## OCCASION

This publication has been made available to the public on the occasion of the 50th anniversary of the United Nations Industrial Development Organisation.

## DISCLAIMER

This document has been produced without formal United Nations editing. The designations employed and the presentation of the material in this document do not imply the expression of any opinion whatsoever on the part of the Secretariat of the United Nations Industrial Development Organization (UNIDO) concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries, or its economic system or degree of development. Designations such as "developed", "industrialized" and "developing" are intended for statistical convenience and do not necessarily express a judgment about the stage reached by a particular country or area in the development process. Mention of firm names or commercial products does not constitute an endorsement by UNIDO.

## FAIR USE POLICY

Any part of this publication may be quoted and referenced for educational and research purposes without additional permission from UNIDO. However, those who make use of quoting and referencing this publication are requested to follow the Fair Use Policy of giving due credit to UNIDO.

## CONTACT

Please contact publications@unido.org for further information concerning UNIDO publications.

For more information about UNIDO, please visit us at www.unido.org

UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION
Vienna International Centre, P.O. Box 300, 1400 Vienna, Austria
Tel: (+43-1) 26026-0 · www.unido.org · unido@unido.org

17823



October 1989

ENVIRONMENT IMPACT ANALYSIS OF
PRAZIQUANTEL SYNTHESIS

1. INFORMATION SOURCE

Dr. Seubert JüRGEN, FRG Patent 25 04 250.6 to Merck Patent GmbH; Priority date: 1 February 1975.

2. PROCESS INFORMATION

2.1 Schematic illustration of the synthesis

3185N

## 2.2 Definition of educts, intermediates, and products

The commoi names, chemical formulae and molecular weights of reactants and auxiliary chemicals are listed in Appendix 1.

## 2.3 Chemical reactions

(a) $C_{12}H_{2}ON_{2}O + 3H_{2} = C_{12}H_{16}N_{2}O$

198.22 6.06 204.27

(b) $C_{12}H_{16}N_{2}O + H_{2}O = C_{10}H_{14}N_{2} + C_{2}H_{4}O_{2}$

204.27 18.01 162.23 60.05

(c) $C_{10}H_{14}N_{2} + C_{7}H_{11}ClO = C_{17}H_{24}N_{2}O + HCl$

162.23 146.61 272.39 36.46

(d) $C_{17}H_{24}N_{2}O + C_{2}H_{2}Cl_{2}O = C_{19}H_{25}ClN_{2}O_{2} + HCl$

272.39 112.94 348.87 36.46

(e) $C_{19}H_{25}ClN_{2}O_{2} = C_{19}H_{24}N_{2}O_{2} + HCl$

348.87 312.41 36.46

(f) Combined equation of the synthesis:

$C_{12}H_{10}N_{2}O + 3H_{2} + H_{2}O + C_{7}H_{11}ClO + C_{2}H_{2}Cl_{2}O$ =

198.22 6.05 18.01 146.61 112.94

$= C_{19}H_{24}N_{2}O_{2} + C_{2}H_{4}O_{2} + 3HCl$

312.41 60.05 109.38

## 2.4 Other reactions considered in the analysis

(g) $C_{2}H_{4}O_{2} + NaOH = CH_{3}COONa + H_{2}O$

60.05 40 82.04 18.02

(h) $NaOH + HCl = NaCl + H_{2}O$

40 36.46 58.44 18.02

(i) $ClCH_{2}COCl + H_{2}O = ClCH_{2}COOH + HCl$

112.94 18.02 94.50 36.46

(j) $C_{4}H_{9}KO + HCl = C_{4}H_{10}O + KCl$

112.21 = 36.46 74.12 74.55

## 2.5 Chemical conversion efficiencies

The molar chemical input conversion factors, F, and the material input coefficients, f, are given in table 1.

Table 1. Material requirements for praziquantel synthesis (quantity/unit output)

| Material input | F | f |
|---|---|---|
| 1-Cyano-2-acetyl-1,2-dihydro-isoquinoline | 0.634 | 1.921 |
| 1-Aminomethyl-2-acetyl-1,2,3,4-THIQ | 0.654 | |
| 1-Aminomethyl-1,2,3,4-THIQ | 0.519 | |
| 1-Cyclohexylcarboxamidomethyl-THIQ | 0.872 | 1.189 |
| 1-Cyclohexylcarboxamidomethyl-2-chloroacetyl-THIQ | 1.117 | 1.297 |
| Cyclohexyl carbonylchloride | 0.469 | 1.567 |
| Chloroacetylchloride | 0.362 | 0.546 |
| Hydrogen | 0.019 | 0.102 |
| Ethyl acetate | | 2.621 |
| Methylene chloride | 6.336 | |
| Raney nickel | | 1.455 |
| Acetonitrile | | 1.781 |
| Pyridine | | 0.844 |
| Hydrochloric acid | | 4.422 |
| Triethylamine | | 0.530 |
| Potassium tertiary-butylate | | 0.520 |
| Sodium hydroxide | | 5.041 |

Data in table 1 were calculated from examples 16, 26 and 28 of the FRG patent referred to in point 1. 90 to 95 per cent recovery and recycling was assumed for solvents. When quantities were not given in the patent (dichloromethane, hydrochloric acid and sodium hydroxide) own estimations were included in the table.

The yields of the studied process are listed in table 2.

Table 2. Praziquantel yields on feedstock intermediates and the main reactants (percentage)

| | | |
|---|---|---|
| 1-Cyano-2-acetyl-1.2-dihydro-isoquinoline | | 33.0 |
| 1-Cyclohexylcarboxamidomethyl - T.H.I.Q. | | 73.3 |
| 1-Cyclohexylcarboxamidemethyl-2-chloro-acetyl - T.H.I.Q. | | 86.1 |
| Cyclohexylcarbonyl chloride | | 29.9 |
| Chloroacetyl Chloride | | 66.3 |
| Yield of steps 1 to 3 | 45.0 | |
| Yield of step 4 | 85.1 | |
| Yield of step 5 | 86.1 | |

The relatively low step-by-step and overall yields allow for two conclusions: first, the process of the laboratory scale synthesis is not optimized, therefore, the quantity of waste is not minimized; secondly, patent descriptions are written in such a way as to extend process protection to a maximum possible degree and to say only the necessary minimum about the process commercially used. As a result, process analyses from patent descriptions show a pessimistic view of economic feasibility and waste generation. Nonetheless, patent descriptions are the best sources of information at the opportunity assessment stage.

2.6 Brief description of process

1-Cyano-2-acetyl-1,2-dihydro-isoquinoline is hydrogenated in ethylacetate solution, under a pressure of 260 atm., in the presence of Raney nickel. The solvent is distilled off, and the 1-aminomethyl-2-acetyl-1,2,3,4-tetrahydro-isoquinoline, (from now on the last part is abreviated as THIQ), is hydrolized in a 25 per cent hydrochloric acid solution, the pH of the reaction medium is made alkaline, and the 1-aminomethyl-1,2,3,4-THIQ is extracted with methylene chloride. The solvent is distilled off, the residue is dissolved in acetonitrile and acetylated by cyclohexylcarbonyl chloride in the presence of pyridine hydrochloride. Acetonitrile is distilled off, the residue is dissolved in dilute aqueous hydrochloric acid, the pH of the medium is made alkaline, and the reaction mixture is extracted with methylene chloride. The solvent is again distilled off. The obtained crude 1-cyclohexylcarboxami - domethyl-1,2,3,4-THIQ is recrystallized from acetone. The purified intermediate is dissolved in methylene chloride and reacted with chloroacetylchloride in the presence of triethylamine. The obtained 1-cyclohexylcarboxamidomethyl-2-chloroacetyl-1,2,3,4-THIQ is recrystallized and the ring-closure reaction is carried out with the aid of potassium tertiary-butylate in acetonitrile solution. After the addition of water, acetonitrile is distilled off and the residue is dissolved in methylene chloride. The reaction mixture is dried with anhydrous magnesium sulphate, the solvent is distilled off and the crude praziquantel is recrystallized from acetone. The overall yield is 33 per cent.

Other reaction routes are also described in the patent however, they are not significantly different from the above-described synthesis as far as environment protection is concerned.

# 3. ENVIRONMENT IMPACT ASSESSMENT

## 3.1 Material flow

The material flow schemas and informative material balances are shown in appendices 2 and 3, respectively.

## 3.2 Material requirements

### 3.2.1 Material consumption by nature of inputs

| | | | |
|---|---|---|---|
| **Reactants:** | | | |
| 1-Cyano-2-acetyl-1,2-dihydro-isoquinoline | 1,921 kg | | |
| Cyclohexylcarbonylchloride | 1,567 kg | | |
| Chloroacetylchloride | 546 kg | | |
| Hydrogen | 102 kg | 4,136 kg | 14.7% |
| **Reaction promoters** | | | |
| Raney nickel | 1,455 kg | | |
| Pyridine | 854 kg | | |
| Triethylamine | 530 kg | | |
| Potassium tertiary-butylate | 520 kg | 3,349 kg | 11.9% |
| **Solvents** | | | |
| Ethylacetate | 2,621 kg | | |
| Acetonitrile | 1,781 kg | | |
| Methylenechloride | 6,339 kg | 1,041 kg | 38.0% |
| **pH adjusters** | | | |
| Hydrochloric acid | 4,422 kg | | |
| Sodium hydroxide | 5,584 kg | 10.006 kg | 35.4% |
| Total: | | 28,232 kg | 100.0% |

The high share of solvents in the total material requirement is explained by the frequently repeated extraction operation. Real solvent use is higher than the calculated figure because solvents used to recrystallize intermediates and the finished product (ethanol, aceton, perhaps methylethylketone) were not quantified in the process description.

The share of hydrochloric acid and sodium hydroxide in the total amount of waste is also relatively high because of the multiple extractions and of the fact that the intermediates are not separated from the reaction mixture in the first three steps of the synthesis.

The quantity of reactants is also high by industrial standards because the overall yield is only about 33 per cent. The combined yield of the first three steps is 45 per cent, whereas the fourth and fifth steps are carried out with 85 per cent and 86 per cent yields, respectively.

The quantities of reaction promoters do not include credits due to recovery, although this is both possible and routinely done in commercial scale processes.

3.2.2 Material consumption by process stage

The material requirement has a'so be analyzed according to the distinct steps in the chemical syntheses:

| | | |
|---|---|---|
| 1-Cyclohexylcarboxamidomethyl-THIQ, (steps 1-3) | 23,388 kg | 82.8% |
| 1-Cyclohexylcarboxamidomethyl-2-chloroacetyl-THIQ (step 4) | 2,854 kg | 10.1% |
| Praziquantel (step 5) | 1,990 kg | 7.1% |
| | 28,232 kg | 100.0% |

About 83 per cent of the material inputs is consumed in the first three steps because their combined yield is only 45 per cent and the extraction operations are encountered in this stage.

3.3 Waste streams and treatments

The following wastes are generated during the manufacture of 1000 kg of praziquantel:

<u>Steps 1-3</u>

| | kg | | |
|---|---|---|---|
| Material inputs, intermediates, non-defined by-products and wastes | 1,598 | | |
| Hydrogen excess | 44 | | |
| Raney nickel | 1,455 | | |
| Pyridine | 844 | | |
| Ethylacetate | 2,621 | | |
| Acetonitrile | 1,050 | | |
| Methylene chloride | 3,861 | | |
| Sodium acetate | 795 | | |
| Sodium chloride | 7,591 | 19,859 | 79.8% |

<u>Step 4</u>

| | | | |
|---|---|---|---|
| Intermediates and non-defined by-products and wastes | 270 | | |
| Triethylamine | 530 | | |
| Hydrochloric acid | 215 | | |
| Methylene chloride | 1,739 | 2,754 | 11.1% |

<u>Step 5</u>

| | | | |
|---|---|---|---|
| Intermediates, finished product and non-defined by products and wastes | 161 | | |
| Potassium tertiaty-butylate | 103 | | |
| Potassium chloride | 277 | | |
| Tertiary butanol | 276 | | |
| Acetonitrile | 731 | | |
| Methylene chloride | 739 | 2,287 | 9.1% |

<u>Summary</u>

| | | | |
|---|---|---|---|
| Material inputs, intermediates, and non-defined by-products and wastes | 2,029 | | |
| Hydrogen excess | 44 | | |
| Raney nickel | 1,455 | | |
| Pyridine | 844 | | |
| Sodium acetate | 795 | | |
| Sodium chloride | 7,591 | | |
| Ethylacetate | 2,621 | | |
| Methylene chloride | 6,339 | | |
| Acetonitril | 1,781 | | |
| Triethylamine | 530 | | |
| Hydrochloric acid | 215 | | |
| Potassium tert. butylate | 103 | | |
| Potassium chloride | 277 | | |
| Tertiary-butanol | 276 | 24,900 | 100.0% |

Organic solvents account for the highest share, 43 per cent, of waste. Salts rank second with a share of 36 per cent. Organic chemical inputs and outputs represent a relatively large amount, 10 per cent, of waste.

3.3.1 Liquid effluent

Water-soluble inorganic salts, left in the aqueous phase after extraction, can be discharged into the public sewage system. This effluent contains also a small portion of water-soluble organic solvents; its amount should not exceed the maximum allowable concentration in the public sewage water.

3.3.2 Air pollutants

The loss of organic solvents during the process contaminates the air. Hydrogen excess used for the reduction of p-nitrophenol is also an air pollutant.

3.3.3 Solid wastes

The exhausted Raney-nickel catalyst can be regenerated. The remnants of solvent recovery and mother liquors contain the major part of solid organic wastes which should be incinerated.

3.4 Industrial safety

3.4.1 Materials

All materials used in praziquantel manufacture are hazardous; chloroacetic acid is very toxic, whereas acetonitrile, chloroacetylchloride, Raney-nickel, sulfuric acid and sodium hydroxide are either toxic or dangerous to handle.

As regards fire and explosion risk, hydrogen is very dangerous, while acetone, acetonitrile, ethylacetate, pyridine, Raney-nickel and triethylamine are dangerous.

Round 35 per cent of the waste is non-poisonous inorganic salt, the rest is harmful to the human health or the external environment.

3.4.2 Chemical conversions

The chemical reactions involved in the synthesis of praziquantel are: catalytic hydrogenation, hydrolysis, acylation, chloroacetylation and cyclization.

The 1-aminomethyl-1,2,3,4-THIQ can also be synthetized from N-glycil-beta-phenylethylamine by Bischler-Napieralski ring closure condensation followed by catalytic hydrogenation (schematic illustration of the synthesis, p. 1)

Backward integration can be increased with both synthesis routes, e.g., as follows:

The number of conversions would increase from five to eight, if the synthesis started from benzylcyanide which is easier to purchase than 1-cyano-2-acetyl-1,2-dihydroisoquinoline or N-glycil-beta-phenylethylamine

## 4. SUMMARY EVALUATION

The environment impact analysis of praziquantel synthesis is based on a patent description. The data come from a laboratory scale process and the major objective is to extend process claims as much as possible without disclosing much about industrial know-how. Consequently, technical conclusions are semi-quantitative in character and the amounts of wastes from the laboratory scale synthesis reveal opportunities for process development. Both the kinds and amounts of organic solvents could be reduced; extraction operations can be elimінted. The solvents can be recycled and the efficiency of recovery can be improved. The manufacturing process should preferably be carried out in a closed system. Raney-nickel should be regenerated and recycled into the process.

The yields of steps 1-3 are very low and their improvement would result in a significant reduction of wastes. Organic solvents should be removed by heat or biological treatment from the effluents. Organic solid wastes can be incinerated. The control of air pollution by organic solvents requires above-the-average complementary investment.

The process starting from N-glycil-beta-phenylethylamine was not been analyzed. Increased backward integration would start production from common petrochemical feedstocks (produced by low-waste technologies). This is important to mention because final environment impact analysis can only be made if all steps of the total synthesis have been evaluated.

Appendix 1 to annex .. of the

ENVIRONMENT IMPACT ANALYSIS OF THE MANUFACTURE OF PRAZIQUANTEL

Reactants, products and auxiliary materials in Praziquantel manufacture

| Compound | Chemical formula | Molecular weight |
|---|---|---|
| 1-Aminomethyl-1,2,3,4-THIQ | $C_{10}H_{14}N_2$ | 162.23 |
| 1-Cyano-2-acetyl-1,2-dihydroisoquinoline | $C_{12}H_{10}N_2O$ | 198.22 |
| 1-Cyclohexylcarbonylaminomethyl-THIQ | $C_{17}H_{24}N_2O$ | 272.39 |
| 1-Cyclohexylcarbonylaminomethyl-2-chloroacetyl-THIQ | $C_{19}H_{25}ClN_2O_2$ | 348.87 |
| 2-Cyclohexylcarbonylaminomethyl-4-oxo-1,2,3,6,7,11b-hexahydro-4H-pirazino(2,1a)isoquinoline | $C_{19}H_{24}N_2O_2$ | 312.41 |
| Hydrogen | $H_2$ | 2.02 |
| Cyclohexylcarbonyl chloride | $C_7H_{11}ClO$ | 146.61 |
| Chloroacetic acid | $C_2H_3ClO_2$ | 94.50 |
| Chloroacetylchloride | $C_2H_2Cl_2O$ | 112.94 |
| Pyridine | $C_5H_5N$ | 79.10 |
| Hydrochloric acid | $HCl$ | 36.46 |
| Triethylamine | $C_6H_{15}N$ | 101.19 |
| Potassium tertiary-butylate | $C_4H_9KO$ | 112.21 |
| Sodium hydroxide | $NaOH$ | 40.00 |
| Acetic acid | $C_2H_4O_2$ | 60.05 |
| Sodium acetate | $CH_3COONa$ | 82.04 |
| Sodium chloride | $NaCl$ | 58.44 |
| Butanol, tertiary | $C_4H_{10}O$ | 74.12 |
| Potassium chloride | $KCl$ | 74.55 |

Appendix 2 to annex .. of the

ENVIRONMENT IMPACT ANALYSIS OF THE MANUFACTURE OF PRAZIQUANTEL

Flow schemas of the manufacturing process of Praziquantel

Appendix 3 to annex .. of the

ENVIRONMENT IMPACT ANALYSIS OF THE MANUFACTURE OF PRAZIQUANTEL

Material balances
for the manufacture of 1000 kg of Praziquantel
(kilogrammes)

| | Inputs | Outputs |
|---|---|---|
| **Steps 1-3** | | |
| 1-cyano-2-acetyl-1,2-DHIQ | 1,921 | . |
| Raney-nickel | 1,455 | 1,455 |
| Hydrogen | 102 | 44 |
| Hydrochloric acid | 4,384 | |
| Sodium hydroxide | 5,585 | |
| Pyridine | 844 | 844 |
| Cyclohexylcarbonyl chloride | 1,567 | 146 |
| Ethyl acetate | 2,621 | 2,621 |
| Acetonitrile | 1,050 | 1,050 |
| Methylene chloride (dichloromethane) | 3,861 | 3,861 |
| Sodium acetate | | 795 |
| Sodium chloride | | 7,591 |
| Water | 175 | 2,516 |
| 1-cyclohexylcarboxamide methyl-THIQ | | 2,641 |
| Total steps 1-3: | 23,563 | 23,564 |

| | | |
|---|---|---|
| Waste | 23,564 | |
| | -2,516 | |
| | -1,189 | 19,859 |

| | Inputs | Outputs |
|---|---|---|
| **Step 4** | | |
| 1-cyclohexylcarboxamide mryhyl-THIQ | 1,189 | |
| Triethylamine | 530 | 530 |
| Chloroacetyl chloride | 546 | |
| Methylene chloride | 1,739 | 1,739 |
| Hydrochloric acid | 39 | 215 |
| Chloroacetic acid | | 44 |
| Water | 8 | |
| 1-cyclohexylcarboxamide methyl-2-chloroacetyl-DHIQ | | 1,523 |
| Total step 4: | 4,051 | 4,051 |

| | | |
|---|---|---|
| Waste | 4,051 | |
| | -1,297 | 2,754 |

Step 5

| | | |
|---|---|---|
| 1-cyclohexylcarboxamid methyl-2-chloroacetyl-THIQ | 1,297 | |
| Potassium tert. butylate | 520 | 103 |
| Acetonitrile | 731 | 731 |
| Methylene chloride | 739 | 739 |
| Potassium chloride | | 277 |
| Butanol tert. | | 276 |
| Praziquantel | | 1,161 |
| Total step 5: | 3,287 | 3,287 |

| | | |
|---|---|---|
| Waste | 3,287 | |
| | -1,000 | 2,287 |

Summary

| | | |
|---|---|---|
| 1-cyano-2-acetyl-1,2-DHIQ | 1,921 | |
| Raney-nickel | 1,455 | 1,455 |
| Hydrogen | 102 | 44 |
| Hydrochloric acid | 4,422 | 215 |
| Sodium hydroxide | 5,584 | |
| Pyridine | 844 | 844 |
| Cyclohexylcabonyl chloride | 1,567 | 146 |
| Ethylacetate | 2,621 | 2,621 |
| Acetonitrile | 1,781 | 1,781 |
| Methylene chloride | 6,339 | 6,339 |
| Sodium acetate | | 795 |
| Sodium chloride | | 7,591 |
| Triethylamine | 530 | 530 |
| Chloroacetylchloride | 546 | |
| Chloroacetic acid | | 44 |
| Water | 183 | 2,516 |
| Potassium tert.butylate | 520 | 103 |
| Potassium chloride | | 277 |
| Butanol tert. | | [illegible] |
| 1-cyclohexylcarboxamide-methyl-THIQ | | [illegible] |
| 1-cyclohexylcarboxamido methyl-2-chloroacetyl-THIQ | | 226 |
| Praziquantel waste | | 161 |
| Praziquantel product | | 1,000 |
| Total: | 28,415 | 28,416 |

| | | |
|---|---|---|
| Waste | 28,416 | |
| | -2,516 | |
| | -1,000 | 24,900 |