or treated with oxidants, such as aq. H$_2$O$_2$ and AcO$_2$H, and stirred with C which removed Fe oxides and oxidn. by-products. From the decolorized filtrate 85–95% cryst. *p*-AcHNC$_6$H$_4$OH was sepd. after evapn. and cooling. L. J. Urbanek

A11.5. 99: 122018b N-Acetyl-p-aminophenol. Vitan, Marin; Dobrescu, Dumitru; Bibian, Stefan Cilianu; Cilianu, Stefan (Intreprinderea de Coloranti "Colorom") Rom. RO 76,864 (Cl. C07C91/44), 30 Aug 1981, Appl. 97,483, 11 May 1979; 2 pp. 4-Aminophenol hydrochloride was treated with NH$_3$ and Ac$_2$O to yield 4-AcNHC$_6$H$_4$OH. Thus, 4-O$_2$NC$_6$H$_4$OH was reduced, HCl was added to give 4-H$_2$NC$_6$H$_4$OH.HCl, and the product was treated with NH$_3$ and Ac$_2$O at 5–20° to give 4-acetamidophenol.

A11.6. 97: 23459y Paracetamol. Domide, Aneta; Harles, Lucian; Prejmereanu, Ion; Anghel, Dumitru (Intreprinderea de Medicamente si Coloranti "Sintofarm") Rom. RO 74,084 (Cl. C07C103/10), 08 Dec 1980, Appl. 92,381, 08 Dec 1977; 3 pp. 4-Nitrosophenol was converted to paracetamol by Na$_2$S redn. to 4-H$_2$NC$_6$H$_4$OH and subsequent *N*-acetylation.

A11.7. 96: 217499m **N-Acetyl-p-aminophenol.** Horyna, Jaroslav; Sadlo, Lubos Czech. CS 197,100 (Cl. C07C91/44), 30 Apr 1982. Appl. 78/4,877, 21 Jul 1978; 5 pp. *p*-$AcNHC_6H_4OH$ (I) was prepd. by feeding simultaneously an aq. $FeSO_4$ soln. and NH_4OH at 60–80° into an aq. suspension of *p*-ZC_6H_4OH (II) (Z = O or *m*-$HO_3SC_6H_4N$) and treating the mixt. with Ac_2O. I was salted out with NaCl or crystd. from a concd. soln. Alternatively, II was added portionwise with stirring at 50–60° into an aq. suspension contg. powd. Fe and HCl, the mixt. was treated with Ac_2O and worked up as above. L. J. Urbanek

A11.8. 95: 61757k **Stepwise reduction of p-nitrophenol** Huber, John, Jr. (Penick Corp.) U.S. 4,264,525 (Cl. 564-223; C07C103/32), 28 Apr 1981, Appl. 53,688, 02 Jul 1979; 6 pp. The redn. of a portion of 4-$O_2NC_6H_4OH$ (I) by H to 4-$H_2NC_6H_4OH$ (II) at pH < 7.0 was followed by the addn. of Ac_2O to acylate II and give HOAc by-product, the remainder of the I was reduced at pH < 7.0, and the newly formed II was *N*-acylated to give 4-$AcNHC_6H_4OH$ at pH < 7.0. I was reduced by H over Pd/charcoal, the mixt. was cooled, Ac_2O was added, the redn. was continued until H uptake stopped, and Ac_2O was added with heating to 95° to give 4-$AcNHC_6H_4OH$.

A11.9. 95: 42649k **Borate reduction of nitrophenols.** Ruopp, Donald C.; Thorn, Mark A. (Penick Corp.) U.S. 4,264,526 (Cl. 564-223; C07C103/32), 28 Apr 1981, Appl. 54,388, 02 Jul 1979; 5 pp. Halonitrobenzenes were converted to aminophenol by alk. hydrolysis to nitrophenol and hydrogenation of the latter in media contg. borate ion, strong acids, and metal catalysts, i.e., Pd. Thus, 4-$O_2NC_6H_4Cl$ was hydrolyzed by NaOH, the 4-$O_2NC_6H_4OH$ obtained was mixed with H_2SO_4, H_3BO_3, and Pd, H was introduced, and the product was acetylated to give 4-$AcNHC_6H_4OH$, useful as an analgesic and antipyretic (no data).

A11.10. 87: 102059q **Preparation of paracetamol.** Hope, Peter; Gourley, Robert N.; Gray, John; Knight, David Halliwell (Kodak Ltd.) Brit. 1,469,099 (Cl. C07C103/38), 30 Mar 1977, Appl. 73/50,331, 30 Oct 1973; 2 pp. Paracetamol (I) was prepd. (86%) by treating an aq. soln. of *p*-aminophenol sulfate and aniline sulfate with NH_3 to pH 5, removing the $PhNH_2$ by distn., and acetylating the *p*-aminophenol with Ac_2O at 20°, the pH being maintained at 5 with NH_3. The product comprised 95% I and 1.4% PhNHAc.

A11.11. 84: 164381k **p-Acetamidophenol.** Kulda, Drahomir; Fuka, Josef; Ott, Jan; Misar, Zdenek Czech. 159,564 (Cl. C07C), 15 Aug 1975, Appl. 9010/72, 28 Dec 1972; 2 pp. *p*-$HOC_6H_4NO_2$ was reduced with Fe in HCl and *p*-$HOC_6H_4NH_2$ (I) acetylated under conditions which minimized contamination of *p*-HOC_6H_4NHAc (II) with by products. Thus, the mixt. contg. I was neutralized with Na_2CO_3 and a portion of the I (30–80%) acetylated with Ac_2O at 55–60°, the insol. contaminants and Fe sludge were trapped by active C, and the mixt. filtered at 85–90°. The filtrate was treated with the necessary amt. of Ac_2O to complete the acetylation and II was salted out with NaCl. L. J. Urbanek

A11.12. 84: 16992v **N-Acetyl-p-aminophenol.** Schulman, Hyman L.; Baron, Frank A.; Weinberg, Alan E. (Mallinckrodt, Inc.) U.S. 3,917,695 (Cl. 260-562A; C07C), 04 Nov 1975, Appl. 33,080, 29 Apr 1970, 4 pp. Pure *p*-$AcNHC_6H_4OH$ (I) was prepd. from *p*-$H_2NC_6H_4OH$ (II) by dissolving it in HOAc, treating it with C, filtering it; the filtrate was treated with Ac_2O to form N.F. grade I which was sepd. The mother liquor was recycled after I sepn. for use as a solvent for treatment of II.

A11.13. 146250j p-Acetamidophenol. Kulda, Drahomir; Fuka, Josef; Ott, Jan; Misar, Zdenek; Liska, Karel Czech. 149,293 (Cl. C 07c), 15 Jun 1973, Appl. 3979–69, 05 Jun 1969; 2 pp. PhOH was coupled with diazotized $PhNH_2$ in dil. NaOH, the mixt. acidified, and the pptd. p-HOC_6H_4N:NPh hydrogenolyzed in MeOH over Pd/C at <60° and 1.5–3 kg/cm² H. Unreacted $PhNH_2$ was steam distd. and the residual p-$HOC_6H_4NH_2$ treated with Ac_2O in AcOH at 15–30° to yield 95–8% p-HOC_6H_4NHAc.
L. J. Urbanek

A11.14. 65995d Electrolytic reduction of nitrosophenols to aminophenols. Greener, George Pallister; Porter, Alan Sidney (Albright and Wilson Ltd.) Ger. Offen. 2,256,003 (Cl. C 07c), 07 Jun 1973, Brit. Appl. 53,169–71, 1t Nov 1971; 33 pp. p-Nitrosophenol (I) and 4-nitroso-m-cresol (prepd. from the phenol and $NaNO_2$) were reduced electrochem to the corresponding aminophenol; 1-nitroso-2-naphthol was similarly reduced. Addn. of Ac_2O in the redn. of I gave $AcNHC_6H_4OH$-p.

A11.15. 27009w p-Acetamidophenol. Bialik, Jozef; Jedrzejewski, Andrzej (Farmaceutyczna Spoldzielnia Pracy "Galena") Pol. 54,012 (Cl. C 07d), 31 Oct 1967, Appl. 20 Apr 1965; 2 pp. The title compd. (I) is prepd. according to the method described by redn. of p-nitrosophenol (II) with satd. aq. soln. of Na_2S at pH 8.8–10.2. Thus, 50 kg. II, contg. 45% H_2O, was added portionwise at a temp. below 45° to 75 l. aq. soln. Na_2S (sp. gr. 1.19 at 20°), the mixt. was stirred at this temp. for 1 hr., and then at 50° for another 1 hr. Aq. soln. (60 l.) of tech. pure $(NH_4)_2SO_4$ (sp. gr. 1.200 at 20°) was added to the warm mixt., the mixt. was heated at 50° for 1 hr., and cooled to 15°. Pptd. tech. pure p-aminophenol (III) was sepd. by filtration and washed with ice-water. III was acetylated with Ac_2O (0.3 kg. per 1 kg. wet III in 0.2 kg. H_2O). For this purpose III was added to H_2O, the mixt. stirred, Ac_2O added, and the mixt. stirred for 3 hrs. and cooled to 15° to crystallize. The crude I was recrystd. from H_2O. Pure I (0.49 kg.) was obtained from 1 kg. wet II in 80% yield.
Karol Butkiewicz

A11.16. 99870h N-Acetyl-p-aminophenol. Bernard F. Duessel and Godfrey Wilbert (to Nepera Chemical Co., Inc.). U.S. 3,341,587 (Cl. 260–562), Sept. 12, 1967, Appl. March 16, 1962, and Oct. 15, 1964; 2 pp. The title compd. (I) was obtained in excellent yield of high purity by the direct acylation of p-$H_2NC_6H_4$-OH formed by the catalytic redn. of certain nitrophenols in an Ac_2O reaction solvent. Thus, 350 lb. p-$O_2NC_6H_4OH$ (II) in 297 lb. Ac_2O was hydrogenated in a N purged autoclave over 770 g. 5% Pd–C catalyst under 40–60 psig. at 80–90°. After 10 hrs. reaction time, unreacted H was vented and the vessel again purged with N. To complete the acylation, 56 lb. Ac_2O was added, the mixt. heated rapidly to 80–90°, making due allowance for the exothermic reaction which takes place. After ~2 hrs. the mixt. was cooled to ~50°, treated with 35 gal. demineralized H_2O, the mass heated again to ~90°, and 100 g. $NaHSO_3$ added to prevent coloration of the product. The mixt. was then filtered at 75–80° to remove the catalyst and the filtrate cooled to 0–5° to yield (during 4 hrs.) 90% I. Using p-ONC_6H_4OH in place of II gave 88% I. With PtO_2 as hydrogenation catalyst comparable results were obtained. I is widely used as an analgesic and antipyretic in various therapeutic compns.

PARACETAMOL

Purification

A11.17. 89: 23947r **Purification of phenols.** Boecker, Ernst; Mannes, Karl; Trescher, Viktor (Bayer A.-G.) Ger. Offen. 2,644,318 (Cl. C07C37/22), 06 Apr 1978, Appl. 01 Oct 1976; 18 pp. Tech. phenols are purified by treatment with Al powder. Thus 300 g 4-$AcNHC_6H_4OH$ in 1600 mL H_2O was treated with 4 g low-FeC, 5 mL HOAc, and 2 g Al powder under N under reflux for 45 min. to give 270 g pure white 4-$AcNHC_6H_4OH$. 2-$HOC_6H_4CO_2Na$, 4-$HOC_6H_4CO_2K$, and *p*-$(HO)_2C_6H_4$ were similarly purified.

A11.18. 9491g **Purification of p-aminophenol.** Harmetz, Ronald; Ruopp, Donald C.; Brown, Bernard Beau (CPC International Inc.) U.S. 3,876,703 (Cl. 260-575; C07c), 08 Apr 1975, Appl. 367,263, 05 Jun 1973; 4 pp. *p*-Aminophenol, prepd. by electrolytic or catalytic redn. of $PhNO_2$ in aq. H_2SO_4, was obtained as a pure product by adding more $PhNO_2$ to the reaction mixt. (if the reaction had gone to completion), adjusting the pH to ~ 5-6.5, and sepg. the $PhNO_2$ phase and the purified *p*-aminophenol phase. The product after acetylation with Ac_2O gave the *N*-acetyl deriv. which met all National Formulary specifications.

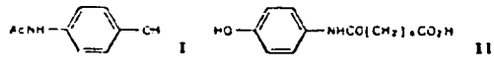
A11.19. 82385t **Purification of N-acetyl-p-aminophenol.** Kosak, John R. (du Pont de Nemours, E. I., and Co.) U.S. 3,781,354 (Cl. 260-562B; C 07c), 25 Dec 1973, Appl. 88,179, 09 Nov 1970; 2 pp. Crude light-pink-colored *p*-$AcNHC_6H_4OH$ (I), prepd. by acetylation of *p*-$H_2NC_6H_4OH$, was refluxed with aq. $FeCl_3$ soln. for 1.5 hr and then treated with activated C to give white cryst. I.

A11.20. 78380z **Purification of N-acetyl-p-aminophenol.** Baron, Frank A. (Mallinckrodt Chemical Works) U.S. 3,748,358 (Cl. 260-562P; C 07c), 24 Jul 1973, Appl. 46,840, 16 Jun 1970; 4 pp. *p*-$AcNHC_6H_4OH$ (I) was purified to N.F. specifications by treating the crude product of acetylation of *p*-$H_2NC_6H_4OH$ (contg. 80% I) in aq. soln. with charcoal, which had been previously washed with an acidic soln., and crystg. I. The Fe content of I was reduced by including a chelating agent (e.g., citric acid, gluconic acid) in the crystn. solvent or in the acid soln. used for washing the charcoal.

PARACETAMOL

Miscellaneous

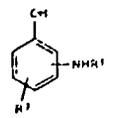
A11.21. 101: 6856g **Acetaminophen analogs, antigens, and antibodies.** Khanna, Pyare (Syva Co.) Eur. Pat. Appl. EP 95,229 (Cl. C07C103/25), 30 Nov 1983, US Appl. 364,836, 02 Apr 1982; 28 pp.



Antisera can be prepd. to protein antigens or enzymes conjugated to carbonyl derivs. of acetaminophen (I). These antisera can be used as reagents in sensitive, highly specific immunoassays for monitoring I levels in biol. fluids. Thus, *adipaminophen* (II) [89519-10-8] was prepd., conjugated to *glucose-6-phosphate dehydrogenase* [9001-40-5], and antisera were prepd. in sheep. By means of the antibodies thus obtained, I at very low concns. in human serum could be detd., with very little cross-reactivity with I-metabolites or with other drugs.

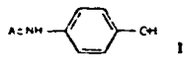
A11.22. 100: 145005b **Tablets by a modified 'wet-granulation' technique.** Rogerson, Alan George (Sterwin A.-G.) Eur. Pat. Appl. EP 100,163 (Cl. A61K9/16), 08 Feb 1984, GB Appl. 82/19,487, 06 Jul 1982; 51 pp. A modified wet granulation method (slurry granulator) is described for prepg. good quality tablets with high dosages of active ingredient and minimal excipients. One or more drugs and excipients are moistened with a predetd. amt. of nonsolvent granulating fluid to form a uniform, moist, coherent, nonpasty mass which is subdivided into individual granules and dried. The dried granules are compressed into tablets. The amt. of granulating fluid comprises ≥90% by wt. of the predetd. amt. of fluid so as to form a homogeneous slurry where the percentage by wt. of solids in the slurry is [total solids (both dissolved and undissolved) × 100/total slurry (fluids + total solids)] = 25% wt./wt. The remaining part of the particulate solid material is moistened by wet granulation with the slurry so as to form the desired pasty mass. Tablets were prepd. from (total quantity in mixt. in milligrams and amt. in slurry in grams given): DL-*methionine* [59-51-8] 250, 125; *paracetamol* [103-90-2] 500, –; *PVP* [9003-39-8] 30, 30; stearic acid 10, –; Na starch glycolate 50, –; and 200 mL H_2O as granulating fluid.

A11.23. 98: 22273a **Accelerators of drug absorption in the intestine.** Sawai Pharmaceutical Co., Ltd. Jpn. Kokai Tokkyo Koho JP 57,145,809 [82,145,809] (Cl. A61K31/60), 09 Sep 1982, Appl. 81/31,713, 04 Mar 1981; 5 pp. The phenol derivs. I (R^1 = H or



acyl; R^2 = H or CO_2H) are accelerators of drug absorption in the intestine. Thus, a suppository was prepd. by combining ampicillin Na 1.5, *4-hexanamidosalicylic acid* [83936-13-4] 1.2, and Witepsol H-15 9.3 g. Nineteen I were synthesized and their effects on drug absorption demonstrated in dogs.

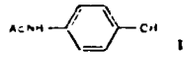
A11.24. 96: 74634p **Spray dried-N-acetyl-p-aminophenol compositions.** Salpekar, Anil M. (Mallinckrodt, Inc.) Eur. Pat. Appl. EP 40,472 (Cl. A61K9/14), 25 Nov 1981, US Appl. 152,052, 20 May 1980; 17 pp. A spray-dried *N-acetyl-p-aminophenol*



I

(I) [103-90-2] compn. is prepd. by forming a slurry of finely divided I and *starch* [9005-25-8] and spray-drying the slurry such that the spray-dried particles have a moisture content between 0.3 and 1.5% by wt.; the starch being gelatinized prior to or during spraying. The spray-dried compns., which may contain other active ingredients, have good compressibility and flow properties facilitating the formation of tablets, capsules, or other dosage forms. Thus, pregelatinized starch 1.5 parts was mixed with an equal quantity of I and charged to a high shear mixer contg. 100 parts H_2O. I had a particle size such that all of it passed through a 200 mesh screen and 75% through a 325 mesh screen. Addnl. I 98.5 parts was added and mixing continued until a smooth slurry was obtained which was sprayed using countercurrent conditions. This spray-dried product was formulated into tablets.

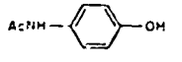
A11.25. 90: 12311y **Paracetamol granulate.** Rupp, Roland; Buecheler, Manfred; Ernst, Joachim; Vosteen, Bernhard (Bayer A.-G.) Ger. Offen. 2,713,197 (Cl. C07C103/38), 05 Oct 1978, Appl. 25 Mar 1977; 8 pp. Preservative-free *paracetamol* (I))



I

[103-90-2] granules (av. particle size 80–200μ) comprise 0.5–3% *poly(vinylpyrrolidone)* (PVP) [9003-39-8] and > 0.3% H_2O, and are prepd. by spray-drying an aq. suspension of 40–60% I contg. 0.5–3% PVP. The spray-drying process was conducted in an inert gas atm. by a direct flow process with an inlet temp. of 150–300° and outlet temp. of 80–150°. For example, a suspension of 500 kg powd. I and 10 kg PVP in 490 kg H_2O was spray-dried with inlet and outlet temps. of 280 and 110°. The granulate had 130 μm diam. spherical particles and contained 0.1% H_2O.

A11.26. 84: 35323u **Paracetamol tablets.** Sterwin A.-G. Fr. Demande 2,247,206 (Cl. A61K), 09 May 1975, Brit. Appl. 40,428/71, 24 Jan 1973; 17 pp. *Paracetamol* (I) [103-90-2], an analgesic, was



I

prepd. for tabletting by crystn. with a polymer, [*GAF S630* (vinylpyrrolidone–vinyl acetate copolymer)(II) [25086-89-9]], without grinding or the addn. of adhesives. Thus, 3500 cm^3 of an aq. soln. contg. 2 Kg I at 100° was added to 60 g II in 200 cm^3 water, underwent crystn. followed by filtration. The filtrate 1000, Solkafloc 20, and Mg stearate 2.5 g were combined and then tabletted.

A11.27. 52896q **Anti-migraine composition.** Wild, Henry Ger. Offen. 2,059,747 (Cl. A 61k, C 07d), 09 Jun 1971, Brit. App. 05 Dec 1969. The title compn. consisted of 1:70–100 1-(*p*-chlorobenzhydryl)-4-(*p*-tert-butylbenzyl)piperazine (Buclizine) and *p*-$AcNHC_6H_4OH$ (Paracetamol).

A11.28. 21900h L-Hydroxyproline and its medicinal combinations in the treatment of rheumatic diseases. Denis, J. C.; Rambaud, J. (Tecpan S. A.). Fr. M4,727 (Cl. A 61k), 06 Feb 1967, Appl. 04 Nov 1965; 2 pp. Hydroxyproline (I) in assocn. with glucosamine–HCl (II) or an antirheumatic (acetylsalicylic acid, acetyl-*p*-aminophenol (III), or 3,5-dihydroxy-1,2-diphenyl-4-butylpyrazolidine (IV)) can be used successfully in different rheumatic affections. Animal tests show that I and esp. I and II together potentiate the effects of antirheumatics and prolong their effects and permit the use of lower and less toxic doses. Thus, pills were prepd. contg. the following: II 0.200, I 0.020 g.; III 0.400, I 0.010 g.; IV 0.100, II 0.1000, I 0.010 g., for use in acute articular rheumatism, rheumatoid polyarthritis, arthrosis, periarthritis, and phlebitis. Janet D. Scott

A11.29. 21894j Medication based on a combination of N-acetyl-p-aminophenol and an enzymic product. Riviere, Jean Fr. M4,825 (Cl. A 61k), 20 Mar 1967, Appl. 13 Sep 1965; 5 pp. Mixts. of varying amts. of *p*-AcNHC$_6$H$_4$OH (I) and 3 enzymic prepns. in a suitable pharmaceutical medium have, by oral or rectal administration, analgesic, antipyretic, anti-inflammatory, and antiedemic actions superior to the individual components. Cited for oral use was a compn. contg. 300 mg. I, 1250 units CEIP amylase, 5000 units Hummel chymotrypsin, and mucopolysaccharidase (100 turbidity redn. units chondrosulfatase and 500 I.U. hyaluronidase) in a base contg. talc 0.02, levilite 0.015, and lactose, q.s.p. 0.6 g. Other formulations plus pharmacol. data, including 9 case histories, are given. D. E. Nettleton, Jr.

A11.30. 1965j Antipyretic and analgesic composition with N-acetyl-p-aminophenol. Jean Riviere. Fr. M3852 (Cl. A 61k), Feb. 21, 1966, Appl. Sept. 4, 1964; 7 pp. An antipyretic and analgesic compd. is prepd. using *N*-acetyl-*p*-aminophenol as active compound, assocd. with a barbiturate (phenobarbital), an antihistamine (promethazine), and a diffusion agent. A study of its toxicity, and pharmacol. activity is also performed.
Juan Castaner Gargallo

A11.31. 88659t Granulating materials for tableting. Lawrence Lowy and William O. Wurtz. U.S. 3,308,217 (Cl. 264–117), March 7, 1967, Appl. Feb. 9, 1964; 4 pp. A granulation process is described that gives tablets of low friability from uniformly sized granules. A mixt. of physiol. active material with physiol. inactive thermoplastic material is heated to soften the thermoplastic material and cause it to agglomerate and the mixt. is cooled to form uniform granules. Thus, ascorbic acid 82, cornstarch 10, and poly(oxyethylene)–polypropylene copolymer (I) 8 parts were blended, heated to 80° for 5 min., cooled to room temp., and compressed into tablets. The tablets were not friable and had high hardness and soln. rates. Similarly, tablets were prepd. from thiamine, riboflavine, *N*-acetyl-*p*-aminophenol pyridoxine, and niacinamide with glyceryl tristearate instead of cornstarch, and poly(oxyethylene) glycol instead of I. COPN

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A12

PROCAINE.HCL

PATENTS

1967-1985

APPENDIX P12

ANALYSIS OF THE ABSTRACTS OF PATENTS

In patents A12.1. and A12.4. only the formation of the chlorohydrate from the base is described.

The same inventor describes in patents A12.2. and A12.3. the direct ester formation of p-nitrobenzoic acid with diethylaminoethanol with subsequent reduction and formation of chlorohydrate with a yield of 90% given in A12.3..

ABSTRACTS OF PATENTS

A12

PROCAINE.HCL

Preparation

A12.1. 102: 119707a Hydrochlorides. Szarvas, Niklos; Horvath, Eva; Cseke, Laszlo; Balint, Janos; Fabian, Ferenc; Kun, Lajos (Biogal Gyogyszergyar) Eur. Pat. Appl. EP 125,542 (Cl. C07C29/00), 21 Nov 1984, HU Appl. 83/1,497, 02 May 1983; 16 pp. HCl salts of compds. contg. protonizable N atoms are formed by incubating the compd. with a sulfonyl chloride, QSO_2Cl, where Q is OH, C_{1-4} alkyl, aryl, or C_{1-4} alkyl–substituted aryl, in an alc. medium. The method is esp. suited for prepg. pharmaceutical salts. Thus, oxytetracycline–Ca silicate complex was stirred with MeOH [67-56-1] and anhyd. $CaCl_2$, followed by gradual addn. of *chlorosulfonic acid* [7790-94-5] in MeOH. Activated C was added, the mixt. was filtered, concd. HCl was added to pH 0.4, and crystals of *oxytetracycline–HCl* [2058-46-0] were obtained by cooling.

A12.2. 48063q Esterification of a benzoic acid with a tert-amino alcohol. Levy, Joseph; Walker, William (Universal Oil Products Co.) U.S. 3,660,411 (Cl. 260-293.81; C07d), 02 May 1972, Appl. 46,514, 15 Jun 1970; 2 pp. p-$O_2NC_6H_4CO_2H$ was esterified with diethylaminoethanol by refluxing in xylene with HCO_2H catalyst to give diethylaminoethyl p-nitrobenzoate (I). I was hydrogenated with Pd/C catalyst and the product was acidified with HCl to give procaine hydrochloride.

A12.3. 5138s Catalytic reduction of ester of a nitrobenzoic acid and tertiary-amino alcohol to the corresponding amine. Levy, Joseph; Walker, William (Universal Oil Products Co.) U.S. 3,728,376 (Cl. 260/472; C 07c), 17 Apr 1973, Appl. 46,513, 15 Jun 1970; 4 pp. Procaine.HCl (I) was prepd. by esterifying p-$O_2NC_6H_4CO_2H$ (II) with $Et_2NCH_2CH_2OH$, reducing the ester by gradually adding it in ~7 hr to a stirred suspension of Pd/C in xylene under 30 psi H at 80–90°, and acidifying the product with HCl. The overall yield of I based on II was ~90%.

A12.4. 35455c Purification of diethylaminoethyl ester of p-aminobenzoic acid. Shitov, G. G.; Myznikova, M. A.; Klimov, V. A. (Novokuznetsk Chemical-Pharmaceutical Plant) U.S.S.R. 292,968 (Cl. C 07c), 15 Jan 1971, Appl. 10 Jun 1968; From *Otkrytiya, Izobret., Prom. Obraztsy, Tovarnye Znaki* 1971, 48(5), 97–8. The title ester was purified by its conversion into the hydrochloride deriv., followed by sepn. of the product as a base. The reaction mass was pretreated with alkali at 50–5° and the resulting mixt. was dild. with water.

PROCAINE.HCL

Miscellaneous

A12.5. 93: 31645s Liquid crystals. Cachita, Dorina M. (Centrul de Cercetari Biologice) Rom. RO 77,251 (Cl. C09K3/34), 30 Aug 1981, RO Appl. 88,423, 15 Nov 1976; 2 pp. Addn. to Rom. 69,653. Liq. crystals are obtained from pure phosphatides from plant parts or from plant aq. exts. by mixing the exts. with an aq. soln. of procaine chlorhydrate of 1–1000 g/L concn. at room temp. To enhance the chem. stability of the liq. crystals, some anhyd. glycerol or glycerol + sucrose soln. in water are added during the prepn. process. A change in the proportion of lecithin, procaine, and glycerol leads to a change in the d. of liq. crystals in a vol. unit. Increased concn. of procaine causes an increase in the d. and size of the formed liq. crystals. Liq. crystals obtained by this procedure are stable at room temp. for ~6 mo. L. Orlowska

A12.6. 95: 39337b Liquid crystals used in an optical display device. Cachita, Dorina Marioara Rom. 69,638 (Cl. C09K3/34), 15 Jan 1980, Appl. 88,423, 15 Nov 1976; 2 pp. Liq. crystals are prepd. from phospholipid- or lipoprotein-contg. aq. plant exts. by treatment with procaine–HCl and eventually cholesterol. Thus, rose or peony tissues (10 g) were mixed with procaine–HCl (1 g/L) followed by filtration and centrifuging. Liq. crystals were obsd. microscopically in the supernatant. For colored tissues, the color of the crystals changed with the pH.

A12.7. 100: 47033f Composition with a rhizogenic action. Cachita, Dorina; Micu, Mircea; Henegariu, Octavian; Baloiu, Ioan; Fiell, Ingrid (Administratia Parcurilor si Strazilor) Rom. RO 79,825 (Cl. A01N5/00), 30 Aug 1982, Appl. 93,727, 21 Sep 1979; 6 pp. *Procaine-HCl* [51-05-8] enhances the rooting-stimulating activity of *NAA* [86-87-3]. Thus, a powder contg. 1000 ppm NAA and 100 ppm procaine-HCl increased rooting of carnation cuttings by 17%.

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A13

PROPRANOLOL

PATENTS

1967-1985

APPENDIX P13

ANALYSIS OF THE ABSTRACTS OF PATENTS

Most of the patents claim processes which are similar to the standard process.

A13.3. and A13.9. start from sodium naphtholate, epichlorohydrine and isopropylamine (in A13.3. wrongly indicated as ethylamine).

Patents A13.2. and A13.6. procees from the intermediate 1-(1-naphthyl-oxy)-2,3-epoxypropane which reacts with isopropylamine carbonate and isopropyaminmagnesiumbromide or isopropylamine lithium respectively

A13.1., A12.4. and A13.10. are interesting alternatives which differ significantly from the standard process.

Patents A13.5. and A13.7. seem to be rather complicated.

In A13.8. dihydropropranolol is claimed and described, according to the abstract. Dehydrogenation to propranolol is probably described in the patent itself.

ABSTRACTS OF PATENTS

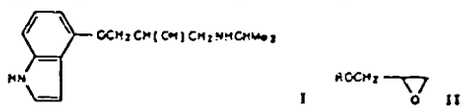
A13

PROPRANOLOL

Preparation

A13.1. 95: 150272r Alkanolamines. Kyowa Hakko Kogyo Co., Ltd. Jpn. Kokai Tokkyo Koho 81 63,945 (Cl. C07C93/06), 30 May 1981, Appl. 79/138,684, 29 Oct 1979; 6 pp. $ROCH_2CH(OH)=CH_2NHCHMe_2$ I (R = 1-naphthyl, 4-indolyl) were prepd. by reaction of $Me_2CHN:CHZR^1$ II (R^1 = alkyl; Z = O, NH) with $ROCH_2R^2$ (III; R^2 = oxiranyl) followed by hydrolysis of the resulting $ROCH_2CH(OH)CH_2N(CHO)CHMe_2$ (IV). Thus, 0.26 g $SnCl_4$ in $CHCl_3$ was added to a mixt. of 2.3 g II (R^1 = Et, Z = O) and 3.56 g III (R = 4-indolyl) in $CHCl_3$ at <15°, the mixt. refluxed 8 h, 3 N NaOH added, and the mixt. stirred at room temp. to give 2.4 g IV (R = 4-indolyl) (V). Refluxing 1 g V in 1.5 N NaOH 1.5 h gave 0.7 g I (R = 4-indolyl). K. Sempuku

A13.2. 95: 80723n Pindolol and propranolol. Kunishige, Tsutomu Jpn. Kokai Tokkyo Koho 81 29,547 (Cl. C07C91/10), 24 Mar 1981, Appl. 79/105,353, 18 Aug 1979; 3 pp. Pindolol (I) and



I II

propranolol were prepd. by treating epoxides II (R = indol-4-yl, 1-naphthyl) with Me_2CHNHM (M = MgBr, Li). Thus, 2.4 g Mg was converted to EtMgBr in THF, treated with 6 g Me_2CHNH_2 at 30° for 0.5 h, and evapd. The residue was stirred with 15 g II (R = indol-4-yl) in THF at 10–33° for 3 h and poured into aq. NH_4Cl to give 14 g I. I. Matsumoto

A13.3. 94: 15445p 1-(Naphthoxy)-3-isopropylamino-2-propanol. Maftei-Mihai, G.; Moldovan, Augustin V.; Popa, Ilie I. (Centrala Industriala de Medicamente, Cosmetice, Coloranti si Lacuri) Ger. Offen. 3,005,562 (Cl. C07C93/06), 28 Aug 1980, Rom. Appl. 96,711, 23 Feb 1979; 6 pp. Propanolol (182 g) of improved purity was obtained by converting 144 g 1-naphthol to its Na salt, adding 185 g epichlorohydrin (I) stepwise with removal of unreacted I by azeotropic distn. with H_2O, adding 337 g $MeCH_2NH_2$ as a 70% aq. soln., and extg. the propranolol into PhMe.

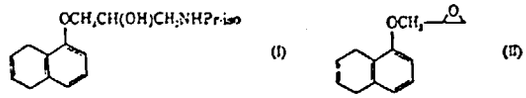
A13.4. 170489b Phenolic ethers. Instituto Luso-Farmaco, S.a r.l. Span. 398,313 (Cl. C 07c), 16 Sep 1974, Appl. 398,313, 13 Dec 1971; 6 pp. The reaction of α-naphthol with 2,3-epoxypropyl(isopropyl)amine or with 2,3-epoxypropyl(propyl)amine gave 1-isopropylamino- and 1-propylamino-3-(1-naphthoxy)-2-propanol, resp. J. Castaner-Gargallo

A13.5. 97382x 1-Isopropylamino-3-(1-naphthoxy)-2-propanol. Kudo, Shiro; Tamaki, Kentaro; Yada, Seiichi (Kyowa Fermentation Industry Co., Ltd.) Japan. Kokai 72 42,636 (Cl. 16 C412), 16 Dec 1972, Appl. 71 28,868, 04 May 1971; 3 pp. 3-(1-Naphthoxy)-1-tosyloxy-2-propanol, prepd. from 3-(1-naphthoxy)-1,2-propanediol (I) by reaction with p-$MeC_6H_4SO_2Cl$, was treated with 2,3-dihydropyran and concd. HCl in C_6H_6 to give 3-(1-naphthoxy)-1-tosyloxy-2-propanol tetrahydropyranyl ether, which with Me_2CHNH_2 gave 3-(1-naphthoxy)-1-isopropylamino-2-propanol tetrahydropyranyl ether (II). Refluxing II in Me_2CO at pH <1 gave 50% the title compd (based on I) of 99.0% purity, a β-adrenergic inhibitor. Y. Tsuji

A13.6. 120306h 1-Aryloxy-3-(isopropylamino)-2-propanols. Daniewski, Wlodzimierz; Borowka, Marian (Przedsiebiorstwo Doswiadczalne Przemyslu Farmaceutycznego POLFA) Ger. Offen. 2,013,527 (Cl. C 07c), 08 Oct 1970, Pol. Appl. 29 Mar 1969; 7 pp. The title compds. $ROCH_2CH(OH)CH_2NHPr$-iso (I) were prepd. Thus, heating 24 g 1-(α-naphthyloxy)-2,3-epoxypropane and 10 g (iso-$PrNH_3)_2CO_3$ in 25 g isoamyl alc. 45 min at 90–100° gave 15 g I (R = α-naphthyl). I (R = p-AcNH-C_6H_4) and I (R = o-CH_2:$CHCH_2OC_6H_4$) were similarly prepd. KCPG

A13.7. 120082g β-Adrenergic blocking 1-alkoxy-3-amino-2-propanols. Yoshizue, Keiro; Saito, Hideo (Sankyo Chemical Industries Co., Ltd.) Ger. Offen. 2,018,263 (Cl. C 07cd, A 61k), 08 Oct 1970, Japan. Appl. 14 Apr 1969; 24 pp. The β-adrenergic blocking title compds., $ROCH_2CH(OH)CH_2NHR^1$ (I) were prepd. by reaction of epichlorohydrin (II) with Schiff bases to give 5-(chloromethyl)oxazolidines, reaction with phenols, and hydrolysis or by reaction of II with phenols, subsequent reaction with Schiff bases and hydrolysis. Thus, reaction of PhCH:NPr-iso with II in the presence of $SnCl_4$ in CCl_4 3 hr at 20° gave 74% 2-phenyl-3-isopropyl-5-(chloromethyl)oxazolidine, which on reaction with PhOH in the presence of NaOMe gave 75% 2-phenyl-3-isopropyl-5-(phenoxymethyl)oxazolidine (III). III was also prepd. by reaction of II with PhOH via 1-phenoxy-2,3-epoxypropane and reaction with PhCH:NPr-iso. Hydrolysis of III with 10% HCl 1 hr at 90–5° gave 93.7% I (R = Ph, R^1 = iso-Pr). Similarly prepd. were I (R and R^1 given): α-naphthyl, iso-Pr; m-tolyl, iso-Pr; o-$MeOC_6H_4$, iso-Pr; m-tolyl, cyclohe[illegible]; p-Cl-C_6H_4, iso-Pr; o-iso-$PrOC_6H_4$, iso-Pr; Ph, Bu; m-tolyl, Et; p-ClC_6H_4, Et. KTPG

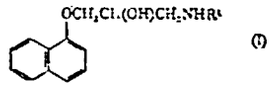
A13.8. 37031z 1-(5,8-Dihydro-1-naphthyloxy)-3-(isopropylamino)-2-propanol. Narayanan, Venkatachala L.; Setescak, Linda L.; Weisenborn, Frank L. (Squibb, E. R., and Sons, Inc.) Ger. Offen. 1,950,742 (Cl. C 07cd), 30 Apr 1970, US Appl. 16 Oct 1968; 21 pp. The title compd. (I) and its acetate were prepd. and could be used as water softening or as antifibrillatory agents.



5,8-Dihydro-1-naphthol, prepd. in ~98% yield by redn. of 1-naphthol with Li in liq. NH_3, reacted with epichlorohydrin to give II. Reaction of II with iso-$PrNH_2$ gave I. KBPG

A13.9. 99907u Manufacture of propanolamine derivatives. Leslie H. Smith and Imperial Chemical Industries Ltd. Brit. 1,079,534 (Cl. C 07c), Aug. 16, 1967, Appl. Feb. 24, 1965; 2 pp. The relevant alc., epoxide and amine are reacted to form the propanolamine deriv.; $R^2OCH_2CH(OH)CH_2NHR^1$, where R^1 is an alkyl group of ≤10 C atoms and R^2 is a naphthyl or tolyl group. Thus, 2.8 parts 1-naphthol, 2 parts epichlorohydrin, 1.7 parts isopropylamine, 0.8 part NaOH, and 20 parts EtOH are heated at 100° in a sealed vessel for 10 hrs. The mixt. is evapd. to dryness in vacuo and shaken with 25 parts 2N HCl and 25 parts ether. The aq. phase is basified with 2N NaOH and filtered to yield 1-isopropylamino-3-(1-naphthyloxy)-2-propanol, m. 96° (cyclohexane). Similarly prepd. is 1-isopropylamino-3-(3-tolyloxy)-2-propanol, m. 78–80°. The derivs. are used in treatment or prophylaxis of heart diseases. H.Carline Barlow

A13.10. 85646a Naphthalene derivatives. Imperial Chemical Industries Ltd. Neth. Appl. 6,604,255 (Cl. C 07c), Oct. 3, 1966; Brit. Appl. March 31, 1965, and Feb. 3, 1966; 5 pp.; cf. preceding abstr. The title compds. I have β-adrenergic blocking activity and are used for the treatment or prophylaxis of heart diseases such as angina pectoris and cardiac arrythmias and for the treatment of hypertensia and pheochromocytoma. Their prepn. is given. Thus, a mixt. of 2.5 parts 1-amino-3-(1-naphthoxy)-2-propanol hydrochloride, 1.23 parts iso-PrBr, 1.68 parts Na_2CO_3, and 20 parts EtOH is heated in a closed tube 20 hrs. at 130°. After filtering, the mixt. is evapd. and the residue is extd.



(I)

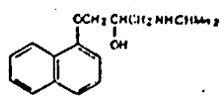
with 25 parts AcOEt. The ext. is filtered and treated with HCl in Et_2O to give the HCl salt of I (R^1 = iso-Pr), m. 162–4° (iso-PrOH). C. van de Westeringh

PROPANOLOL

Miscellaneous

A13.11. 98: 2496p Reagents and method for determining ligands in a sample of biological liquids. Wang, Chao Huie Jeffrey; Stroupe, Stephen Denham; Jolley, Michael Ernest (Abbott Laboratories) Ger. Offen. DE 3,205,506 (Cl. G01N33/54), 16 Sep 1982, US Appl. 235,259, 17 Feb 1981; 49 pp. Tracers are described for ligand (esp. drugs and hormones) detn. in body fluids by fluorescence polarization immunoassay. The tracers are ligand analogs with a single reactive primary or secondary amino group which are bound to carboxyfluorescein. For example, prepn. of an aminophenobarbital–carboxyfluorescein conjugate is described, as well as assay procedures, for detn. of phenobarbital. Numerous other examples are given.

A13.12. 95: 55037j Propanolol antigen conjugates and antibodies. Pirio, Marcel R.; Singh, Prithipal (Syva Co.) U.S. 4,241,177 (Cl. 435-7; C12Q1/66), 23 Dec 1980, Appl. 937,248, 28 Aug 1978; 7 pp. *Propranolol* (I) [525-66-6] was derivatized and



I

these derivs. were conjugated to various protein carriers (i.e. bovine serum albumin and globulin, glucose-6-phosphate dehydrogenase). These conjugates were useful as immunogens for the induction of I-specific antibodies and as indicator mols. in I enzyme immunoassays.

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B1

DIPHENYLHYDANTOIN

PATENTS

1967-1985

APPENDIX P14

ANALYSIS OF THE ABSTRACTS OF PATENTS

There is only one synthesis patent starting from benzoin which reacts with urea in presence of potassiumhydroxide and sulfur.

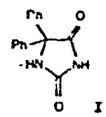
ABSTRACTS OF PATENTS

B1

DIPHENYLHYDANTOIN

Preparation

B1.1. 140814n 5,5-Diphenylhydantoin. Kolbeck, Winfried; Bayerlein, Friedrich (Diamalt A.-G.) U.S. 3,646,056 (Cl. 260-309.5; C 07d), 29 Feb 1972, Appl. 10,317, 10 Feb 1970; 2 pp.



I

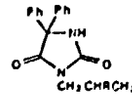
Treatment of benzoin and NH_2CONH_2 with aq. KOH and S gave 67–83% 5,5-diphenylhydantoin (I).

DIPHENYLHYDANTOIN

Miscellaneous

B1.2. 99: 209278k Assay method. Allen, Gerald John (Amersham International PLC) Eur. Pat. Appl. EP 92,344 (Cl. G01N33/54), 26 Oct 1983, GB Appl. 82/10,928, 15 Apr 1982; 14 pp. Assays for analytes (esp. antigens) are described which employ a specific binding partner for the analyte (esp. antibodies), a fluorescent compd.-analyte conjugate, and solid particles which have a material which is not a member of the binding pair but which controls the extent of binding of the labeled deriv. The solid particles are preferably of C, either coated with albumin or carrying a receptor for the binding partner. The albumin coating acts as a mol. sieve to accept labeled analytes but not antiserums and complexes thereof. For example, phenytoin amine was detd. with a phenytoin–fluorescein label, antiserum, and albumin-coated charcoal. Fluorescence was measured at 490 nm excitation and 520 nm emission. Serum phenytoin amine was detd. in the range 0–100 μg/mL.

B1.3. 99: 22468e 3-(γ-Amino-β-hydroxypropyl)-5,5-diphenylhydantoin derivatives. Zejc, Alfred; Kiec-Kononowicz, Katarzyna (Polska Akademia Nauk, Instytut Farmakologii) Pol. PL 114,751 (Cl. C07D403/06), 30 Dec 1982, Appl. 202,530, 30 Nov 1977; 4 pp.



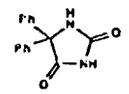
I

The title compds. I [R = OH, R^1 = 4-(R^2-substituted) piperazino, R^2 = CH_2CH_2OH, $CH_2CHMeOH$, Me, CH_2Ph, Ph, C_6H_4Cl-*p*, *p*-tolyl] were prepd. by treating I (R = OH, R^1 = Cl; RR^1 = O) with the corresponding *N*-substituted piperazine. Thus, 5,5-diphenylhydantoin Na salt 27.2 and then epichlorohydrin 9.2 g were dissolved in H_2O 100 mL and the mixt. refluxed 1 h and then frozen. After 24 h the soln. was decanted and the solid recrystd. from PrOH to give 23 g (73%) I (RR^1 = O), which (3.1 g) was refluxed 6 h with *N*-(β-hydroxyethyl)piperazine 1.4 g in PhMe 20 mL to give 2.7 g (65%) I [R = OH, R^1 = 4-(β-hydroxyethyl)piperazino].

B1.4. 98: 122427p Stabilization of glucose oxidase apoenzyme. Ruppchock, Patricia A.; Tyhach, Richard J. (Miles Laboratories, Inc.) U.S. US 4,366,243 (Cl. 435-7; C12N9/04), 28 Dec 1982, Appl. 255,310, 17 Apr 1981; 17 pp. Glucose oxidase apoenzyme is stabilized by poly(vinyl alc.) and serum albumin for ligand binding assays. The stabilized apoenzyme can be incorporated into test strips for immunoassays. In such assays an FAD–antigen conjugate is the label, and FAD–antigen conjugate which is not bound to the antibody is available for glucose oxidase apoenzyme activation. For example, test strips were prepd. for dinitrophenyl caproate immunoassay which contained buffer, a glucose oxidase detection system, apoglucose oxidase, dinitrophenol antibody, and dinitrophenol–FAD conjugate. Inclusion of poly(vinyl alc.) and albumin increased the heat stability of the test strips. Test strips for theophylline and phenytoin are also described.

B1.5. 98: 6845de Homogeneous specific binding assay test device having a copolymer enhancing substance. Tabb, David L.; Tyhach, Richard J. (Miles Laboratories, Inc.) U.S. US 4,362,697 (Cl. 422-56; G01N33/52), 07 Dec 1982, Appl. 255,759, 20 Apr 1981; 15 pp. Test strips are described for ligand detn. by homogeneous specific binding assays with reflection spectrometric detection. The test strips are impregnated with the appropriate reagents and an enhancer substance (e.g. Gafquat). For example, *N*-(2,4-dinitrophenyl)-ε-aminocaproic acid was detd. by test strips impregnated with apoglucose oxidase, 2,4-DNP–FAD conjugate, antibody, and a glucose oxidase detection reagents. This system responded to 2,4-DNP by exhibiting color due to the activation of apoglucose oxidase by the 2,4-DNP-FAD conjugate. The presence of Gafquat 734 markedly improved the color response. Theophylline and phenytoin were also detd. by the title system.

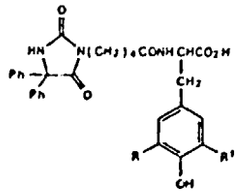
B1.6. 97: 66393q Fluorescent reagent and method for determining immunofluorescence. Tsay, Yuh Geng; Chen, Janet H.; Palmer, Richard J. (International Diagnostic Technology, Inc.) Eur. Pat. Appl. EP 47,459 (Cl. G01N33/58), 17 Mar 1982, US Appl. 185,235, 08 Sep 1980; 23 pp. Fluorescent diagnostic



I

reagents are prepd. which contain a hydrophobic hapten, a hydrophilic compd. such as an aminoglycoside, peptide, protein, or *polyacrylamide hydrazine* [30601-03-7], and a hydrophobic fluorescent compd. such as a deriv. of *fluorescein* [2321-07-5], *umbelliferone* [93-35-6], or *fluorescamine* [38183-12-9]. The hydrophobic hapten and the hydrophobic fluorescent compd. are both bound to the hydrophilic compd. but sepd. from each other. The reagents are used in the solid-phase fluorescence immunoassay of e.g. *diphenylhydantoin* (I) [57-41-0], *phenobarbital* [50-06-6], and *primidone* [125-33-7] in blood serum and eliminate the disadvantages of previously used reagents. Thus, for the detn. of the hydrophobic compd. I, a reagent was prepd. by coupling a carboxylated deriv. of I and *FITC* [27072-45-3] with the hydrophilic compd. *gentamicin* [1403-66-3]. The resulting hydrophilic conjugate has increased water soly., less susceptibility to fluorescence quenching by albumin and other serum proteins, and improved antigenicity.

B1.7. 89: 129930v Labeled 5,5-diphenylhydantoin derivatives for radioimmunoassay. Parsons, George H., Jr.; Eller, Thomas (Baxter Travenol Laboratories, Inc.) U.S. 4,092,479 (Cl. 548-312; C07D233/72), 30 May 1978, Appl. 673,853, 05 Apr 1976; 4 pp. Radioiodinated derivs. of hydantoin I (R = R¹ = H)



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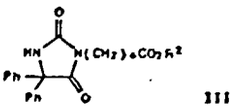

III

(II), useful in radioimmunoassays, were prepd. Thus, 5,5-diphenylhydantoin 3-Na salt was treated with $Br(CH_2)_4CO_2Me$ to give hydantoinvaleric acid ester III (R^2 = Me), which was hydrolyzed to III (R^2 = H), which was condensed with tyrosine via the $ClCO_2Et$ mixed anhydride method to give II. II was iodinated with $Na^{125}I$ to give I (R = ^{125}I, R^1 = H; R = R^1 = ^{125}I). The radioiodinated derivs. were used in the radioimmunoassay of 5,5-diphenylhydantoin in rabbits.

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B2

ISONIAZID

PATENTS

1967-1985

ANALYSIS OF THE ABSTRACTS OF PATENTS

Two patents are claimed for the preparation of isoniazid. B2.1. starts from isonicotinic acid and B2.2. from isonicotinic nitrile.

ABSTRACTS OF PATENTS

B2

ISONIAZID

Preparation

B2.1. 120269p Carboxamides and carbohydrazides. Stanley, Robert H.; Shaw, Barry Leigh (British Titan Ltd.) Ger. Offen. 2,364,059 (Cl. C 07c, B 01j), 18 Jul 1974, Brit. Appl. 513/73, 04 Jan 1973; 10 pp. Five $RCOR^1$ (R = Me, Ph, or 4-pyridyl; R^1 = NHPh or $NHNH_2$) were prepd. in 80–99% yield by reaction of RCO_2H with R^1H in the presence of $(BuO)_4M$ (M = Ti or Zr).

B2.2. 96629f Isonicotinic hydrazide. Seefluth, Horst; Moll, Karl K.; Baltz, Hans; Bruesehaber, Ludwig; Schrattenholz, Gisela Ger. (East) 63,493 (Cl. C 07d), 05 Sep 1968, Appl. 27 Dec 1967; 3 pp. An improved method for the prepn. of the title compd. (I) from isonicotinonitrile (II) and hydrazine hydrate (III) is described. Heating (100°) II in aq. soln. (10–50%) in the presence of an alk. catalyst such as the oxide, hydroxide, or carbonate of an alkali metal and addg. III dropwise results in improved yields of I and without the formation of insol. by-products.
E. Tobler

ISONIAZID

Miscellaneous

B2.3. 89: 204222w Pharmaceutical preparation specific for nodular thelitis. Laboratoire TECHNA Fr. Demande 2,361,117 (Cl. A61K47/00), 10 Mar 1978, Appl. 76/24,840, 09 Aug 1976; 6 pp. A topical prepn. for treating nodular thelitis in ruminants contains *kanamycin monosulfate* [25389-94-0], *hexamidine isethionate* [659-40-5], *isoniazid* [54-85-3], and *diaminodiphenyl sulfone* [80-08-0] in an oil-in-water emulsion. The preferred vehicle is 10 parts DMSO to 80 parts of a lanolin, lanette N, and propylene glycol mixt. After several weeks of treatment with the prepn. the nodules become soft and cease being painful. In most cases, the nodules eventually disappear.

B2.4. 93: 49669n Technetium-99m-labeled isonicotinic acid hydrazide and a pharmaceutical agent containing this compound. Yamada, Norihisa; Koizumi, Kiyoshi; Hisada, Kinichi (Ikeda Mohando Co., Ltd.) Ger. Offen. DE 3,216,026 (Cl. C07D213/86), 11 Nov 1982, JP Appl. 81/65,981, 30 Apr 1981; 20 pp. ^{99m}Tc-labeled isonicotinic acid hydrazide was prepd. by reacting $Na^{99m}TcO_4$ with isonicotinic acid hydrazide in the presence of a reducing agent. ^{99m}Tc-labeled isonicotinic acid hydrazide was useful in diagnosing tumors (Yoshida sarcomas in rats and Ehrlich ascites tumors in mice).

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B3

LIDOCAINE.HCL

PATENTS

1967-1985

APPENDIX P16

ANALYSIS OF THE ABSTRACTS OF PATENTS

The only patent abstracted concerns a proces. in which 2,6-xylidine reacts with diethyl diethylaminomalonate.

ABSTRACTS OF PATENTS

B3

LIDOCAINE.HCL

Preparation

B3.1. 101111g ω-Diethylamino-2,6-dimethylacetanilide. Nitta, Yoshihiro; Takamura, Keiichi; Asada, Takaaki (Chugai Pharmaceutical Co., Ltd.) Japan. 72 24,547 (Cl. C 07c), 06 Jul 1972, Appl. 66 28,041, 04 May 1966; 3 pp. 2,6-Xylidine (1 mole) was made to react with >10 (preferably, 12–18) moles diethyl diethylaminomalonate, the reaction mixt. treated with an inorg. acid, bis(2,6-dimethylanilide) diethylaminomalonate salt removed, and the residual 2,6-dimethylanilide monoethyl diethylaminomalonate heated in the presence of an inorg. acid to give the title product, useful as a local anesthetic.

Hiroshi Kataoka

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B4

NIACIN

PATENTS

1967-1985

APPENDIX P17

ANALYSIS OF THE ABSTRACTS OF PATENTS

42 Synthesis patents reflect significant research activity in this field.

Hydrolysis of cyanopyridine is claimed in the following patents: B4.13., B4.14. and B4.17..

Oxidation of ß-picoline is claimed in the following patents: B4.5., B4.7., B4.9., B4.11., B4.20. - B4.22., B4.24. - B4.27., B4.29., B4.30., B4.33., B4.35., B4.37., B4.39. and B4.42.. In B4.25. a yield of 98.3% is indicated with 97.4% purity. The yield in B4.42. is 92%..

Oxidation of 5-ethyl-2-methylpyridine is claimed in the following patents: B4.7., B4.8., B4.11., B4.12., B4.15., B4.18., B4.19., B4.20., B4.23., B4.32., B4.35., B4.38. and B4.40.In B4.8. a yield of 91% is indicated with a purity of 99.8%, in B4.32. 84-95% yield and 99.6% purity are given.

The use of complex hydrides for synthesis of niacin is described in B4.6..

Patents B4.43. - B4.47. describe processes for the purification of niacin, in B4.48. - B4.50. processes for removal of isonicotinic acid and recovery from mother liquors are described.

ABSTRACTS OF PATENTS

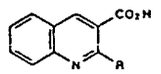
B4

NIACIN

Preparation

B4.1.

102: 113321y **Oxidation of alkyl groups to carboxyl groups under basic conditions.** American Cyanamid Co. Jpn. Kokai Tokkyo Koho JP 59,199,637 [84,199,637] (Cl. C07B3/00), 12 Nov 1984, US Appl. 485,769, 18 Apr 1983; 6 pp. Alkyl groups were

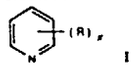


I

oxidized by M_mO_n (M = Cu, Co, Ag; m = 1, 2; n = 2–6) at 25–95° under basic conditions. Thus, 20 mL 15% NaOCl was added to a soln. of CuO 3.8, H_2O 7.5, 50% aq. NaOH 3, and quinoline deriv. (I; R = Me) 1.0 g at 70° and stirred 18 h to give 92% dicarboxylic acid I (R = HO_2C).

B4.2.

102: 102453s **Electrochemical oxidation of pyridine bases.** Toomey, Joseph E., Jr. (Reilly Tar and Chemical Corp.) U.S. US 4,482,439 (Cl. 204–78; C25B3/02), 13 Nov 1984, Appl. 597,014, 05 Apr 1984; 7 pp. Improved electrochem. oxidns. of I were carried out



I

in a membrane cell on a PbO_2 anode. In I, x = 1–3 and R = $-CH_3$, a C_{3-6} primary or secondary alkyl, a C_{3-6} cycloalkyl, an aralkyl of the formula [$-(CH_2)_n$–aryl], where n = 1–3, $-(CH_2)_mCOR^1$ or $-(CH_2)_mCHOHR^1$, where m = 0–5 and R^1 = H, or a C_{1-6} cycloalkyl, aryl or aralkyl group having C_{3-6} and wherein 2 adjacent R groups on the ring may be a fused cycloaklyl or a fused aryl group. Thus, 2-picoline was oxidized to picolinic acid at c.d. 20 mA/cm² to give a product yield of 80% and a current efficiency of 67%. Using c.d. 80 mA/cm², current efficiencies of ~90% were obtained in subsequent expts.

B4.3.

99: 139754m **Aromatic or heteroaromatic carboxylated compounds.** Fox, Marco; Bencini, Elena (Montedison S.p.A.) Eur. Pat. Appl. EP 81,384 (Cl. C07C51/10), 15 Jun 1983, IT Appl. 81/25,502, 09 Dec 1981; 31 pp. RCO_2R^1 (R = arom., heteroarom.; R^1 = H, alkyl, cation) were prepd. by treating an arom. or heteroarom. halide with CO in the presence of a Co carbonyl, an org. halide, and an acid acceptor. Thus, 2-naphthoic acid was prepd. in 91% yield by carbonylating 2-chloronaphthalene in the presence of $Co(CO)_8$, K_2CO_3, and $ClCH_2CO_2Me$ in MeOH, followed by sapon.

Hughes, Leslie Richard (Imperial

B4.4.

97: 54017g **Nicotinic acid.** Kuliev, A. M.; Dzhafarov, E. D.; Kulieva, D. M.; Shakhgel'diev, M. A. (Institute of the Chemistry of Additives, Academy of Sciences, Azerbaidzhan S.S.R.) U.S.S.R. SU 910,617 (Cl. C07D213/80), 07 Mar 1982, Appl. 2,851,447, 18 Apr 1980. From *Otkrytiya, Izobret., Prom. Obraztsy, Tovarnye Znaki* 1982, (9), 83. *Nicotinic acid* [59-67-6] is produced from 3-alkylpyridine by ferm. with *Bacillus* species.

B4.5.

90: 87294d **Highly selective oxidation for manufacturing pyridine carboxylic acids.** Stoppani, Luigi, S.p.A. Belg. 868,261 (Cl. C07D), 16 Oct 1978, Ital. Appl. 77/25,812, 18 Jul 1977; 13 pp. The alkali dichromate oxidn. of alkylpyridines at 150–300° and pH 4.5–8.5 yielded the resp. pyridinecarboxylic acids. β-Picoline was treated with $Na_2Cr_2O_7$ in water at 250° and ≤38 kg/cm² to give nicotinic acid.

B4.6. 87: 135089c Nicotinic acid from pyridine. Kawamata, Motoo; Fujikake, Shiro; Tanabe, Hidenori (Mitsui Toatsu Chemicals, Inc.) Japan. Kokai 77 36,670 (Cl. C07D213/80), 22 Mar 1977, Appl. 75/110,875, 16 Sep 1975; 3 pp. Nicotinic acid was prepd. by treating pyridine with CO_2 in the presence of a metal hydride. Thus, 420 mmol pyridine and 105 mmol $LiAlH_4$ in 100 mL THF was heated for 1 h and treated with 100 mL/min CO_2 at 0-5° for 3 h to give 62% nicotinic acid based on $LiAlH_4$. The yield was raised to 80-90% with dioxane or $BuOCH_2CH_2OBu$ as the solvent or with 20 kg/cm² CO_2 at 10°. NaH, LiH, $NaBH_4$, or $LiAlH(OCMe_3)_3$ instead of $LiAlH_4$ gave 24-58% yields. I. Matsumoto

B4.7. 87: 135084x Niacin. Lundin, Sten Tore; Jaraas, Sven Gunnar (Aktiebolag Bofors) Ger. Offen. 2,647,712 (Cl. C07D213/80), 18 May 1977, Swed. Appl. 75/11,816, 22 Oct 1975; 24 pp. Niacin was prepd. (up to 68% selectivity) by the oxidn. of 3-picoline or 2-methyl-5-ethylpyridine in the gas phase in the presence of a V_2O_5 catalyst with TiO_2 promoter.

B4.8. 86: 139875h Nicotinic acid. Masuda, Keiji; Kizawa, Hidenori; Otaki, Yasuhiko (Nippon Soda Co., Ltd.) U.S. 4,001,257 (Cl. 260 295.5R; C07D213/55), 04 Jan 1977, Appl. 303,028, 02 Dec 1972; 7 pp. Nicotinic acid was produced in ~91% yield with 99.8% purity by oxidizing 2-methyl-5-ethylpyridine with 100-8% of the stoichiometric amt. of HNO_3 at 225-35°, 30-45 kg/cm² and pH 2.1-2.4 for 12-16 min.

B4.9. 86: 121171r Nicotinic or isonicotinic acid from 3- or 4-picolines. Treszczanowicz, Edward; Lipka, Barbara; Burzynska, Barbara; Musierowicz, Jerzy; Stefaniak, Lech; Wawer, Antoni; Grzybowska, Maria (Instytut Chemii Przemyslowej) Pol. 75,601 (Cl. C07D31/38), 20 Dec 1975, Appl. 155,466, 19 May 1972; 4 pp. The known prep. methods of the title acids were simplified. Thus, ammoxidn. of 3- or 4-picoline in the presence of 15-35% by wt. H_2O gave 3- or 4-cyanopyridine, which was sepd. by sublimation at 10-14° and hydrolyzed in NH_4OH. The ammonium salts of the acids were thermally decompd. to give high purity title acids. K. Butkiewicz

B4.10. 85: 123773s Nicotinic acid. Suvorov, B. V.; Kagarlitskii, A. D.; Emel'yanov, V. L. (Institute of Chemical Sciences, Academy of Sciences, Kazakh S.S.R.) U.S.S.R. 289,731 (Cl. C07D31/34), 05 Mar 1976, Appl. 1,365,607, 04 Sep 1969. From *Otkrytiya, Izobret., Prom. Obraztsy, Tovarnye Znaki* 1976, 53(9), 216. Nicotinic acid prepn. by ammoxidn. of pyridine derivs. and hydrolysis and decarboxylation of the intermediate isocinchomeronic dinitrile was improved by using substituted 2- or 5-alkenylpyridines as the starting materials.

B4.11. 85: 94233h Nicotinic acid from β-alkylpyridines. Inoue, Toshio; Hara, Tadanori (Nippon Steel Chemical Co., Ltd.) Japan. Kokai 76 29,483 (Cl. C07D213/80), 12 Mar 1976, Appl. 74/100,952, 04 Sep 1974; 3 pp. Nicotinic acid was prepd. by gas-phase oxidn. of β-alkylpyridines with a V_2O_5-B_2O_3 catalyst on TiO_2. Thus, an aq. soln. of vanadyl oxalate and H_3BO_3 was kneaded with TiO_2, pelletized, and calcined at 500° to give a 4:1 molar V_2O_5-B_2O_3 catalyst (10% V_2O_5 based on TiO_2). The catalyst (500 ml) was packed into a tubular reactor and treated with 800 hr^{-1} air, 30 g 2-methyl-5-ethylpyridine (I)/m^3 air, and 35 g steam/g I at 285° 15 days to give 66% nicotinic acid, 98% pure. I. Matsumoto

B4.12. 84: 121660h **Nicotinic acid.** Suvorov, B. V.; Kagarlitskii, A. D.; Lebedeva, O. B.; Pavlov, B. A.; Kutzhanov, R. T. (Institute of Chemical Sciences, Academy of Sciences, Kazakh S.S.R.) U.S.S.R. 236,473 (Cl. C07d), 25 Dec 1975, Appl. 1,172,555, 17 Jul 1967. From *Otkrytiya, Izobret., Prom. Obraztsy, Tovarnye Znaki* 1975, 52(47), 169. Nicotinic acid prepn. by ammoxidn. of alkylpyridines was improved by using 2-methyl-5-ethylpyridine; the latter was prepd. from isocinchomeronic acid dinitrile by sapon. with aq. NH_3 and decarboxylation of the intermediate ammonium salt in an autoclave at 250–80° and 40–65 atm.

B4.13. 84: 90016w **Pyridine nitriles and carboxylic acids.** Gelbein, Abraham P.; Sze, Morgan C.; Paustian, John E. (Lummus Co.) U.S. 3,929,811 (Cl. 260-295.5R; C07D), 30 Dec 1975, Appl. 415,991, 15 Nov 1973; 8 pp. Nicotinonitrile (I) was prepd. by reaction of 2,3-lutidine or 2-methyl-5-ethylpyridine with NH_3 in the absence of O and in the presence of V_2O_5 catalyst; I was hydrolyzed by heating with aq. NH_3 to give an aq. soln. of NH_4 nicotinate, which was stripped with steam or steam–N at elevated temp. to give nicotinic acid. A flow diagram of the app. was given.

B4.14. 178572q **Catalytic acid hydrolysis of aromatic or heterocyclic nitriles to their corresponding acids.** Norton, Richard V. (Sun Ventures, Inc.) Ger. Offen. 2,438,263 (Cl. C07C), 17 Apr 1975, US Appl. 404,966, 10 Oct 1973; 8 pp. Arom. nitriles, e.g., p-$C_6H_4(CN)_2$, were hydrolyzed to the corresponding carboxylic acids by refluxing the aq. nitrile soln. with an acid catalyst, e.g., AcOH or $EtCO_2H$, at ~250°, followed by distn. to remove the acid catalyst in the form of the amide. Hydrolysis of *m*-$C_6H_4(CN)_2$ under these conditions gave 86% *m*-$C_6H_4(CO_2H)_2$; 2,6-$C_{10}H_6(CN)_2$ and nicotinonitrile were also hydrolyzed.

B4.15. 164003t **Pyridinecarboxylic acids.** Yasui, Hirochi; Inoue, Toshio; Hara, Tadanori (Nippon Steel Chemical Industry Co., Ltd.) Japan. Kokai 75 46,670 (Cl. C07D, B01J), 25 Apr 1975, Appl. 73 92,409, 20 Aug 1973; 4 pp. Pyridinecarboxylic acids were prepd. by vapor phase contact oxidn. of alkylpyridines or quinoline (I) in the presence of catalysts contg. V_2O_5, Fe_2O_3, and SnO_2. Thus, a mixt. of vanadyl oxalate, $Fe(NO_3)_3$, $Sn(NO_3)_4$, and TiO_2 in H_2O was molded, dried, and calcined at 500° to form a catalyst (100:15:100 molar V_2O_5-Fe_2O_3-SnO_2; 1:10 V_2O_5-TiO_2 by wt.). A mixt. of 2-methyl-5-ethylpyridine (II), air, and steam was passed on the catalyst at 290° and 1000 hr^{-1} space velocity to give 60.8 wt.% nicotinic acid (III). Selectivity coeff. for III was 60.6 mole%. I and 3-ethylpyridine were also used in place of II. K. Sempuku

B4.16. 97037s **Pyridine derivatives.** Gelbein, Abraham P.; Sze, Morgan C.; Paustian, John E. (Lummus Co.) Ger. Offen. 2,403,121 (Cl. C07D), 22 May 1975, US Appl. 415,991, 15 Nov 1973; 18 pp. Nicotinonitrile was prepd. in 10 mole % yield by treating 2,3-dimethylpyridine with NH_3 on a 40% V_2O_5 on SiO_2-Al_2O_3 (87:13) catalyst with a pore vol. 0.75 cm^3/g, surface area 200 m^2/g and particle size 60μ at 371° and a linear spatial velocity of 600 hr^{-1}.

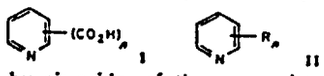
B4.17. 97036r **Pyridine mononitrile.** Sze, Morgan C.; Gelbein, Abraham P.; Paustian, John E. (Lummus Co.) Ger. Offen. 2,435,134 (Cl. C07D), 22 May 1975, US Appl. 415,991, 15 Nov 1973; 30 pp. Nicotinonitrile was manufd. continuously by treating 2,3-lutidine or 2-methyl 5-ethylpyridine with NH_3 on a catalyst contg. 40% V_2O_5 on SiO_2-Al_2O_3(87:13) with pore vol. 0.75 cm^3/g, surface area 200 m^2/g, and particle size 60μ at 440°. The nitrile was hydrolyzed to a nicotinic acid.

B4.18. 43205b Nicotinic acid. Masuda, Keiji; Kizawa, Hidenori; Otaki, Yasuhiko (Nippon Soda Co., Ltd.) Brit. 1,385,920 (Cl. C07D), 05 Mar 1975, Appl. 18,896/73, 19 Apr 1973; 7 pp. Addn. to Brit. 1,385,919. Isocinchomeronic acid-free nicotinic acid (I) was prepd. from dialkylpyridine mixts. by successive HNO_3 oxidn., concn. of the reaction mixt., and cooling. Thus, I was prepd. continuously by treating a mixt. of 2-methyl-5-butylpydine 60, 2-propyl-5-ethylpyridine 30, and 2-methyl-5-ethylpyridine (II) 10 wt % with the quantity of HNO_3 theor. required for the oxidn. at 230° and 35 kg/cm² for 10 min. The reaction-terminated soln., pH 2.2, was concd. and the pH adjusted to 3.2 by adding II; subsequent cooling to 0-5° gave 73.3 wt. % of 99% pure I. The mother liquor was recycled.

B4.19. 28116e Nicotinic acid. Nippon Soda Co., Ltd. Fr. Demande 2,228,776 (Cl. C07d), 06 Dec 1974, Appl. 72 40,742, 16 Nov 1972; 5 pp. Addn. to Fr. 2,165,850 (See Ger. Offen. 2,256,508 CA 79;31894e). Nicotinic acid was manufd. in 68.5% yield with 96.4% conversion by oxidizing a mixt. of 2-methyl-5-ethylpyridine, 2-propyl-5-ethylpyridine, and 2-methy-5-butylpyridine (1:3:6) with the stoichiometric amt. of 28% HNO_3 at 230° and 35 kg/cm² for 10 min.

B4.20. 120493g Pyridinecarboxylic acids from alkylpyridines. Nakajima, Kazuhisa; Sato, Tsuneo (Japan Synthetic Chemical Industry Co., Ltd.) Japan. Kokai 74 61,173 (Cl. 16 E431), 13 Jun 1974, Appl. 72 102,566, 12 Oct 1972; 4 pp. Alkylpyridines, e.g., β-picoline, γ-picoline, or collidines, are oxidized to pyridinecarboxylic acids in the gas phase with O-contg. gas in the presence of a V oxide catalyst contg. Ti, Al, and (or) Ni oxides. Thus, 118 g V_2O_5 and 246 g $TiCl_4$ in concd. HCl was dild. with H_2O, adjusted to pH 7.0, and the solid heated to 500° and pelletized. The catalyst (40 ml) of 1.07:1 V–Ti atomic ratio was treated at 335° with 172 g 6.08% aq. β-picoline and 70.5 l. air over 1 hr to give 81.2% nicotinic acid, together with 3.91 g unchanged β-picoline. Similarly, γ-picoline and 5-ethyl-2-picoline were oxidized to isonicotinic and nicotinic (sic) acids, resp.

B4.21. 120789n Pyridinecarboxylic acids. Hanotier, Jacques D. V.; Hanotier-Bridoux, Monique G. S. (Labofina S. A.) Ger. Offen. 2,242,386 (Cl. C 07d), 07 Feb 1974, Fr. Appl. 72 26,867, 26 Jul 1972; 9 pp. Five pyridinecarboxylic acids I (n = 1, 2, or 3)



were manufd. by air-oxidn. of the appropriate alkylpyridine derivs. II (R_n = 2, 3, or 4-Me, 3,4-Me_2, 4-Et, or 2,4,6-Me_3) over a Co(III) carboxylate catalyst with maintaining a definite Co(III) ion concn., i.e. >0 1 g/l., by addn. of regenerating AcH. Thus, 100 l. air/hr was passed into 0.120*M* II (R_n = 2-Me) and 0.240*M* Co(III) acetate in HOAc 6 hr at 60°, 10 kg/cm² air, and >0.1 g/l. Co(III) ion concn. (maintained by addn. of 35% AcH in HOAc at 5 g/hr) to give, at 100% selectivity, 95% I (R_n = 2-CO_2H).

B4.22. 146416t Pyridinecarboxylic acids. Yokoyama, Ryoichi; Sawada, Katsumi (Teijin Chemicals Ltd.) Brit. 1,330,135 (Cl. C 07d, B 01j), 12 Sep 1973, Appl. 47,743/70, 07 Oct 1970; 8 pp. Pure 3- and 4-pyridinecarboxylic acids were prepd. in high yield by air or O oxidn. of β- or γ-picoline at 350-450° in the presence of steam and a V oxide-Cr oxide catalyst contg. a metal oxide promotor, e.g. Sn and Sb oxide. Thus, 0.8 g Sb_2O_3 and 4 g $SnCl_4.3.5H_2O$ sep. dissolved in HCl were added to 25 g NH_4VO_3 and 25 g $(NH_4)_2CrO_4$ in 1 l. H_2O. The suspension was poured onto 100 ml SiC carrier sp. surface area 1.2 m²/g and av. particle diam. 2.0 mm and the impregnated product presintered at 400–50° and calcined 2 hr at 700°. γ-Picoline at a concn. of 25.0 g/Nm³ of air was continuously passed 3 hr with 195 ml H_2O/g of γ-picoline/hr and 200 l./hr air through a reactor tube contg. 40 ml catalyst at 350°. The air was divided into 2 portions; one portion was passed through a H_2O-evaporator and the other through a γ-picoline-evaporator. The portions were mixed and fed into the reactor via a preheater. Crude isonicotinic acid, 106.0 wt. % of 96.1% purity, was sepd. from the discharged vapor by air- and water-coolers.

B4.23. 31894e Nicotinic acid. Masuda, Keiji; Kizawa, Hidenori; Otaki, Yasuhiko (Nippon Soda Co., Ltd.) Ger. Offen. 2,256,508 (Cl. C 07*d*), 24 May 1973, Japan. Appl. 71 92,142, 17 Nov 1971; 23 pp. Nicotinic acid was prepd. in 85–90% yield by continuously oxidizing 2-methyl-5-ethylpyridine with 100–117% of the stoichiometric amt. of HNO_3 at 205–25° and 30–45 kg/cm² with residence times of 7–45 min.

B4.24. 29627f Catalytic manufacture of pyridinecarboxylic acids. Teijin Chemicals Ltd. Fr. 2,110,607 (Cl. C 07*d*, B 01*j*), 07 Jul 1972, Appl. 70 38,300, 23 Oct 1970; 17 pp. Oxidn. catalysts for picolines contain V and Cr (in the ratio 1:0.5–1), Sb_2O_3 and $SnCl_4$, Ge_2O_3, $NbCl_5$, $TaCl_3$, Ga_2O_3, or $ZrCl_4$, and are calcined at >560°. Thus, a catalyst was prepd. by treating 25 g NH_4VO_3 and 25 g $(NH_4)_2CrO_4$ in 1 l. H_2O with 0.8 g Sb_2O_3 and 4 g $SnCl_4.3.5H_2O$, pouring over 100 ml SiC, prefritting at 400–50°, and calcining for 2 hr at 700°. γ-Picoline was quant. oxidized over the catalyst to 96.1% pure isonicotinic acid.

B4.25. 139828j Nicotinic acid from β-picoline. Yokoyama, Ryoichi; Sawada, Katsumi (Teijin Chemical Industry Co., Ltd.) Japan. 72 27,515 (Cl. C 07*d*, B 01*j*), 22 Jul 1972, Appl. 68 30,390, 07 May 1968; 3 pp. Addn. of water to O in the catalytic vapor-phase oxidn. of β-picoline (I) increased the yield of nicotinic acid (II) by 20–40 wt. %. E.g., O (200 l./hr) contg. 25 g I/m³ O and 133 ml H_2O/g I/hr were fed to 100:15:4:1 V-Cr-Sm-Sb catalyst on silicon carbide carrier at 365–75° to give 98.3% II (purity 97.4%).

K. Sempuku

B4.26. 126435d Pyridinecarboxylic acids. Kubo, Masayoshi; Horikawa, Takeshi (Daicell Co., Ltd.) Ger. Offen. 2,165,035 (Cl. C 07*d*), 13 Jul 1972, Japan. Appl. 70 122,247, 30 Dec 1970; 11 pp. Nicotinic acid (I) and isonicotinic acid were prepd. by oxidn. of β- or γ-picoline, resp., with O in the presence of Zr salts, Co acetate, Mn acetate, and NH_4Br. Thus, 20 l. air/hr was passed into 186 parts β-picoline, $ZrO(OAc)_2$, Co acetate, Mn acetate, and NH_4Br (each 1.86 parts) in 559 parts HOAc at 200° and 20 kg/cm². After 2 hr, 80% I was obtained.

B4.27. 61822f Pyridinecarboxylic acids. Dieterich, Dieter (Farbenfabriken Bayer A.-G.) Ger. Offen. 2,055,102 (Cl. C 07*d*), 18 May 1972, Appl. P 20 55 102.4, 10 Nov 1970; 24 pp. Se loss in the oxidn. of alkylpyridines to dinicotinic acid is reduced by using oleum contg. ≥60% SO_3 at 270–300°. Thus 138 g pyridine stock contg. 85.5% 3,5-dimethyl-, 7.3% 3-ethyl-5-methyl-, and 1.4% 3-methylpyridine in 1.5 kg 65% oleum was added during 2–3 hr at 270–90° to 400 g H_2SO_4, 100 g 65% oleum, and 4 g Se, preheated to 225°, to give 76% dinicotinic acid. Nicotinic and isonicotinic acids were similarly prepd. The dinicotinic acid was also recovered as the di-Me, di-Et, di-Pr, and diisopropyl esters.

B4.28. 85713b Continuous manufacture of isocinchomeronic acid and nicotinic acid. Avedikian, Souren Z. Ger. Offen. 2,125,653 (Cl. C 07*d*), 09 Dec 1971, US Appl. 28 May 1970; 17 pp. A continuous process is described by which Cu isocinchomeronate (prepd. according to U.S. 3,081,307) is converted to niacin by treating it with NaOH, sepg. the CuO, and treating the Na isocinchomeronate with H_2SO_4 to give the free acid, which is continuously decarboxylated under pressure.

B4.29. 14348a Pyridine carboxylic acids. Costea, Teodor; Camarasu, Constantin (Institutul de Cercetari Chimico-Farmaceutice) Rom. 53,589 (Cl. C 07*d*), 25 Aug 1971, Appl. 05 Feb 1968; 2 pp. High yields of the title compds. were obtained by continuously refluxing an alkylpyridine sulfate, NH_4 vanadate, and counterflow HNO_3 vapors at atm. pressure, and the resulting mother liquor mixed with alkylpyridine up to the initial concn. and recycled.

C. T. Papadopol Calimah

B4.30. 110193w Nicotinic acid. Tyupalo, N. F.; Yakobi, V. A.; Kozorez, L. A.; Gangrskii, P. A.; Nikiforov, A. A. (Lenin, V. I., Polytechnic Institute, Kharkov) U.S.S.R. 306,848 (Cl. A 61k, C 07d), 21 Jun 1971, Appl. 02 Jul 1969; no pp. given. From *Otkrytiya, Izobret., Prom. Obraztsy, Tovarnye Znaki* 1971, 48(20), 15-16. Nicotinic acid was prepd. by the oxidn. of 3-methylpyridine by an O_2–air mixt. in H_2SO_4 contg. a mixt. of salts of variable valence metals, such as Mn and Cr.

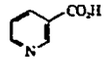
B4.31. 98452v Nicotinic acid. Skryabin, G. K.; Golovleva, L. A. (Institute of Biochemistry and Physiology of Microorganisms, Academy of Sciences, U.S.S.R.) U.S.S.R. 302,341 (Cl. C 07d), 28 Apr 1971, Appl. 30 Dec 1969; From *Otkrytiya, Izobret., Prom. Obraztsy, Tovarnye Znaki* 1971, 48(15), 80. Nicotinic acid was prepd. by the oxidn. of 3-methylpyridine using *Nocardia* microorganisms.

B4.32. 48924e Nicotinic acid. Stocker, August; Marti, Othmar; Pfannmatter, Theodul; Schreiner, Gerhart; Brander, Stephan (Lonza Ltd.) Ger. Offen. 2,046,556 (Cl. C 07d), 22 Apr 1971, Swiss Appl. 24 Sep 1969; 11 pp. Nicotinic acid (I) (99.6% pure) was manufd. in 84–95% total yield by oxidn. of 2-methyl-5-ethylpyridine with 33% HNO_3 at 330°, 290 atm gage, 5.5 sec residence time, and 95% conversion in a tubular flow reactor, crystn. of I·HNO_3 salt at 0°, and crystn. of I liberated at 95° and pH 3.3.

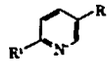
B4.33. 48914b Catalytic manufacture of pyridinecarboxylic acids. Yokoyama, Ryoichi; Sawada, Katsumi (Teijin Ltd.) Ger. Offen. 1,940,320 (Cl. C 07d, A 61k), 25 Feb 1971, Appl. 07 Aug 1969; 22 pp. β-Picoline or γ-picoline (I) yields 64–79 mole % β-picolinic or 68–94.5 mole % γ-picolinic acids (II), resp., when it is oxidized at 320–450° in the vapor phase with air contg. H_2O. The oxidn. is catalyzed by a mixt. of V and Cr oxides, contg. 1–15% Sn and Sb or Ge, In, Nb, W, Ga, Zr oxides. The catalyst was calcined at 560–850°. Thus, 25 g ammonium vanadate and 25 g ammonium chromate were dissolved in 1 l. H_2O, and 0.8 g Sb_2O_3 dissolved into a little amt. of HCl and 4 g $SnCl_4.3.5H_2O$ were added. This suspension was poured onto 100 ml. silicon carbide granules. The soaked granules were sintered at 400–450° and calcined 2 hr at 700°. An air stream contg. I and H_2O was passed over the catalyst at 350° 3 hr to give 80 mole % yield of 96.1% pure II.

B4.34. 64213g Nicotinic acid. Kimura, Goro; Takada, Minoru; Yamamoto, Kosuke (Mitsui Toatsu Chemicals Co., Ltd.) Japan. 70 31,179 (Cl. C 07d), 08 Oct 1970, Appl. 09 Jan 1967; 2 pp. An oligomer (I) obtained as a side product in a reductive dimerization of acrylonitrile with Na-Hg is hydrogenated, dehydrogenated, and the resulting 3-substituted-pyridine is oxidized. Thus 109 g I in 150 ml MeOH is subjected to catalytic redn. with 10 g Raney Co in an autoclave with 100 atm H at 120° 4 hr, the resulting piperidine deriv. heated 5 hr at 220° in an H stream with 20 g 10% Pd/C, the resulting pyridine deriv. gradually added to 2 kg concd. H_2SO_4 (d = 1.42), and the mixt. heated 2–3 hr to give 73 g nicotinic acid. Hiroshi Kataoka

B4.35. 45352q Nicotinic acid by oxidation of pyridines with nitric acid. Stocker, August; Marti, Othmar; Pfammatter Theodul; Schreiner, Gerhart (Lonza Ltd.) Ger. Offen. 1,956, .7 (Cl. C 07d), 11 Jun 1970, Swiss Appl. 08 Nov 1968-19 Sep 1969; 11 pp. The title compd. (I) was prepd. by oxidn. of II (R = Me or Et, R^1 = H or Me) or quinoline with 40–400% excess HNO_3 at



(I)



(II)

230–330° and 50–300 atm to give I.HNO_3 (Ia) and subsequent crystn. of I by adjusting aq. Ia to the isoelec. point of I with the starting pyridines. Thus, a mixt. contg. 6.3% II (R = Et, R^1 = Me) (IIa) and 28.1% HNO_3 was passed through a reactor tube 35 min at 239° and 56 atm, subsequently concd. by evapn. and cooled at 5° to give 354.2 g Ia. Ia was dissolved in H_2O, heated at 60°, adjusted to pH 3.3 by addn. of IIa, and heated at 90° to give 66.9% I. The combined mother liquors contg. 77.3 g I and 244.31 g IIa were mixed with IIa and HNO_3 to get the starting concns. and were recycled. KSPG

B4.36. 43476p Nicotinic and isonicotinic acid. Eilhauer, Dieter; Hoefling, Wilhelm; Reckling, Gerhard; Meinicke, Karl H.; Fahrig, Peter Ger. (East) 68,229 (Cl. C 07d), 05 Aug 1969, Appl. 15 Jul 1968; 2 pp. Crude pyridine base mixts. (b. 140–50°) are treated with aq. HCHO soln. to give a distillate free of hydroxymethyl derivs. and a residue contg. methylolated compds. Oxidn. of these fractions yields nicotinic (I) and isonicotinic acid (II), resp. Thus, 815 kg picoline mixt., contg. 24% 4-picoline, 42% 3-picoline (III), 6% 2-picoline (IV), 18% 2,6-lutidine (V), and 8% 2-ethylpyridine (VI), was refluxed 40 hr with 835 kg 37% aq. HCHO soln. After steam distn., 700 kg hydroxymethyl-4-picoline mixt., contg. 40% H_2O, remained. This was added to 2800 kg 30 wt.% boiling aq. HNO_3 in 30 hr, and 1400 kg H_2O was distd. to give a distillate contg. <1% HNO_3. The reaction mixt. was dild. with 400 kg H_2O and the pH was adjusted to 3.5 with 10% NaOH to give 80% II. The steam distillate (1500 kg), representing a 36% aq. soln., composed of 58% III, 6% IV, 29% V, and 7% VI, was distd. to give a first fraction (560 kg) contg. 39% base, consisting of 17% III, 14% IV, 52% V, and 17% VI, and a second fraction (900 kg) contg. 39% base, consisting of 94% III, 5% V, and 1% VI. The latter mixt. (900 kg) was oxidized with 1450 kg $KMnO_4$ at 50–70° to give 180 kg I.

B4.37. 49785q Nicotinic acid. Suvorov, B. V.; et al. (Institute of Chemical Sciences, Academy of Sciences, Kazakh S.S.R. and Karaganda Metallurgical Plant) U.S.S.R. 235,764 (Cl. C 07d), 24 Jan 1969, Appl. 04 Nov 1966; *From Otkrytiya, Izobret., Prom. Obraztsy, Tovarnye Znaki* 1969, 46(6), 27. The title compd. is prepd. by oxidative ammonolysis of 3-picoline in the presence of a V oxide catalyst modified with Sn oxides, or promoted with W oxides followed by hydrolysis of the nicotinamide and nicotinonitrile. MGCL

B4.38. 68170f Nicotinic acid. Zundel, Jean Fr. 1,509,120 (Cl. C 07d), 12 Jan 1968, Appl. 28 Nov 1966, 3 pp. 5-Ethyl-2-methylpyridine (I) (350 g.), 1350 g. 60% HNO_3, and 700 ml. H_2O reacted in the autoclave at 160–80° and satd. with air under pressure until the oxidn. step was terminated, at 24 bars and 200°, the mixt. satd. with air and steam, cooled, and neutralized with Na_2CO_3 gave 237 g. nicotinic acid (II) [contg. 0.5–1% isocinchomeronic acid (III)]. Mother liquors contain 28 g. I, 29 g. II, and 17 g. III. A tech. procedure is also described.

B4.39. 37658s Nicotinic acid and isonicotinic acid. Ruetgerswerke und Teerverwertung A.-G. Brit. 1,132,746 (Cl. C 07*d*), 06 Nov 1968, Ger. Appl. 24 Jun 1965; 4 pp. Nicotinic acid or isonicotinic acid is prepd. by oxidn. of a substituted pyridine (3-alkylpyridine or 4-alkylpyridine) in an org. solvent which remains chem. unchanged, and the resulting soln. heated in the presence of SeO_2 to 130–200° with introduction of NO_2 into the soln. Thus, 94 g. 3-methylpyridine of 98% purity was dissolved in 750 g. 1,2,4-trichlorobenzene, 1 g. SeO_2 added, and at 130°, 0.5 g. NO_2/min. introduced to a total amt. 65 g. NO_2. The mixt. was heated to 180°, with continuation of addn. of NO_2 to an addnl. amt. of 70 g., cooled, and worked up to give 90 g. crude acid. The acid was dissolved in 400 ml. water and 40 ml. concd. HCl and adjusted to the isoelec. point with NaOH. The mother liquor was concd. to give a total of 79 g. nicotinic acid, m. 235–7°. From the trichlorobenzene soln., 11.7 g. and from the water mixt. 9.36 g. methylpyridine was obtained to give a total yield of nicotinic acid of approx. 85%. Similarly, an 87.8% yield of isonicotinic acid was obtained from 4-methylpyridine, and com. mixts. of 4-methylpyridine, 3-methylpyridine, and small amts. of 2,6- and 2,4-dimethylpyridine, 2-ethylpyridine, and 2-methylpyridine were converted to mixt. of isonicotinic and nicotinic acids. BRPN

B4.40. 37657r Nicotinic and isonicotinic acids. Aries, Robert Fr. 1,509,049 (Cl. C 07*d*), 12 Jan 1968, Appl. 28 Nov 1966; 3 pp. Alkyl- and dialkylpyridines are treated with reduced amts. of HNO_3 to give the title acids. Thus, a mixt. of 1.4 kg. 5-ethyl-2-methylpyridine, 5.4 kg. 60% HNO_3, and 2.8 l. water is agitated at 160°/18 atm., air introduced at 3500 l./hr. at up to 180°, air then introduced at 1000 l./hr., and steam introduced at 3000 l./hr. The mixt. is heated to 200°, the pressure increased to 24 atm., and the introduction of the air-steam mixt. continued (until CO_2 evolution stops) to give 1070 g. nicotinic acid. Similarly prepd. is isonicotinic acid. BDPF

B4.41. 104997t Nicotinic acid. Eastern Scientific-Research Coal-Chemical Institute (by N. D. Rus'yanova, N. V. Malysheva, L. P. Yurkina, and V. K. Kondratov). U.S.S.R. 191,562 (Cl. C 07*d*), Jan. 26, 1967, Appl. Oct. 12, 1965. The title compd. is prepd. by oxidn. of quinoline or its derivs., e.g. 8-hydroxyquinoline, with ozonized O. The process is simplified and yield increased by conducting the oxidn. in dil. AcOH at the b.p. of the reaction mixt. From *Izobret., Prom. Obraztsy, Tovarnye Znaki* 44(1), 35(1967). MGCL

B4.42. 90685n Preparation of nicotinic acid. Robert D. Lokkerg, Raymond A. Jensen, and William Buiter (to Chemlek Laboratories, Inc.). U.S. 3,313,821 (Cl. 260-295.5), April 11, 1967, Appl. Aug. 3, 1964; 4 pp. Compds. contg. a pyridine nucleus are converted to the salts and oxidized with $Na_2Cr_2O_7$ to prep. nicotinic acid (I) in high yields. Thus, β-picoline (II), H_2SO_4, 123, and water 786 g. is mixed, 596 g. $Na_2Cr_2O_7 \cdot 2H_2O$ added, and, in a sealed autoclave capable of withstanding 1000 psi, the mixt. was heated at 450° for 42 hrs. I (92%, yield) was isolated as described in U.S. 2,415,147 (C.A. 41, 2754g). I was also prepd. from β-picoline·HCl and the H_2SO_4 salts of β-picoline, 2-methyl-5-ethylpyridine, and quinoline. CNPN

NIACIN

Purification

B4.43. 170701q **Purification of pyridinecarboxylic acids.** Inoue, Toshio (Nippon Steel Chemical Industry Co., Ltd.) Japan. Kokai 74,124,070 (Cl. 16 E431), 27 Nov 1974, Appl. 73 35,590, 30 Mar 1973; 3 pp. Pyridinecarboxylic acids (I) were purified by passing gases contg. I through layers of adsorbent particles below the pptn. temp. of I. Thus, 30 g nicotinic acid (II) (purity 97%) in N was sublimed at 230° and 610 mm Hg and gaseous II passed at 230° over 339 g electrically fused Al_2O_3 (contg. 86% Al_2O_3; preheated 5 hr at 250°) to give 94.7% II (purity >99%). Porcelain Al_2O_3, SiO_2–Al_2O_3 (87:13), active terra alba, silicon carbide, and kieselguhr brick were also used. K. Sempuku

B4.44. 170685n **Recrystallization of pyridine derivatives having polar substituents.** Kato, Satoru; Inoue, Toshio; Hara, Tadanori (Nippon Steel Chemical Industry Co., Ltd.) Japan. Kokai 74 100,087 (Cl. 16 E431), 20 Sep 1974, Appl. 73 11,194, 29 Jan 1973; 3 pp. Pyridine derivs. with polar substituents are recrystd. from a solvent contg. H_2O and alcs. Thus, 15 g nicotinic acid of 98.7% purity, prepd. by gas-phase oxidn. of alkylpyridines, was recrystd. from 193 g 7:3 MeOH–H_2O with C to recover 82.3% colorless acid, >99.8% pure. Recrystn. from MeOH or H_2O alone gave a colored product. $MeOCH_2CH_2OH$–H_2O (7:3) was also a good solvent. Similarly, nicotinamide was recrystd. from 1:1 aq. EtOH. I. Matsumoto

B4.45. 170684m **Pyridinecarboxylic acid purification.** Inoue, Toshio (Nippon Steel Chemical Industry Co., Ltd.) Japan. Kokai 74 100,086 (Cl. 16 E431), 20 Sep 1974, Appl. 73 11,193, 29 Jan 1973; 2 pp. Crude pyridinecarboxylic acids are recrystd. first from alcs. and then from H_2O. Thus, 15 g nicotinic acid of 99.1% purity, prepd. by gas-phase oxidn. of alkylpyridines and sublimed, was recrystd. first from 135 g EtOH and then from 135 g H_2O with C to recover 66.7% pure acid, which was less colored than the control (the solvent order reversed). I. Matsumoto

B4.46. 135981p **Purification of pyridinecarboxylic acids.** Inoue, Toshio; Yasui, Hiroshi; Kato, Satoru; Hara, Tadanori (Nippon Steel Chemical Industry Co., Ltd.) Japan. Kokai 74 49,966 (Cl. 16 E431), 15 May 1974, Appl. 72 92,939, 18 Sep 1972; 3 pp. Pyridinecarboxylic acids (I) were purified after heating crude I. Activated clay may be added to crude I before heating. E.g., 300 g nicotinic acid (II) (purity 96.6 wt. %) was heated with 5 wt. % activated clay for 10 hr at 220° in the air, treated with activated C in H_2O, to give 68.3% II (purity 99.9 wt. %). K. Sempuku

B4.47. 120503v **Pharmaceutical grade nicotinic acid.** Fahrig, Peter; Angermann, Werner; Meinicke, Karl H. Ger. (East) 72,525 (Cl. C 07d), 20 Apr 1970, Appl. 18 Dec 1968; 2 pp. Tech. nicotinic acid prepd. by $KMnO_4$ oxidn. of 3-picoline contains mineral salts and dipicolinic acid which are difficult to remove by the customary recrystn. from H_2O. The title process is characterized by the use of $FeSO_4$ as a complexing agent for the quant. elimination of dipicolinic acid. Tech. nicotinic acid (75 kg contg. 3% K_2SO_4 and 2% dipicolinic acid) and 1.9 kg $FeSO_4$.$7H_2O$ in 600 l. tapwater stirred 2 hr under reflux and cooled to 20° gave 45 kg pharmaceutical grade homogeneous white nicotinic acid. The deep red combined mother-liquors and filtrates was concd. and the crystal mash filtered off, returned to a new batch of tech. nicotinic acid, and again treated with $FeSO_4$.$7H_2O$. C. R. Addinall

NIACIN

Separation

B4.48. 43409p Separation of a eutectic mixture of nicotinic and isonicotinic acids. Bialek, Jerzy; Porada, Slawomira (Instytut Chemii Ogolnej) Pol. 57,343 (Cl. C 07*d*), 30 Jun 1969, Appl. 29 Dec 1966; 2 pp. An efficient method is described for the sepn. of nicotinic acid (I) and isonicotinic acid I (II) from their eutectic mixt. by crystn. Thus, 15 g of a eutectic mixt. contg. I 75 and II 25%, was dissolved in 310 ml H_2O, the pH of the soln. was brought with gaseous NH_3 to 4.5, and the soln. was evapd. to 170 ml and left to crystallize: 8 g of I, contg. <5% II was obtained and after recrystn. pure I was obtained, m. 235.5–7°. Crystn. mother liquors were evapd. to dryness and the ammonium salts of the pyridinecarboxylic acids were decompd. at 120–30°. The residue, contg. 86.5% of I and II in the ratio 6:4 was sepd. by conventional method, e.g. according to Pol. 50,079. Cf. Pol. 34,921 and 35,452; U.S. 2,748,136; Austrian 242,699.
Karol Butkiewicz

B4.49. 3842g Separation of nicotinic and isonicotinic acid. Hoelting, Wilhelm; Eilhauer, Hans D.; Krautschik, Gerd; Mohrhauer, Rolf Ger. (East) 58,090 (Cl. C 07*d*), 05 Oct 1967, Appl. 26 Jan 1967; 2 pp. Mixts. of nicotinic acid (I) and isonicotinic acid (II) were sepd. by an extn. with substituted pyridines (III) at 50-120° followed by an extn. with HNO_3 at 0-30°. Thus, 1 kg. I and 1 kg. II in 3 kg. III (b. 115-250°) was stirred 2 hrs. at 97°, the suspension filtered, the filter-cake washed with 1 l. MeOH, and dried to yield 770 g. II (purity 94.1%). The filtrate was evapd. to dryness, the residue (1205 g.) treated with 1690 g. 64% aq. HNO_3 at 50°, the reaction product filtered off and dried to give 1.4 kg. nitrate of I (purity 93%). For further purification, the nitrate was stirred with 1120 g. 20% aq. HNO_3 2 hrs. at 20–25°, filtered off, and dried to give 1315 g. nitrate (purity 95.5%). This substance was suspended in 2630 g. distd. water, aq. KOH added to ppt. I at pH 3.5, the ppt. filtered off, washed with MeOH, and dried to yield 855 g. I (purity 97%). The washings and the mother liquor were worked up in a similar manner to give 285 g. of a mixt. of 28.5% I and 71.5% II which was used for the next extn. process.
A. Roders

B4.50. 40629p Recovery of nicotinic and isonicotinic acid. Eilhauer, Hans D.; Krautschick, Gerd; Kurtschinkski, Gerhard Ger. (East) 61,544 (Cl. C 07*d*), 05 May 1968, Appl. 28 Aug 1967; 3 pp. The title compds. (I) are recovered from mother liquors contg. 2–5% I by continuous countercurrent extn. at 0–100° with an org. base satd. with H_2O, followed by extn. with concd. (till 50%) aq. NaOH at 0–120°. A description of a pilot-plant is given and a table contg. results with various bases, % recovery etc.
H. Pouwels

NIACIN

Miscellaneous

B4.51. 135975q Catalysts for oxidation of alkylpyridines. Morita, Masamichi; Inoue, Toshio; Hara, Tadanori (Nippon Steel Chemical Co., Ltd.) Japan. Kokai 74 39,591 (Cl. 2[illegible]/9)G112, 13(9)G113, 16 E431), 13 Apr 1974 Appl. 72 82,849, 21 Aug 1972; 4 pp. V, Sn, Ti, Bi, Sb, [illegible] W compds. were used as catalysts for the air oxidn. of β- or γ-alkylpyridines. E.g., 1 l. 2-methyl-5-ethylpyridine vapor was air-oxidized in the presence of a catalyst contg. 1 kg TiO_2, 117 g NH_4VO_3, 175 g $SnCl_4.5H_2O$, 100 g $Bi(NO_3)_3.6H_2O$, and 850 ml H_2O to give 61.2% nicotinic acid.

B4.52. 99510b Catalyst composition for gas phase catalytic oxidation of picoline. Yokoyama, Ryoichi; Sawada, Katsumi (Teijin Chemical Industry Co., Ltd.) Japan. 72 00,805 (Cl. C 07c, B 01j), 11 Jan 1972, Appl. 04 Mar 1968; 2 pp. A mixt. of V_2O_5 and Cr_2O_3 (V:Cr = 1:0.5 to 1:1) was calcined preferably at 650–750° in the presence of O to give a desired catalyst. Eg., a mixt. of V, Cr, Sn, and Sb (100:75:4:1) carried on SiC (8–10 mesh) was heated at 650° in the presence of O to give a catalyst. β-Picoline was oxidized using the resulting catalyst at 390° with 200 l./hr air to give 86.8% 3-pyridinecarboxylic acid of 98% purity.
Hiroshi Kataoka

B4.53. 101: 191699w T-Butylphenoxyalkylene esters of benzoic and nicotinic acids, compositions containing them and their antihistaminic method of use. Berger, Frank M.; De Graw, Joseph I., Jr.; Johnson, Howard L. U.S. US 4,[illegible]51,474 (Cl. 424-266; C07D213/55), 29 May 1984, US Appl [illegible]4,183, 22 Jan 1980; 15 pp. Cont.-in-part of U.S. Ser. No. 114,183, abandoned. 3,4-$RR^1C_6H_3O(CH_2)_m(CR^2_2)_n(CH_2)_pOR^3$ (I, R = H; R^1 = alkyl; RR^1 = alkylene; R^2 = H, alkyl; R^3 = H, acyl; *m*, *n*, *p* = 0–10) were prepd. and 4-$Me_3CC_6H_4O(CH_2)_qOR^4$ (II, R^4 = nicotinoyl, *q* = 3, 4; R^4 = Bz, *q* = 4) were claimed. Thus, 4-$Me_3CC_6H_4OH$ was treated with $Cl(CH_2)_4OAc$ to give II (R^4 = Ac, *q* = 4) which was sapond. to give II (R^4 = H, III). III was esterified with nicotinoyl chloride to give II (R^4 = nicotinoyl, *q* = 4, IV). The histamine release–inhibiting activity of III and IV relative to that of chlorphenesin was 10.0 and 20.0, resp.
101: 191700q 1,4-Dihydropyridine esters and drugs containing these esters. Sunkel Letelier, Carlos; Pau de Casa-Juana Munoz, Miguel; Statkov, Peter R.; Straumann, Danielle (Cermol S. A.)

B4.54. 101: 97664j Antidepressants containing L-tryptophan and a monoamine oxidase inhibitor. Coppen, Alec James Brit. UK Pat. Appl. GB 2,129,299 (Cl. A61K45/06), 16 May 1984, Appl. 82/31,975, 09 Nov 1982; 3 pp. Antidepressants contain *L-tryptophan* [73-22-3] at lower doses when combined with a *monoamine oxidase* [9001-66-5] inhibitor, e.g., *phenelzine* [51-71-8] or *tranylcypromine* [155-09-9]. The antidepressant action of the compn. is greater than either compd. alone in their usual dosages. The compns. may also contain *folic acid* [59-30-3], *ascorbic acid* [50-81-7], *pyridoxine* [65-23-6], *thiamine* [59-43-8], *riboflavin* [83-88-5], *nicotinic acid* [59-67-6] or *nicotinamide* [98-92-0].

B4.55. 101: 92147h **Latent curing agents for epoxy resins.** Takeuchi, Koji; Abe, Masahiro; Ito, Nobuo; Hirai, Kiyomiki (Ajinomoto Co., Inc.) Eur. Pat. Appl. EP 104,837 (Cl. C08G59/56), 04 Apr 1984, JP Appl. 82/164,557, 21 Sep 1982; 32 pp. The curing agents, useful in formulating novel stable 1-package heat-curable epoxy resin-based compns., are prepd. by treating a polyfunctional epoxy compd. and a compd. having a tertiary group and ≥1 OH, SH, COOH, and $CONHNH_2$ groups, and by treating the 2 above components and an org. compd. having ≥2 active H atoms (excluding compds. having epoxy or tertiary amine groups). Thus, a mixt. contg. *Epon 828* (I) [25068-38-6] 100, ZnO 3, TiO_2 2, and curing agent, prepd. by treating I with *1-(2-hydroxy-3-phenoxypropyl)-2-phenylimidazole* (II) [91454-81-8] 20 parts, had onset temp. 90°, peak temp. 135°, curing temp. and time 120° and 60 min, resp., and storage stability at 30° >1 mo, compared with 60°, 170°, 100°, 60 min, and <1 day, resp. for a similar compn. contg. unreacted II.

B4.56. 101: 53697t **Supplementary food containing vitamins and/or minerals and optionally further components.** Van der Eijnden, Cornelis Maria Joseph (Van Melle Nederland B. V.) Eur. Pat. Appl. EP 102,663 (Cl. A23L1/30), 14 Mar 1984, NL Appl. 82/3,150, 10 Aug 1982; 12 pp. A food product is prepd. from water, carbohydrates, and vegetable oils, and fortified with vitamins and minerals. The product may be used to supplement food in areas of malnutrition. Thus, a mixt. of *sucrose* [57-50-1] 42, glucose syrup 42, hydrogenated cocoa fat 8, *gum arabic* [9000-01-5] 1, and water 7% was boiled at 123° to 7% residual moisture, cooled to 70°, and treated with 4.5 g of a mixt. of *vitamin A* [11103-57-4], *vitamin D_3* [67-97-0], *vitamin E* [1406-18-4], *vitamin C* [50-81-7], *vitamin B_1* [59-43-8], *vitamin B_2* [83-88-5], *vitamin B_5* [8059-24-3], *vitamin B_{12}* [68-19-9], *folic acid* [59-30-3], *niacin* [59-67-6], and *pantothenic acid* [79-83-4]. The mass was mixed, cooled, formed into blocks, and packaged.

B4.57. 98: 3538r **Concentrated GTF chromium complex brewers yeast.** Szalay, Andrew U.S. US 4,343,905 (Cl. 435-256; C12N1/16), 10 Aug 1982, Appl. 166,454, 07 Jul 1980; 5 pp. Brewers' yeast contg. ~2000 μg Cr/mg, >80% of which is present as glucose tolerance factor (GTF)-active org. Cr complex, is prepd. by culturing the yeast in a medium contg. Cr oxide ~29, nicotinic acid 29-32, glucine 17-20, L-glutamic acid 17-20, and L-cysteine-HCl 19.3%, based on wt. of solids. The yeast nutrient was prepd. by dissolving nicotinic acid, glycine, and L-glutamic acid in H_2O at 90° with const. agitation; a soln. of Cr oxide in H_2O was added slowly, followed by L-cysteine-HCl. The soln. was stirred for 1 h at 90°, and allowed to settle and cool for 48 h. A suspension of brewers' yeast in H_2O at 35° was added, and the mixt. agitated for 24 h at 35°, and heated to 90° for 3 h. The killed yeast was spray dried, hydrolyzed with a proteolytic enzyme, the cell fragments were removed by centrifuging, and the sol. material was spray dried and assayed. The org. Cr content was 60% of the total Cr. When administered to normal subjects with abnormal glucose control, mature diabetics, and juvenile diabetics at 200 μg Cr/day for 4 mo, blood cholesterol and triglyceride levels decreased, and high-d. lipoproteins increased. Glycosylated Hb levels in diabetics were normalized.

B4.58. 94: 69228p **Charge for melting vanadium ferroalloy.** Bairamov, B. I.; Zaiko, V. P.; Ryss, M. A.; Shcherbakov, S. S.; Pigasov, V. E.; Sibilev, Yu. P. (Chelyabinsk Electrometallurgical Combine) U.S.S.R. 765,384 (Cl. C22C33/04), 23 Sep 1980, Appl. 2,598,527, 03 Apr 1978. From *Otkrytiya, Izobret., Prom. Obraztsy, Tovarnye Znaki* 1980, (35), 170. The loss of metal by slag is decreased and the sepn. of slag from metal in a solid form improved by adding 10-25% sludge from manuf. of *nicotinic acid* [59-67-6] (MnO_2 50-60, NaOH 0.7 1.2, Pb 0.01-0.1%, balance H_2O) to the title charge contg. V material 30-40, Si-contg. reducing agent 8-15, C-contg. reducing agent 2-5%, balance Ca-contg. flux.

B4.59.

105298d Trapping nicotinic acid. Hara, Tadanori; Inoue, Toshio (Nippon Steel Chemical Industry Co., Ltd.) Japan. Kokai 74 62,475 (Cl. 16 E431), 17 Jun 1974, Appl. 72 104,440, 20 Oct 1972; 3 pp. Nicotinic acid (I) was trapped by introducing I-contg. gases at 100–200° onto the layers bearing fillers of inactive particles of 0.5–10 mm in diam. E.g., 13.5 g crude I (purity 97%) was sublimed 8 hr under 30 l./hr N current at 235° and 610 mm. The sublimed vapor (220°) was passed over 100 ml fused Al_2O_3 (1–1.4 mm in diam.; inlet temp. 180°, outlet temp. 140°) to trap 13 g I (purity >99%, 0.5–1 mm in diam.).
K. Sempuku

B4.60.

43287b Nicotinic acid esters. Azerbaev, I. N.; Erzhanov, K. B.; Kasymkhanona, U. F. (Institute of Chemical Sciences, Academy of Sciences, Kazakh S.S.R.) U.S.S.R. 351,849 (Cl. C 07*d*), 21 Sep 1972, Appl. 13 Aug 1970. From *Otkrytiya, Izobret., Prom. Obraztsy, Tovarnye Znaki* 1972, 49(28), 72. Heating nicotinoyl chloride hydrochloride with acetylenic glycols in the presence of a tertiary amine afforded the corresponding title esters.

B4.61.

123706v Microbiological production of protein-vitamin concentrates. Dikanskaya, E. M.; Balabanova, A. A. (All-Union Scientific-Research Institute of Protein Biosynthesis) Brit. 1,226,477 (Cl. C 07*d*), 31 Mar 1971, Appl. 28 May 1969; 3 pp. Protein-vitamin concs. fortified with riboflavine are produced by *Eremothecium ashbyii* in a yeast medium produced from petroleum hydrocarbons. Thus, yeast produced on a mixt. of petroleum *n*-paraffins was dild. to a concn. of 6 wt. %, sterilized in 500 ml rocking flasks, and inoculated with a 2% 2-day culture of *E. ashbyii* grown on similar yeast medium. The culture was grown under different aeration conditions for 6 days. With aeration of 0.4, 2.2, and 3.5 g O/hr, 280, 1330, and 1730 mg of riboflavine/kg of dry prepn. were formed after 2 days; 10,330, 11,600, and 10,980 mg/kg were formed after 6 days. The fungus was then grown in a 500 ml fermentation tank with 300 ml of yeast medium prepd. as above. Biomycin antibiotic, 200 units/ml, was added and the medium was inoculated with 10 vol. % of flask culture of *E. ashbyii*. Fermentation was carried out with aeration and mixing; oleic acid was added to control foaming. The temp. was kept at 30°. In 24 hr the medium turned yellow due to riboflavine. In 48 hr the vitamin B_2 content was 500 μg/ml and in 70 hr it was 880 μg/ml, which corresponded to 9000 mg/kg of dry prepn. After 70 hr the culture mass was dried at 100°. The dry powder contained crude protein 40%, riboflavine 9000, pantothenic acid 540, pyridoxine 20, nicotinic acid 500, thiamine 10, and biotin 0.2 mg/kg.
S. P. Marino

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B5

NIKETHAMIDE

PATENTS

1967-1985

ANALYSIS OF THE ABSTRACTS OF PATENTS

The patents B5.1. - B5.6. are held by the same firm and describe syntheses starting from nicotinic acid by reaction with diethylamine, phosgene and similar compounds. In B5.7. nicotinic acid reacts with diethylacetamide and in B5.8. a gasphase reaction of nicotinic acid witn diethylamine on silicagel is described.

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ABSTRACTS OF PATENTS

B5

NIKETHAMIDE

Preparation

B5.1. 85: 32655p N,N-Disubstituted carboxylic amides. Grega, Erzsebet; Gribovszky, Pal; Marosvolgyi, Sandor; Pinter, Zoltan; Szilagyi, Gyula; Szita, Istvan; Tarr, Csaba; Tasi, Laszlo (Eszakmagyarorszagi Vegyimuvek) U.S. 3,941,783 (Cl. 260-247.7V; C07D), 02 Mar 1976, Appl. 421,642, 04 Dec 1973; 6 pp. Nineteen I [$RCONR^1R^2$ (R = $Me(CH_2)_{14}$, $ClCH_2$, Ph, substituted phenyl, 3-pyridyl, Ph_2CH; R^1,R^2 = same or different C_{1-4} alkyl or Ph; or NR^1R^2 = morpholino)] were prepd. by reaction of RCO_2H with $ClCONR^1R^2$ at 110-220°.

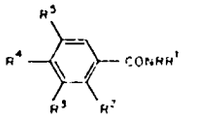
B5.2. 84: 179901d N,N-Disubstituted carboxylic acid amides. Eszakmagyarorszagi Vegyimuvek Neth. Appl. 73 17,053 (Cl. C07C), 16 Jun 1975, Appl. 73 17,053, 12 Dec 1973; 19 pp. $RCONR^1R^2$ (I; R = C_{1-18} alkyl or haloalkyl, Ph, or substituted phenyl; R^1, R^2 = the same or different C_{1-14} alkyl or substituted alkyl, Ph, or substituted phenyl, or R^1R^2N = a N heterocycle) were prepd. by reacting RCO_2H with R^1R^2NH or with $ClCONR^1R^2$, with elimination of HCl and CO_2. Thus, $Me(CH_2)_{14}CO_2H$ with Bu_2NH gave 75% I (R = n-$C_{15}H_{31}$, R^1 = R^2 = Bu), and BzOH with $ClCONPhCHMe_2$ gave 78% $BzNPhCHMe_2$. Eighteen other I were prepd.

B5.3. 84: 58967w N,N-Disubstituted aromatic and aliphatic carboxylic amides. Gribovski, Erzsebet P.; Marosvolgyi, Sandor; Pinter, Zoltan; Szilagyi, Gyula; Szita, Istvan; Tarr, Csaba; Tasi, Laszlo (Eszakmagyarorszagi Vegyimovek) Fr. Demande 2,253,735 (Cl. C07CD), 04 Jul 1975, Appl. 73 43,898, 10 Dec 1973; 22 pp. Amidation of benzoic acids or Ph_2CHCO_2H with amine-phosgene mixts. and with carbonyl chlorides gave twelve $RCONR^1R^2$ (I; R = Ph, substituted phenyl, $CHPh_2$; R^1 = C_{1-4} alkyl; R^2 = Ph, C_{1-4} alkyl; NR^1R^2 = morpholino). Similarly prepd. were seven I (R = pentadecyl, $ClCH_2$; R^1 = Bu, $CHMe_2$, Ph, alkoxymethyl; R^2 = Bu, Ph, dialkylphenyl). I are useful as herbicides and analeptics and in the treatment of arteriosclerosis.

B5.4. 84: 4690g N,N-Disubstituted carboxylic acid amides. Grega, Erzsebet; Gribovszki, Pal; Marosvolgyi, Sandor; Pinter, Zoltan; Szilagyi, Gyula; Szita, Istvan; Tarr, Csaba; Tasi, Laszlo Austrian 323,123 (Cl. C07C), 15 Sep 1974, Appl. 10,088/73, 03 Dec 1973; 10 pp. The title amides were prepd. in high yield in 1 step by treating the acid with the secondary amine and $COCl_2$ or the carbamoyl chloride. Thus $Me(CH_2)_{14}CONBu_2$ was obtained in 75% yield by treating $Me(CH_2)_{14}CO_2H$ with $COCl_2$ and $NHBu_2$, or in 74.8% yield by treating $Me(CH_2)_{14}CO_2H$ with Bu_2NCOCl. Other amides similarly prepd. include $BzNPhCHMe_2$, $ClCH_2CONPh_2$, *N,N*-diethylnicotinamide, and *N*-benzoylmorpholine.

B5.5. 163852g **N,N-Disubstituted carboxylic acid amides.** Grega, Erzsebet; Gribovszki, Pal; Marosvolgyi, Sandor; Pinter, Zoltan; Szilagyi, Gyula; Szita, Istvan; Tarr, Csaba; Tasi, Laszlo (Eszakmagyarorszagi Vegyimuvek) Ger. Offen. 2,365,451 (Cl. C07C), 31 Jul 1975, Appl. P 23 65 451.5-42, 11 Dec 1973; 28 pp. Division of Ger. Offen. 2,361,604. $RCONR^1R^2$ (R, R^1, R^2 = alkyl, Ph; NR^1R^2 = morpholino) were prepd. by heating a carboxylic acid with a disubstituted carbamoyl chloride at 110-180° without a solvent. Thus, 3,5-$(O_2N)_2C_6H_3CO_2H$ was heated with Bu_2NCOCl at 140-60° to give 74% 3,5-$(O_2N)_2C_6H_3CONBu_2$.

B5.6. 96777w **N,N-Disubstituted benzamides.** Grega, Erzsebet; Gribovszki, Pal; Marosvolgyi, Sandor; Pinter, Zoltan; Szilagyi, Gyula; Szita, Istvan; Tarr, Csaba; Tasi, Laszlo (Eszakmagyarorszagi Vegyimuvek) S. African 74 00,572 (Cl. C07c), 24 Oct 1974, Appl. 74 0572, 29 Jan 1974; 24 pp. Benzoic acids reacted with amine-phosgene mixts., or carbamoyl chlorides, to give eleven benzamides [I; R and R^1 (same or different) are $CHMe_2$, Ph, Bu, Et, CH_2CHMe_2, CHMeEt, and NRR^1 = 4-morpholinyl; R^2 = H, Cl; R^3 = H, Cl, NO_2, OMe; R^4 = H, Cl, OMe; R^5 = H, NO_2, OMe]. Similarly prepd. were six $RCONR^1R^2$ [II; R = pentadecyl, CH_2Cl, $CHPh_2$; R^1 and R^2 (same or different) are Bu, $CHMe_2$, Ph, Me]. I and II are useful in the treatment of arteriosclerosis and as tranquilizers, analeptics, and herbicides.



I

B5.7. 112810w **N,N-Diethylnicotinamide.** Moulin, Francois (Lonza Ltd.) Swiss 473,123 (Cl. C 07*d*), 15 Jul 1969, Appl. 22 Feb 1966; 2 pp. Through a mixt. of 30 g. nicotinic acid (I) and 36 g. $AcNEt_2$ (II) was passed 120 ml./hr. N and the flask heated so that, at a vapor temp. of 130-50°, 5 ml. of mixt. AcOH-II distd./hr. In 9 hrs., 43.5 ml. distillate was collected and 40 ml. II added to the mixt. After cooling 6.9 g. I crystd. and the residue distd. to give II and 89.7% title compd., b_{10} 155-7°.
Gerben Sipma

B5.8. 106567e *N,N*-Diethylamide of nicotinic acid. Dormeshkin, N. V.; Ostrovchenkov, B. F.; Parkerov, M. I. (Voronezh Technological Institute) U.S.S.R. 218,185 (Cl. C 07d), 07 May 1968, Appl. 06 Dec 1966; From *Izobret., Prom. Obraztsy, Tovarnye Znaki* 1968, 45(17), 26. Title compd. is prepd. from nicotinic acid and Et_2NH in the vapor phase in the presence of a silica gel catalyst.
N.S.C.L.

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C1

METRONIDAZOLE

PATENTS

1967-1985

APPENDIX P19

ANALYSIS OF THE ABSTRACTS OF PATENTS

There are two main groups of patents both starting from 2-methyl-5-nitroimidazole. In Cl.1., Cl.2. and Cl.8. this compound reacts with ethylenoxide and in Cl.3. - Cl.6. it reacts with chloroethanol. In Cl.5. a yield of 71.8% is given.

Other processes Cl.7. - Cl.9. at a first analysis do not reveal significant advantages compared to the standard processes.

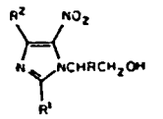
ABSTRACTS OF PATENTS

C1

METRONIDAZOLE

Preparation

C1.1. 147480d 1-Hydroxyalkyl-5-nitroimidazoles. Frank, Anton; Karn, Helmut; Spaenig, Hermann (BASF A.-G.) Ger. Offen. 2,359,625 (Cl. C07D), 05 Jun 1975, Appl. P 23 59 625.0, 30 Nov 1973; 11 pp. 1-Hydroxyalkyl-5-nitroimidazoles (I, R = R^2

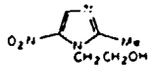


I

= H, R^1 = Me, H, Et, $CHMe_2$; R = R^1 = Me, R^2 = H; R = R^1 = H, R^2 = Me; R = R^2 = Me, R^1 = H) were obtained in 53.6–78.4% yields by treatment of a 5-nitroimidazole with ethylene or propylene oxide in a mixt. of $(HCO)_2O$ and Ac_2O and 25–30°. I are polymn. catalysts and condensation catalysts.

C1.2. 97648p 1-(2-Hydroxyethyl)-2-methyl-5-nitroimidazole. Muhlbrod, Jan (Starogardzkie Zaklady Farmaceutyczne "Polfa") Brit. 1,301,225 (Cl. C 07*d*), 29 Dec 1972, Pol. Appl. 138,-251, 19 Jan 1970; 3 pp. The title compd. (I) was prepd. in 80% yield from 2-methyl-5-nitroimidazole sulfate and ethylene oxide in mixts. of H_2SO_4 and a satd. aliph. compd. having an O-contg. functional group or an O heterocycle. Thus, 200 g 2-methyl-5-nitroimidazole (II) was poured and 158 g H_2SO_4 added dropwise to 140 ml Me_2CO and 23 ml ethylene glycol below 40°. A total of 320 g ethylene oxide and 66 g H_2SO_4 were alternatively added in portions over 100 min to the reaction mixt. at 45–50°. After pptn. of unreacted II by diln. with 450 ml H_2O the mixt. with 35% NaOH at 35° pptd. 205 g crude product which gave 141 g I.

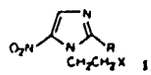
C1.3. 101618c 2-Substituted-1-(hydroxyethyl)-5-nitroimidazoles. Klosa, Josef; Thomas, Gottfried; Friese, Johannes Ger (East) 88,028 (Cl. C 07*d*), 20 Feb 1972, Appl. WP 12p/145,335, 05 Feb 1970; 3 pp. The imidazole (I) was obtained in 71.8–



I

4.5% yield of 18.3–19.2% conversion by hydroxyethylating methylnitroimidazole with ethylene chlorohydrin, satd. with HCl gas at 125–7° for 9.5–10.5 hr.

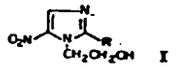
C1.4. 101609a Antiparasitic 1-substituted 5-nitroimidazoles. Valles, Paolo (CRC Compagnia di Richerche Chimiche S. A.) Swiss 520,090 (Cl. C 07*c*), 28 Apr 1972, Appl. 3211/67, 06 Mar 1967; 5 pp. The antiparasitic title compds. (I) were prepd.



I

from alkylene dihalide and 1*H*-imidazoles in the presence of HCO_2H, HOAc, or $EtCO_2H$. Thus, 6.3 g 2-methyl-5-nitroimidazole, 84.6 g $Br(CH_2)_2Br$, and 21 g HOAc was heated 48 hr at 110–14° to give 1.4 g I (R = Me, X = Br). Similarly prepd. were I (R = Me, X = I and OH). H. J. Nitzschke

C1.5. 110314m 1-(β-Hydroxyethyl)-2-alkyl-5-nitroimidazoles. Klosa, Josef Ger. Offen. 2,001,432 (Cl. C 07*d*), 15 Jul 1971, Appl. 08 Jan 1970; 7 pp. The title imidazoles (I) are prepd. by



I

treatment of 2-alkyl-5-nitroimidazoles with $HOCH_2CH_2Cl$ in the presence of HCl at a raised temp. Thus, 2-methyl-5-nitroimidazole (m. 252–4°) in $HOCH_2CH_2Cl$ satd. with dry HCl stirred 10.5 hr at 125–7° gave in the basic residue 2-methyl-4(5)-nitroimidazole. The filtrate made alk. with NaOH to pH 10 and the H_2O and iso-PrOH-washed ppt. dried yielded 71.8% I (R = Me), m. 158.5–60.5°. Similarly was obtained I (R = Et), m. 87–9°.
C. R. Addinall

C1.6. 22129s Chemotherapeutic nitroimidazoles. Toth, Joszef; Fekete, Gyorgy; Gorog, Sandor; Gorgenyi, Katalin; Szporny, Laszlo; Boor, Anna; Holly, Sandor (Richter, Gedeon, Vegyeszeti Gyar R. T.) Austrian 269,135 (Cl. C 07*d*), 10 Mar 1969, Hung. Appl. 26 Nov 1966; 8 pp. I and II, wherein R is H or low alkyl were prepd. Thus, 20.5 g. 2-methylimidazole is refluxed 3 hrs. in 60 ml. $ClCH_2CH_2OH$ giving 40 g. light yellow oil,

(I, 4-NO_2)
(II, 5-NO_2)

b_{9-10} 140–240° which yielded 12.44 g. 1-(2-hydroxyethyl)-2-methylimidazole, m. 63–5° (AcOEt); hydrochloride m. 125–7°; picrate m. 154–6°; nitrate (III)-HCl, m. 108–15°, nitrate picrate m. 160–2°. III was stirred at 20–30° while 78 ml. HNO_3 was added dropwise. P_2O_5 (16.6 g.) was added and after 10–15 hrs. at 20–75° worked up to give 41:59 I–II (R = H) m. 128–30° and m. 157–9°, resp.; nitrates m. 98–100° and 69–70°, resp. Also prep. were I (R = Ac) m. 142–4° and II (R = Ac), m. 70–3°. The new compds. are of therapeutical value as chemotherapeutics against trichomonas infections. Friedrich Epstein

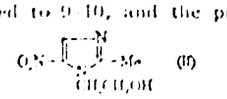
C1.7. 87814k 1-(2-Hydroxyethyl)-2-methyl-5-nitroimidazole. K R K A Tovarna Zdravil Brit. 1,138,805 (Cl. C 07*d*), 01 Jan 1969, Yugoslavia Appl. 20 Jun 1966; 2 pp. A mixt. of 11.7 g. 1-(2-bromoethyl)-2-methyl-5-nitroimidazole, 39 ml. $HCONH_2$, 1.8 ml. water, and 0.3 ml. 98–100% HCO_2H is heated 3 hrs. at 110–15°, 27–8 ml. $HCONH_2$ distd. at 0.7–0.8 mm., and the residue worked up to give 69% 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole, m. 160–2°.
BDPN

C1.8. 77973x 1β-(Hydroxyethyl)-2-methyl-5-nitroimidazole. Aldea, Vasilichia; Banulescu, Virginia; Cilianu, Stefan B.; Pelloni, Viorica (Romania, Institute for Chemical-Pharmaceutical Research) Rom. 51,308 (Cl. C 07*d*), 16 Sep 1968, Appl. 11 Oct 1967; 2 pp. The title product (I) had pharmacol. activity. Thus, 13 HCO_2H, 1.4 crude 2-methyl-5-nitroimidazole and 2.8 kg. ethylene oxide was treated at 25–30° for 90 min., kept 75 min. at this temp. and worked up to give 75–6% I, 153–9°.
Marcel M. Gregorian

C1.9. 28918z Imidazole derivatives. Toth, Jozef; Fekete, Gyorgy; Boor, Mrs. Lajos; Szporny, Laszlo; Gregenyi, Mrs. Akos; Gorog, Sandor; Holly, Sandor (Richter, Gedeon, Vegyeszeti Gyar R. T.) Hung. 154,716 (Cl. C 07*d*), 30 Apr 1968, Appl. 26 Nov 1966; 33 pp. Ethylolation of 2-methylimidazole (I) with $ClCH_2CH_2OH$, $(CH_2)_2O$, or $(CH_2O)_2CO$ affords 1-(2-hydroxyethyl)-2-methylimidazole (II), which is then esterified, the nitrate (III) and acetate esters are nitrated, and the 4- and 5-nitro derivs. are sepd., followed by hydrolysis of the ester group. The ratio of 4- and 5-nitro derivs. varied depending on the reaction conditions. Thus, a mixt. of 20.5 g. I and 60 ml. $ClCH_2CH_2OH$ was refluxed 2 hrs., concd. in vacuo and fractionated, the fraction $b_{0.1}$ 140–240° taken up in EtOH, the HCl content neutralized with KOH, and the soln. filtered and concd. in vacuo, to yield II, m. 63–5° (EtOAc); hydrochloride m. 125–7°; picrate m. 154–6°. II (25.2 g.) was added with stirring to 100 ml. 96% HNO_3 at 0° and the mixt. stirred at room temp. 2 hrs., poured onto ice and extd. with $CHCl_3$ at pH 10 (NaOH) to yield 92% III, a pale yellow oil; hydrochloride m. 108–15°; picrate m. 160–2°. II (12.6 g.) was dissolved in 42.7 ml. Ac_2O at 0°, the soln. kept at 110–20° 3 hrs., and concd. in vacuo, the oily residue added in portions to 12.6 ml. concd. HNO_3 and 15.7 g. P_2O_5 at 0–20°, and kept 5 hrs., 4.2 ml. concd. HNO_3 added at room temp., and the whole kept at room temp. 15 hrs., dild. with 100 ml. H_2O at 0°, and neutralized with 115 ml. 40% KOH soln. with cooling to pH 10 to deposit 7.8 g. 1-(2-acetoxyethyl)-2-methyl-4-nitroimidazole, m. 142–4° (H_2O). The mother liquor was extd. with CH_2Cl_2 and worked up to yield 1-(2-acetoxyethyl)-2-methyl-5-nitroimidazole, m. 70–3° (iso-Pr_2O). The acetyl group was removed by heating in *N* HCl at 90° several hrs. to give 1-(2-hydroxyethyl)-2-methyl-4-nitroimidazole (IV), m. 128–30°, 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole (V), m. 158–60°. A mixt. of 200 g. I, 268 g. $(CH_2O)_2CO$, 20 g. K_2CO_3, and 500 ml. $HCONMe_2$ was stirred at 140–5° 3 hrs., filtered at 60°, and concd. in vacuo, the residue added in portions with stirring to 1060 ml. concd. HNO_3 at 0–10°, the mixt. stirred at room temp. 1 hr., 356 g. P_2O_5 added at 0–10°, the whole stirred at room temp. 18 hrs., added to 1600 g. ice, extd. with CH_2Cl_2, and made alk. with 2550 ml. 50% NaOH (pH 10), the alk. soln. was extd. with CH_2Cl_2, and the org. phase worked up to yield 214.6 g. 1-(2-hydroxyethyl)-2-methyl-4-nitroimidazole and 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole nitrate esters (VI and VII, resp.) in a ratio of 40:60. A soln. of a mixt. of 42:58 VI and VII in 98 ml. 5*N* H_2SO_4 was kept at 100° 2 hrs., dild. with 100 ml. H_2O, and neutralized to pH 5 with 70 ml. 40% NaOH soln. to deposit 19.3 g. V. The mother liquor was extd. with EtOAc at pH 9 and worked up to yield IV. T. Mohacsi

C1.10. 19156b 1-(β-Hydroxyethyl)-2-methyl-5-nitroimidazole. Kraft, M. Ya.; Kochergin, P. M.; Tsyganova, A. M.; Shlikhunova, V. S.; Ordzhenikidze, S. (All-Union Scientific-Research Chemical-Pharmaceutical Institute) U.S.S.R. 201,416 (Cl. C 07*d*), 08 Sep 1967, Appl. 14 Jan 1966. From *Izobret., Prom. Obraztsy, Tovarnye Znaki* 1967, 44(18), 38. The title compd. is prepd. by treating 2-methyl-4(5)-nitroimidazole with Et_2O in the presence of org. acids. The process is conducted in a mixt. of H_3PO_4 and AcOH. MGCL

C1.11. 21910v 1-(2-Hydroxyethyl)-2-methyl-5-nitroimidazole. C.R.C. Compagnia di Ricerca Chimica S.A. Neth. Appl. 6,603,513 (Cl. C 07*d*), Dec. 22, 1966; Swiss Appl. June 21, 1965; 6 pp. A suspension of 20 g. $MeCH{:}NCH{:}CHNO_2$ in 500 ml. dry dioxane is heated with stirring at 50° until complete soln. and, after cooling to 10°, 20 g. $HON{:}CHCH_2OAc$ is added. The mixt. is heated 20 hrs. at 90°, dioxane is removed in vacuo, the residue is acidified with $(CO_2H)_2$, and kept 10 hrs. at −10° to give 4 g. $AcOCH_2CH{:}NCH(NO_2)CH(OH)N{:}CHMe$ (I), m. 128–32° (AcOEt). To a soln. of 4 g. I in 300 ml. dioxane at −10° is added slowly 10 g. P_2O_5, keeping the temp. <5°. After 10 hrs. at 5° the mixt. is neutralized with 10% NaOH, kept 10 hrs. at 90°, and concd. in vacuo. The residue is suspended in 400 ml. H_2O, the pH adjusted to 9–10, and the product extd. with



(II)

EtOAc to give 1.9 g. 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole (II), m. 144–9° (EtOAc). II has antimicrobial activity. G. Bodnarov

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C2

SULFAMETHOXAZOLE

PATENTS

1967-1985

APPENDIX P20

ANALYSIS OF THE ABSTRACTS OF PATENTS

There are only two new synthesis patents. C2.1. mainly deals with the approach to the isoxazolamine, whereas C2.2. describes an interesting alternative to protect the amine group of p-aminosulfonyl-chloride.

ABSTRACTS OF PATENTS