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TECHNICAL AND ECONOMIC ANALYSIS OF THE MANUFACTURE OF ETHAMBUTOL HYDROCHLORIDE

Sectoral Studies Series
No. 21

SECTORAL STUDIES BRANCH
DIVISION FOR INDUSTRIAL STUDIES

Main results of the study work on industrial sectors are presented in the Sectoral Studies Series. In addition a series of Sectoral Working Papers is issued.

This document presents major results of work under the element Studies on Pharmaceutical Industries in UNIDO's programme of Industrial Studies 1984/85.

Preface

This study addresses the problem of the decision-making in the process development for the manufacture of pharmaceutical chemicals and intermediates by organic chemical synthesis. It discusses in detail some of the important factors (e.g., available plant facilities, cost savings, convertible currency savings, availability of starting materials and commercial-scale technology) which must influence the initiation and conduct of a typical development programme as well as the final selection of pharmaceutical chemicals and their intermediates for such programmes. Nevertheless, further more detailed and definitive studies of technical feasibility and economic viability are strongly recommended prior to the actual initiation of such programmes or the purchase of a particular technology for use in a specific geographical area.

The subject has been studied because of its industrial importance and social benefits to developing countries. This particular report is concerned with ETHAMBUTOL Hydrochloride, a drug which is specifically effective against most strains of actively-growing Mycobacteria tuberculosis. The three other reports in the series are concerned with isoniazid, frequently administered concurrently with ETHAMBUTOL for the treatment of tuberculosis; with chloroquine phosphate,*/ used widely in the therapy and prophylaxis of malaria; and with acetylsalicylic acid, a common analgesic. Collectively, these four documents will serve as the basis for a preliminary, generalized decision-making study.

The Sectoral Studies Branch wishes to acknowledge the contribution of Professor Barna Mezey, Budapest Technical University, Hungary, for the provision of essential information and for his comments and criticism in the course of this work.

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*/ Technical and economic analysis of the manufacture of CHLOROQUINE Phosphate, UNIDO/IS.518.

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EXPLANATORY NOTES

Prices and market values are given in United States dollars.

A comma (,) is used to distinguish thousands and millions.

A full stop (.) is used to indicate decimals.

A slash between dates (e.g. 1980/81) indicates a financial year.

Use of hyphen between dates (e.g., 1980-2000) indicates the full period involved, including the beginning and end years.

The following forms have been used in tables:

Three dots (...) indicate that data are not available or are not separately reported.

A dash (-) indicates that the amount is nil or negligible.

A blank indicates that the item is not applicable.

Totals may not add up precisely because of rounding.

Besides the common abbreviations, symbols and terms and those accepted by the International System of Units (SI), the following abbreviations have been used in this study:

CAS	Chemical Abstracts
WHO	World Health Organization
(+)-2AlB	(+)-2-Amino-1-butanol
$(\bar{+})$-2AlB	$(\bar{+})$-2-Amino-1-butanol
(+)	Dextrorotatory enantiomer
(-)	Levorotatory enantiomer
$(\bar{+})$	Racemic mixture
$\bar{C}_{tp}$	Total production costs

KEY WORDS

For the purpose of this study, certain repeatedly used terms are defined as follows:

1. Basic patent is the patent which describes first (a) a new process and the product/s/ prepared by this process, or (b) a new product or products prepared by known processes. Priority is determined by the date of application and not by the date of approval/publication of the patent.

2. Chemical input conversion coefficient is the number of units of a chemical input required for the production of one unit of a chemical output.

3. Material input consumption coefficient is the number of units of a material input required for the production of one unit of chemical output. The material input consumption coefficient differs from the chemical input conversion coefficient in that it accounts also for the material loss occuring during physical operations, such as crystallization, drying, etc.

4. Convertible currency saving is the difference between the world-market price of one kg of the pharmaceutical chemical and the cost of imported materials to produce the same, both expressed in $US, disregarding the single $US expenditure of the investment and those elements of the conversion costs, e.g. energy, that might also have to be paid in $US.

5. Integraced ETHAMBUTOL Hydrochloride manufacturer is a producer who synthesizes his (+)-2A1B starting from (±)-2A1B or from a more remote degree of backward integration.

6. Key intermediate is a chemical input which plays a dominant role in the direct material costs.

7. Model is a representation of an actual phenomenon such as an actual system or process.

8. Pharmaceutical chemical is a chemical substance used as the active ingredient of pharmaceutical preparations.

9. Yield: is the real quantity of a chemical output, expressed as percentage of the theoretical quantity of the same chemical output with reference to a specified chemical input.

1. INTRODUCTION

UNIDO has drawn up an illustrative list of pharmaceutical chemicals and intermediates for local production in developing countries. This list furnishes a basis for countries to identify their own priorities and to make their own selection. This case study on ETHAMBUTOL Hydrochloride is one of four intended to illustrate some important technical and economic factors, which affect the decision-making process of selecting potential candidates for local production by organic chemical synthesis.[1/]

This study provides basic information that should be taken into account also when operating and expanding an ETHAMBUTOL Hydrochloride production plant, but it should not be interpreted as a feasibility or pre-feasibility study. Plans for actual investment would, of course, require in-depth marketing, engineering and financial studies.

The study has been organized so that the syntheses of chemicals and the relevant patent information as well as the lists of manufacturers and suppliers are given in the annexes, whereas the technical and economic aspects of the production are analyzed in chapters 5 to 9.

The technical levels of the studied technologies of ETHAMBUTOL Hydrochloride and key intermediates were estimated by comparing quantitative parameters, such as chemical conversion coefficients, material input consumption coefficients and yields and by analyzing the brief descriptions of the chemical processes.

The process economics of ETHAMBUTOL Hydrochloride production were assessed taking into account three cost factors:

- Key intermediates,
- Direct material inputs, and
- Conversion costs.

1/ The other studies in the series concern Isoniazid, Chloroquine Phosphate and Acetylsalicylic Acid.

Costs of key intermediates and direct material inputs were calculated by using the material input consumption coefficients of the technology studied and annual average import prices of materials in different countries in 1982.

In the analysis, an overall estimate variable has been used for the conversion costs which approximates the real costs of a large producer in a developing country.

Profitability and convertible currency savings were estimated by subtracting the total production costs and direct material costs, respectively, from the world-market price of ETHAMBUTOL Hydrochloride to conclude the economic feasibility of the process alternative studied.

The patent information given in this study shows the result of the computer search in all issues of chemical abstracts published between 1 January 1967 and 31 December 1984. This patent information should not be taken as a guarantee that other process patents of ETHAMBUTOL Hydrochloride do not exist and/or are not valid in a given country.

2. OBJECTIVES OF THE STUDY

The main objective of the study is to outline a sectoral decision-making model which can be used in the production programme research stage of the pre-investment phase of the project development cycle to generate technically feasible and economically promising, or at least acceptable, ideas and to transform them into broad investment propositions.

To this effect, an attempt has been made to assess available sources of technical and economic microdata for the manufacture of ETHAMBUTOL Hydrochloride and its intermediates, and to illustrate what can be done with the available information. Advantages and disadvantages of alternative strategies as a function of backward integration of the manufacturing process are described.

It is hoped that this work will assist interested developing countries in the evaluation of offers for transfer of technology in the pharmaceutical sector as well as in setting technical development targets, estimating prices of imported chemical inputs and convertible currency demand for such imports for the local production of ETHAMBUTOL Hydrochloride.

3. BACKGROUND AND HISTORY

The antituberculosis effect of hydroxydiamines[2], among them ETHAMBUTOL, was discovered in 1960. The basic patent (U.S. pat. 3,176,040 to American Cyanamide Co.) described the racemate. Yields indicated in this basic patent were low.

Subsequent studies revealed that the (+)-enantiomorph of the substance exhibited 200 times more activity than did the (-)-isomer.[3]

Twenty-six process patents were granted for the manufacture of ETHAMBUTOL in the years 1967-1976; these related not only to preparation of optically active compounds but also to the improvement of quality and production yields. The intensive technical development has also been reflected in the twenty-four process patents devoted to the preparation of the key intermediates, (±)-2A1B and (+)-2A1B, in the years 1967-1984.

No new patents for ETHAMBUTOL Hydrochloride have been published since 1976.[4] Although the basic patent has expired,[5] a few process patents, mostly concerning intermediates, are still valid.

The introduction in the 1960s of two new drugs for the chemotherapy of tuberculosis - ETHAMBUTOL and rifampin - changed many of the concepts and practices that, were prevalent until that time. ETHAMBUTOL Hydrochloride has a distinct advantage over other antituberculosis drugs in that bacterial resistance is very unlikely to develop rapidly. However, its price has precluded its more widespread use in developing countries where it is often

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2/ German pat. 1,251,770: Verfahren zur Herstellung von aliphatischen Hydroxydiaminen und deren Säureadditionssalzen (1961).

3/ Goodman and Gilman's The Pharmacological Basis of Therapeutics, VIth Edition, MacMillan Publishing Co., Inc., New York, 1980, p. 1206.

4/ U.S. pat. 3,944,618.

5/ U.S. pat. 3,176,040.

reserved for retreatment. Consequently, ETHAMBUTOL Hydrochloride is very probably still in the ascending phase of the life-cycle curve, gaining wider acceptance as its price declines.

According to UNIDO estimates, about 425 tons of ETHAMBUTOL are sold annually worldwide. The total value of the market to manufacturers is some $US 23 million per year and the total retail value falls in the region of $US 46 million, assuming that manufacturers' price amounts to 50 per cent of the price to the consumer.

4. METHODOLOGY OF THE ANALYSIS OF PROCESS ECONOMICS

The process selected as standard reference to discuss the manufacturing technology of ETHAMBUTOL Hydrochloride is illustrated in figure 1. Step-by-step technical and economic details are not all immediately available. However, at this preliminary level in the decision-making, these are generally not necessary so, here, the manufacturing processes for different degrees of backward integration have been considered as single-step chemical reactions. Thus, e.g., the maximum degree of backward integration of the studied process may be described by the following equation:

$4\ C_4H_8$	+	$4\ Cl_2$	+	$4\ C_2H_3N$	+	$4\ H_2O$	+	$4C_4H_6O_6$	+	$4\ Ca(OH)_2$	+	$C_2H_4Cl_2$	=
4 x 56.11		4 x 70.91		4 x 41.05		4 x 18.02		4 x 150.09		4 x 74.09		98.96	
224.44		283.64		164.20		72.08		600.36		296.36		98.96	

$C_{10}H_{26}Cl_2N_2O_2$	+	$2C_4H_{11}NO$	+	$4C_4H_4CaO_6$	+	$4C_2H_4O_2$	+	$8HCl$
277.23		2 x 89.14		4 x 188.15		4 x 60.05		8 x 36.46
277.23		178.28		752.60		240.20		291.68

This permitted the calculation of overall material input consumption coefficients in spite of the fact that such a reaction does not take place in the real manufacturing process.

4.1 Data

In table 1, the chemical formulae of ETHAMBUTOL Hydrochloride, its intermediates and raw materials were taken from various sources. The molecular weights are those given in the United States Pharmacopeia or were calculated using atomic weights recommended by the International Union of Pure or Applied Chemistry in 1978; the results have been rounded up to two decimals.

Table 1 does not contain data concerning reactants and products which are used in reactions not evaluated separately during the analysis of backward integration of ETHAMBUTOL Hydrochloride production.

Figure 1. Schematic illustration of the studied process of ETHAMBUTOL Hydrochloride synthesis

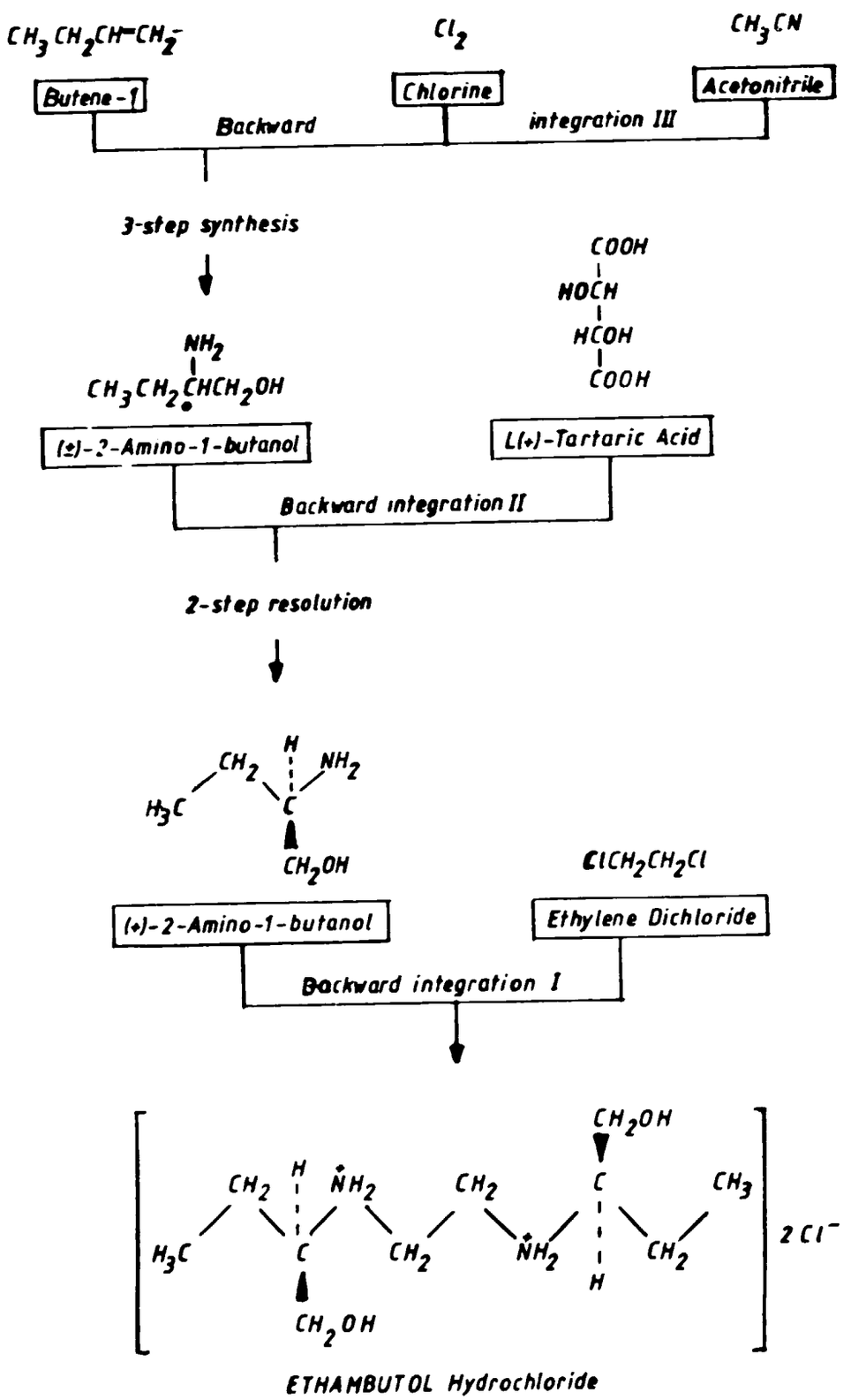

Table 1. Definition of important chemical inputs and outputs in the manufacture of ETHAMBUTOL Hydrochloride

Name	CAS registry number	Chemical formula	Molecular weight
ETHAMBUTOL Hydrochloride	[1070-11-7]	$C_{10}H_{26}Cl_2N_2O_2$	277.23
ETHAMBUTOL	[7 -55-5]	$C_{10}H_{24}N_2O_2$	204.31
(+)-2-Amino-1-butanol	[96-20-8]	$C_4H_{11}NO$	89.14
Ethylene Dichloride	[107-06-2]	$C_2H_4Cl_2$	98.96
(±)-2-Amino-1-butanol	[96-20-8]	$C_4H_{11}NO$	89.14
L(+) Tartaric Acid	[87-69-4]	$C_4H_6O_6$	150.09
(+)-2-Amino-1-butanol L(+)-Tartrate	a/	$C_8H_{17}NO_7$	239.22
Calcium Hydroxide	[1305-62-0]	$Ca(OH)_2$	74.09
Calcium Tartrate	[3164-34-9]	$C_2H_4CaO_6$	188.15
Butene-1	[106-98-9]	C_4H_8	56.11
Chlorine	[7782-50-5]	Cl_2	70.91
Acetonitrile	[75-05-8]	C_2H_3N	41.05
Hydrochloric Acid	[7647-01-0]	HCl	36.46
Acetic Acid	[64-19-7]	$C_2H_4O_2$	60.05
Water	[7732-18-5]	H_2O	18.02

a/ Non-commercial compound; no CAS registry number available.

The molar chemical input conversion coefficient, F, was calculated by dividing the molecular weight of the chemical on hand with that of ETHAMBUTOL Hydrochloride.

Material input consumption coefficients and/or yields (table 2) refer basically to the same technology, hence data from different sources[6/] were pooled and the simple arithmetic average was taken for the average performer (f_1 and y_1 values), whereas the best consumption coefficients published in the literature (f_2 and y_2 values) were used to describe an ideal performer. Better figures were sometimes known, e.g. a large manufacturer reported a 0.82 (+)-2AlB f_2 value, but they were disregarded in the calculations if not published.

Table 2. Chemical input conversion coefficients and percentage yields of two hypothetical ETHAMBUTOL Hydrochloride producers

Name	F	f_1	y_1	f_2	y_2
(+)-2-Amino-1-butanol	0.64	0.99	65	0.85	75
Ethylene Dichloride	0.36	0.48	75	0.45	80
Hydrochloric Acid gas	0.26	0.27	96	0.26	100
(±)-2-Amino-1-butanol	1.29	2.41	54	1.93	67
L(+)-Tartaric Acid	2.17	4.11	53	3.21	68
Butene-1	0.81	3.65	22	2.68	30
Chlorine	1.02	4.22	24	3.40	30
Acetonitrile	0.59	4.29	14	2.26	26

6/ Wilkinson, Shepherd et.al., J. Am. Chem. Soc. 83,2212 (1961); UNIDO unpublished working paper; UNIDO/ID/WG.304/6 (1979); UNIDO/ID/WG.331/4 (1980); UNIDO/PC.14 (1981); unpublished country project proposal; UNIDO/PC.52 (1982); U.S. pat. 3,553,257, 3,855,300 and 3,944,617; UNIDO correspondence (1983).

The chemical conversion efficiency was expressed in the literature in different ways. Data were given sometimes as weights of the input and corresponding output, or real input conversion coefficients, or yields. When converting these data into each other, f_1 and f_2 values were rounded up to two decimals whereas yields to integer numbers, because neither the accuracy of the data nor the objectives of the study justify greater precision. F values were also rounded up to two decimals.

The 1981-1982 c.i.f. import and domestic market prices of chemicals were available from different sources[7/] and the following values, converted into $US when necessary, were selected for the techno-economic analysis (table 3).

Table 3. Prices of important chemical intermediates, raw materials, and by-products in the manufacture of ETHAMBUTOL Hydrochloride ($US/kg)

Name	Unit price
ETHAMBUTOL Hydrochloride	54.00
(+)-2-Amino-1-butanol	46.50
Ethylene Dichloride	0.53
Hydrochloric Acid, gas	0.18
(+)-2-Amino-1-butanol	8.92
L(+) Tartaric Acid	1.69
Calcium Hydroxide	0.05
Calcium Tartrate	0.51
Butene-1	0.62
Acetonitrile	1.00
Chlorine	0.17
Isopropanol	0.55
Methanol	0.20
Ethanol	0.42
Hydrochloric Acid	0.07
Sulphuric Acid	0.08
Sodium Hydroxide, 50% solution	0.21
Sodium Hydroxide flakes	0.30
Sodium Carbonate	0.16
Carbon active	2.53

7/ Drug Statistics, Ministry of Chemicals and Fertilizers, Government of India, Chemical Marketing Reporter, UNIDO document PC.52 of 13 Sept. 1982; and UNIDO correspondence with buyers and suppliers in 1982.

It is worth also mentioning that the prices of intermediates increased more than the price of ETHAMBUTOL Hydrochloride in the studied period of time.

4.2 Brief description of the Model

The molar chemical input conversion coefficients, F, were calculated from the molecular weights given in table 1.

In table 2, the yields, y_1 and y_2, or the real material input consumption coefficients, f_1 and f_2, were calculated by using the following formula:

$$y_{ij} = \frac{F}{f_{ij}} \; 100 \qquad (1)$$

and, the unit direct material costs were calculated:

$$C_{ij} = f_{1j}p_1 + f_{2j}p_2 + \ldots + f_{ij}p_i + c_{hj} \qquad (2)$$

taking the unit prices, p_1, $p_2 \ldots p_i$ from table 3. Data for cost of auxiliary materials of smaller importance, such as organic solvents and adsorbents, were not available for all degrees of backward integration and a proxy was added for the unit cost of other materials, c_{hj}, to arrive at unit direct material costs, C_{ij}. The proxy was based on published data[8/] and on own estimations taking into account real material input consumption coefficients and available unit prices. Data were scarce, or not available, for other elements in variable costs such as direct wages and salaries, consumable stores, repairs and maintenance, etc. or in fixed costs such as depreciation, factory and administrative overheads, etc. Since these costs vary according to the size and location of a plant, even within the same country, another proxy, C_c, based on published information in a developing country in 1982 was used.[9/] The unit gross profit or loss was obtained by subtracting the unit total production costs, C_{tp}, from the unit world market

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8/ UNIDO/PC.52 of 13 September 1982.

9/ Ibid.

price of ETHAMBUTOL Hydrochloride, or vice versa. The world market price of $US 54 per kilo reflects the arithmetic average of the f.o.b. quotations of several European trading companies for the delivery of 1,000 kg of ETHAMBUTOL Hydrochloride in 1982.[10/]

Material costs were based on uniform quality specification of chemical inputs. Adequate power, water and transport facilities were assumed available at the plant site.

Three criteria were used in the evaluation of the different degrees of backward integration: technical feasibility, profitability and convertible currency saving. The methodology does not take into account any additional convertible currency investment costs in new or existing pharmaceutical chemical plants. The methodology will therefore serve as a tool to arrive at a first selection of technically feasible and economically promising alternatives, which should be studied in closer detail if a decision is taken to prepare an investment pre-feasibility study.

Whenever the methodology described is used for decision-making in the selection of potential candidate compounds for domestic production, cost estimation sheets should be completed to conform to local conditions and to improve the reality of estimates in this study.

10/ Dangschat; Karl O. Helm; K & K Greef; Marsing; Medimpex; Oxyde and Polfa.

5. ANALYSES OF THE PRODUCTION OF ETHAMBUTOL HYDROCHLORIDE BULK SUBSTANCE AND KEY INTERMEDIATES

5.1 ETHAMBUTOL Hydrochloride production from imported (+)-2-Amino-1-butanol and Ethylene Dichloride

ETHAMBUTOL Hydrochloride is synthesized by reacting (+)-2AlB with Ethylene Dichloride; distilling the excess (+)-2AlB off under vacuum for eventual re-use; and diluting the residue with isopropanol or other solvents. The product is then precipitated as the hydrochloride by the addition of Hydrochloric Acid gas.

The cost and cost structure estimates of the average performer and ideal performer are shown in table 4.

Table 4. Cost and cost structure estimates of ETHAMBUTOL Hydrochloride production. Backward integration I

Cost element	C_1 US$	C_1 %	C_2 US$	C_2 %
(+)-2-Amino-1-butanol	46.04	84.1	39.53	84.9
Key intermediate costs	46.04	84.1	39.53	84.9
Ethylene Dichloride	0.25	0.5	0.24	0.5
Isopropanol	1.83	3.3	1.23	2.6
Other materials	1.17	2.1	0.90	1.9
Direct material costs	49.29	90.0	41.90	90.0
Conversion costs	5.45	10.0	4.68	10.0
Production costs	54.74	100.0	46.58	100.0

C_1 ... unit costs of the average performer
C_2 ... unit costs of the ideal performer

Table 4 shows that (+)-2AlB accounts for about 93 per cent of direct material and over 84 per cent of total production costs. The total costs of the average performer closely approach but are not lower than the unit price of $US 54 for ETHAMBUTOL Hydrochloride given in table 3; however, the ideal performer falls almost 14 per cent below. Probably the major cost reduction factor in this process is the more efficient recovery of all excess (+)-2AlB for re-use.

Thus, costs of the average performer reflect a unit gross loss of $US 0.74 while those of the ideal performer show a unit gross gain of $US 7.42. Predicated upon direct material costs, convertible currency savings are $US 4.71 for the average performer but nearly triple that amount, $US 12.10 for the ideal operation.

A one per cent increase in the price of (+)-2AlB would increase the direct material costs of both producers by about 0.8 per cent. This would result in an increased gross loss of the average performer by $US 0.46 or 62 per cent, and in decrease of the gross gain of the ideal performer by $US 0.40 or about five per cent.

A one per cent improvement in the material input consumption coefficient of (+)-2AlB will result in an equivalent reduction in direct material costs and, conversely, an increase in the gross gain, assuming no change in the conversion costs.

The advantages of this particular method of synthesis of ETHAMBUTOL Hydrochloride are that the gross loss for the average producer may be close enough to the break-even point to be easily converted to a gross gain; that the gross gain for the ideal performer is, at least, acceptable; that production may be carried out in a multi-purpose batch reactor, possibly utilizing excess capacity; and that both the key intermediate, (+)-2AlB, and the commercial-scale technology are available in international markets.

The major disadvantages are that (+)-2AlB has been available from only a few suppliers and, consequently, its cost has remained relatively high.

5.2 ETHAMBUTOL Hydrochloride production from imported (±)-2-Amino-1-butanol and Ethylene Dichloride

In this process, L(+) Tartaric Acid is used to resolve the (±)-2A1B before it is reacted with Ethylene Dichloride. The economic feasibility of this production is aided, somewhat, by the recovery of as much as 90 per cent of the Tartaric Acid in form of Calcium Tartrate as shown in table 5.

Table 5. Cost and cost structure estimates of ETHAMBUTOL Hydrochloride production. Backward integration II

Cost element	C_1 $US	C_1 %	C_2 $US	C_2 %
(±)-2-Amino-1-butanol	21.50	50.9	17.22	50.6
Key intermediate costs	21.50	50.9	17.22	50.6
Ethylene Dichloride	0.25	0.6	0.24	0.7
Isopropanol	1.83	4.3	1.21	3.6
L(+)-Tartaric Acid	6.95	16.5	5.42	15.9
Other materials	1.77	4.2	1.37	4.0
L(+)-Tartaric Acid, recovered	-1.89	-4.5	-1.47	-4.3
Direct material costs	30.41	72.0	23.99	70.6
Conversion costs	11.81	28.0	10.01	29.4
Production costs	42.22	100.0	34.00	100.0

C_1 ... unit costs of the average performer
C_2 ... unit costs of the ideal performer

In this procedure (±)-2A1B accounts for about 71 per cent of the direct material costs but only about 51 per cent of total production costs.

The average and the ideal performer show unit gross gains of $US 11.78 and $US 20.00 over the $US 54 price previously provided; convertible currency savings are $US 23.59 and $US 30.01, respectively.

One per cent increase in the price of (+)-2AlB would increase the direct material costs of both producers by about 0.70 per cent, reducing the gross gain of the average performer by $US 0.22 or 1.9 per cent and of the ideal performer by $US 0.17 or about 0.9 per cent.

A one per cent improvement in the chemical input conversion coefficient will, conversely, decrease the direct material costs of both producers, increasing both the convertible currency gain and the gross gain of the average performer by $US 0.22 and of the ideal performer by $US 0.17, once again assuming no variation in conversion costs.

Utilizing this particular method, the proportionate share of all chemical inputs other than the key intermediate rises to about 27 per cent or more than triple that in backward integration I; the exact amount may vary, depending upon the successful recovery of the L(+)-Tartaric Acid.

The advantages of this synthesis are that direct material costs are substantially reduced; that gross gain of about 28 per cent is shown instead of a gross loss of about 1 per cent for the average producer, and the gross profit is more than doubled for the ideal producer; that production may be carried out in multi-purpose batch reactors; that the required intermediates as well as the commercial-scale technology are available in international trade; and that the production does not require a much higher technical level than backward integration I.

One of the critical factors affecting the economics of this process is the price of L(+)-Tartaric Acid which, as noted earlier, has fluctuated over a wide range in recent years. The unit price of $US 2.53 quoted for this chemical at the end of 1984[11/] was about 50 per cent higher than listed in table 3. L(+)-Tartaric Acid at this latter price would increase direct material costs of both performers by about 15 to 16 per cent and the C_{tp} of the average performer by about 7 per cent and the C_{tp} of the ideal performer by about 12 per cent, respectively. In turn, gross gains would be reduced to $US 8.30 and $US 17.30 and convertible currency savings to $US 20.10 and

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11/ Chemical Market Reporter, 10 December 1984, p. 42.

$US 27.31, rendering the adoption of this method less attractive, particularly for an average performer. In a European country, on the other hand, the price of L(+)-Tartaric Acid was lower in 1984 than the reference price given in table 3. Whatever is the case, the cost of L(+)-Tartaric Acid in the studied process represents about 23 or 16 per cent, respectively, of the direct material costs and C_{tp} without recovery, and about 17 or 12 per cent, respectively, if 90 per cent of L(+)-Tartaric Acid excess is recovered from the mother liquor. Hence, fluctuations in the price of L(+)-Tartaric Acid affect significantly both the C_{tp} and gross profit of ETHAMBUTOL Hydrochloride manufacture, because the changes in L(+)-Tartaric Acid price cannot be fully reflected in the selling price of the pharmaceutical chemical.

Another point to be considered is that the final yield from this process can be somewhat lower than those from backward integration I; of major importance in maximizing this yield is the optimum recovery of excess (+)-2A1B.

5.3 ETHAMBUTOL Hydrochloride production from Acetonitrile, Butene-1, Chlorine and Ethylene Dichloride

A third option is a more basic synthesis of ETHAMBUTOL Hydrochloride, beginning with Acetonitrile, Butene-1 and Chlorine.

Table 6 shows that both direct material and total production costs are lower than with either of the preceding methods. Consequently, the two performers show respective gross gains of $US 16.71 and $US 24.70 over the comparable unit price of ETHAMBUTOL Hydrochloride. Convertible currency savings also increase to $US 36.96 and $US 41.47.

Generally speaking, minor fluctuations in the prices of individual intermediates should not have as serious an effect on production costs for this method because, proportionately, none are as significant as the (+)-2A1B or (±)-2A1B utilized in backward integrations I and II. Nevertheless, as with backward integration II, a notably high price for L(+)-Tartaric Acid would reflect unfavourably upon the economies of the process. Once again, applying 1984 prices, direct material costs would increase by about 18 per cent for the average and 20 per cent for the ideal performer; however, because of the

larger share of the C_{tp} accounted for by conversion costs in this process, its increase would remain at about the same magnitude as in backward integration II, around 9 per cent. Thus, convertible currency savings would be $US 33.50 and $US 38.70 and gross profits $US 13.20 and $US 22.00, respectively. The proportion still would be attractive from the standpoint of saving convertible currency but less attractive, particularly for the average performer, from that of gross gains.

Table 6. Cost and cost structure estimates of ETHAMBUTOL Hydrochloride production. Backward integration III

Cost element	C_1 US$	C_1 %	C_2 US$	C_2 %
Acetonitrile	4.22	11.3	2.26	7.7
Butene-1	2.26	6.1	1.66	5.7
Chlorine	0.73	2.0	0.58	2.0
L(+)-Tartaric acid	6.95	18.6	5.42	18.5
Ethylene Dichloride	0.25	0.7	0.24	0.8
Isopropanol	1.83	4.9	1.23	4.2
Other materials	2.69	7.2	2.61	8.9
L(+)-Tartaric acid, recovered	-1.89	-5.1	-1.47	-5.0
Direct material costs	17.04	45.7	12.53	42.8
Conversion costs	20.25	54.3	16.77	57.2
Production costs	37.29	100.0	29.30	100.0

C_1 ... unit costs of the average performer

C_2 ... unit costs of the ideal performer

Additionally, it has been reported that the best results are obtained in the reaction with Acetonitrile if an excess of Acetonitrile is used.[12/] This does not appear to be the major contributor to the success of the ideal performer, judging from the data shown in table 6; however, it is a subject for consideration because Acetonitrile is one of relatively expensive

12/ U.S. pat. 3,944,618.

components in the process and its price has risen steadily over the years. Recovery of Acetonitrile and Isopropanol, say with an efficiency of 95 per cent, would play therefore an important role.

There is no key intermediate in backward integration III, but special attention should be paid to the consumptions of L(+)-Tartaric Acid and Acetonitrile, because they strongly affect both direct material costs and C_{tp}. All of the required materials are available in international trade and, although the process is more lengthy and complex than that in backward integration II, it is technically feasible. However, it is still covered by a U.S. patent issued in 1976,[13/] which may present a problem for prospective users seeking commercial-scale technology.

The share of the conversion costs in C_{tp} is higher than that of direct materials, therefore, general and technical management will play a dominant role also in process economics.

13/ Op. cit.

6. EFFECT OF BACKWARD INTEGRATION ON THE PROCESS ECONOMICS OF ETHAMBUTOL HYDROCHLORIDE MANUFACTURE

The cost estimates of the average and ideal performers provided in tables 4, 5 and 6 are compared in table 7 which indicates how the three different degrees of backward integration affect the C_{tp}. Costs shown for L(+)-Tartaric Acid here have been reduced from those originally shown, based upon the amount of chemical which is expected to be recovered during the processes.

Table 7. Effect of backward integration on the unit total production costs of ETHAMBUTOL Hydrochloride ($US/kg)

Cost element	Degree of backward integration I		II		III	
	C_1	C_2	C_1	C_2	C_1	C_2
(+)-2-Amino-1-butanol	46.04	39.53	-	-	-	-
(±)-2-Amino-1-butanol	-	-	21.50	17.22	-	-
Key intermediate costs	46.04	39.53	21.50	17.22	-	-
Acetonitrile	-	-	-	-	4.22	2.26
L(+)-Tartaric Acid	-	-	5.06	3.95	5.06	3.95
Butene-1	-	-	-	-	2.26	1.66
Isopropanol	1.83	1.23	1.83	1.21	1.83	1.23
Chlorine	-	-	-	-	0.73	0.58
Ethylene Dichloride	0.25	0.24	0.25	0.24	0.25	0.24
Other materials	1.17	0.90	1.77	1.37	2.69	2.61
Direct material costs	49.29	41.90	30.41	23.99	17.04	12.53
Conversion costs	5.45	4.68	11.81	10.01	20.25	16.77
Production costs	54.74	46.58	42.22	34.00	37.29	29.30
Gross profit	-0.74	7.42	11.78	20.00	16.71	24.70
Convertible currency saving	4.71	12.10	23.59	30.01	36.96	41.47

C_1.. average performer
C_2.. ideal performer

Table 7 illustrates the decrease in total unit cost of not only the key intermediates but of all materials directly employed as the degree of backward integration increases; in fact, these costs can be reduced by 60 to 70 per cent by employing the third choice in preference to the first.

Despite the fact that an expansion in backward integration is also accompanied by a concurrent rise in conversion costs, the savings in both total production costs and convertible currency continue to increase dramatically. This may be better appreciated by reviewing the percentages provided in table 8.

Table 8. Effect of backward integration on the production cost structure of ETHAMBUTOL Hydrochloride (per cent)

Cost element	Degree of backward integration I		II		III	
	C_1	C_2	C_1	C_2	C_1	C_2
(+)-2-Amino-1-butanol	84.1	84.9	-	-	-	-
(±)-2-Amino-1-butanol	-	-	50.9	50.6	-	-
Key intermediate costs	84.1	84.9	50.9	50.6	-	-
Acetonitrile	-	-	-	-	11.3	7.7
L(+)-Tartaric Acid	-	-	12.0	11.6	13.5	13.5
Butene-1	-	-	-	-	6.1	5.7
Isopropanol	3.3	2.6	4.3	3.6	4.9	4.2
Chlorine	-	-	-	-	2.0	2.0
Ethylene Dichloride	0.5	0.5	0.6	0.7	0.7	0.8
Other materials	2.1	1.9	4.2	4.0	7.2	8.9
Direct material costs	90.0	90.0	72.0	70.6	45.7	42.8
Conversion costs	10.0	10.0	28.0	29.4	54.3	57.2
Production costs	100.0	100.0	100.0	100.0	100.0	100.0
Gross profit	-1.4	15.9	27.9	58.8	44.8	84.3
Convertible currency saving	8.7	22.4	43.7	55.6	68.4	76.8

C_1 average performer

C_2 ideal performer

Here, it can also be seen that the costs of the two key intermediates play a dominant role in backward integration stages I and II, contributing very significantly to the high proportionate share of direct materials in the overall syntheses; in stage III, the importance of the combined cost of all other chemicals, rather than one key agent employed, becomes dominant.

Additionally, it is apparent that as the processes become more complex and the share of the C_{tp} accounted for by the conversion costs rises, the need for qualified and experienced technical and administrative management will become more and more significant as a means of not only controlling but also possibly reducing total production costs.

Nevertheless, predicated upon the C_{tp} shown for each performer at backward integration stage III, the average producer realizes a gross saving or profit on the C_{tp} of more than 44 per cent and the ideal producer one of about 84 per cent against the assumed $US 54 price of imported ETHAMBUTOL Hydrochloride. Additionally, both benefit from convertible currency savings of 31 to 46 per cent.

7. AVAILABILITY OF ETHAMBUTOL HYDROCHLORIDE, ITS KEY INTERMEDIATES AND THEIR MANUFACTURING TECHNOLOGY

In an attempt to assess the availability of ETHAMBUTOL Hydrochloride, its key intermediates and their manufacturing technology, enquiries were sent to 75 addresses given in various directories.[14/]

Twenty-five positive replies were received, 22 from industrialized and three from developing countries. The information contained in these replies is given in annex 4 and 5.

Although the lists given in this study are based on correspondence with manufacturers and suppliers, they may contain mistakes and be incomplete. They reflect the situation as at the end of 1985.

In addition to direct transactions between headquarters and affiliates, large quantities of ETHAMBUTOL Hydrochloride are sold on the open market through international trading houses, which keep stocks of the pharmaceutical chemical. Hence, ETHAMBUTOL Hydrochloride is freely available in international trade.

(+)-2AlB is manufactured and used in the pharmaceutical industry, exclusively for the production of ETHAMBUTOL Hydrochloride. The number of (+)-2AlB suppliers is few and its market has an oligopolistic character.

(±)-2AlB is manufactured in the petrochemical industry and is used in the synthesis of surface-active agents, vulcanization accelerators and pharmaceuticals. As an emulsifying agent, it is also used in the cosmetic industry. The number of suppliers is few but the market price depends mainly on value acceptable to the large users,which is a favourable factor for pharmaceutical producers.

14/ Directory of Chemical Producers, Western Europe, SRI International, CHEM Sources - United States, 1983; Pharmaceutical Technology: Chemical Raw Materials and Pharmaceutical Ingredients, July 1982; JNIDO: Directory of Pharmaceutical Chemicals and Intermediates, 1984; SCRIP No. 965, 16 January 1985.

Practically all of the L(+)-Tartaric Acid sold today is a by-product of the wine industry. It is used mainly in the soft drink industry, confectionary products, bakery products, etc., as an acidulant. Since the outputs of the wine industry, including by-products, depends on the quantity and quality of grape harvest and this changes from year to year, the current price of L(+)-Tartraric Acid is primarily determined by the supply side because the demand is relatively stable and predictable. The pharmaceutical industry has to pay the price of the principal users of L(+)-Tartaric Acid. Traditional manufacturers are located in Europe, hence the $US price depends also on the rate of exchange of the national currency against the dollar.

Ethylene Dichloride, Butene-1, Acetonitrile, Hydrochloric Acid, Calcium Hydroxide, etc. are petrochemical intermediates or basic inorganic chemicals, respectively, and they are mainly used for purposes other than the manufacture of ETHAMBUTOL Hydrochloride. They are produced in large quantities by the chemical industries and are freely available on the world market at competitive prices.

With the exception of (+)-2A1B, ETHAMBUTOL Hydrochloride and its key intermediates are produced both in industrialized and developing countries. Laboratory-scale technology is available from the literature, including alternative processes and routes, both for ETHAMBUTOL Hydrochloride and its key intermediates.

8. OTHER POSSIBLE USES OF THE AVAILABLE INFORMATION AND DESCRIBED METHODOLOGY

Different users have different, sometimes conflicting interests when using the available information for their own purpose. For example, decision-makers concerned with health may want to purchase their supplies of ETHAMBUTOL Hydrochloride at the lowest possible cost, without regard to source, whereas decision-makers who are more concerned with international balance of payments may be more interested in saving substantial amounts of convertible currency. For still others, the benefits of increased domestic industrialization may be the governing factor. Superimposed overall, potential investors are seeking profits and existing manufacturers are spending money to further develop their technology as well as to reduce production costs in general. The data provided in this paper should aid in analyzing aspects related to the above or other objectives.

8.1 Estimation of the quantities and values of materials required for the manufacture of ETHAMBUTOL Hydrochloride

Chemical input conversion coefficients are regularly used to estimate direct material requirements for the production of a specific quantity of a given chemical in a given period. The same data reflect also the convertible currency saving and the profit or loss for the same quantities and time.

Table 9 shows data for backward-integration degrees II and III of the manufacture of ETHAMBUTOL Hydrochloride. Here it can be seen that if 100 tons of the drug were produced locally, using backward integration II, an average performer might realize a convertible currency saving of about $US 2.4 million and a gross gain of over $US 3.0 million against the cost of the imported material. For the ideal performer, comparable currency savings would be about 25 per cent higher, $US 4.1 million, but the gross profit would almost double to $US 2.0 million. These figures assume that not only the key intermediate but also all other requisite materials cited are imported. Additionally, the gross profit will be taken in local currency if the total output is finished and consumed domestically. The importance of L(+)-Tartaric Acid revovery can also be appreciated by the approximately $US 190,000 or $US 150,000 credit, respectively, to the annual total production costs of 100 tons of ETHAMBUTOL Hydrochloride.

Table 9. Material requirements (tons) and some financial aspects of the annual production of 100 tons of ETHAMBUTOL Hydrochloride (thousand $US)

Name	Average performer		Ideal performer	
	quantity	value	quantity	value
Backward integration II				
(+)-2-amino-1-butanol	241	2,150	193	1,722
L(+)-Tartaric Acid	411	695	321	542
Isopropanol	332	183	223	121
Ethylene Dichloride	48	25	45	24
Other materials		177		137
		3,230		2,546
L(+)-Tartaric Acid, recovered		- 189		- 147
Total material requirement		3,041		2,399
Convertible currency saving		2,359		3,001
Gross profit		1,178		2,000
Backward integration III				
Acetonitrile	422	422	226	226
Butene-1	365	226	268	166
Chlorine	429	73	340	58
L(+)Tartaric acid	411	695	321	542
Ethylene Dichloride	48	25	45	24
Isopropanol	332	183	223	123
Other materials		269		261
		1,893		1,400
Tartaric Acid, recovered		- 189		- 147
Total material requirement		1,704		1,253
Convertible currency saving		3,696		4,147
Gross profit		1,671		2,470

8.2 Estimation of the disaggregated yield. . d chemical input conversion coefficients

The yields of individual or smaller groups of chemical reactions can be calculated by dividing the overall yield of the reactants by the overall yield of the relevant product (intermediate). The corresponding f value is obtained by dividing the relevant F with the disaggregated yield.

Thus, it can be seen in table 10 that the most significant difference in the conversion efficiency between average and ideal producers of ETHAMBUTOL Hydrochloride is in the use of Acetonitrile in backward integration stage III, L(+)-Tartaric Acid in stage II and (+)-2-Amino-1-butanol in stage I. Both (+)-2AlB in backward integration I and Acetonitrile in backward integration III should be used in excess in the condensation reactions. Hence, their recovery is very important as regards the process economics. The same applies to the chemical recovery of L(+)-Tartaric Acid from (-)-2AlB L(+)Tartrate. The

Table 10. Estimated disaggregated yields and chemical input conversion coefficients in the manufacture of ETHAMBUTOL Hydrochloride

Name	y		F	f	
	a	i		a	i
ETHAMBUTOL Hydrochloride					
(+)-2-Amino-1-butanol	65	75	0.64	0.99	0.85
Ethylene dichloride	75	80	0.36	0.48	0.45
(+)-2-Amino-1-butanol					
(+)-2-Amino-1-butanol	83	89	2.00	2.41	2.25*/
L(+) Tartaric acid	82	91	3.37	4.11	3.70
(±)-2-Amino-1-butanol					
Butene-1	41	45	0.63	1.54	1.40*/
Chlorine	44	45	0.80	1.82	1.78
Acetonitrile	26	39	0.46	1.77	1.18*/

*/ Figures differ from those of table A.1 due to rounding.
y... yield of the chemical output with reference to the given chemical input;
f... conversion efficiency of the chemical input with reference to the chemical output under which it is listed;
a... average performer;
i... ideal performer.

differences in the relevant material input consumption coefficients of the average and ideal performers can probably be attributed to the difference in their recovery operations.

8.3 Setting technical development targets

The comparison of the disaggregated chemical yields of the average performer and ideal performer for all backward-integration stages of ETHAMBUTOL Hydrochloride reveals that there are possibilities for improving conversion efficiencies at each level. The most notable among these have been cited already in section 8.2 above. Table 11 ranks them in descending order by per cent of difference.

Table 11. Possibilities of improving yields of chemical reactions in the manufacture of ETHAMBUTOL Hydrochloride (percentage)

Product	Reactant	Yield improvement (%)
(+)-2-Amino-1-butanol	Acetonitrile	50
ETHAMBUTOL Hydrochloride	(+)-2-Amino-1-butanol	15
(+)-2-Amino-1-butanol	L(+) Tartaric acid	11
(+)-2-Amino-1-butanol	(±)-2-Amino-1-butanol	10
(+)-2-Amino-1-butanol	Butene-1	10
ETHAMBUTOL Hydrochloride	Ethylene Dichloride	7
(+)-2-Amino-1-butanol	(±)-2-Amino-1-butanol	7
(±)-2-Amino-1-butanol	Chlorine	2

If only the possibilities of improving the chemical conversion efficiency are taken into account, then the order of technical development targets would be as follows:

(a) Upgrading the technology of (±)-2A1B production with the specific aim of improving the chemical conversion coefficients of Acetonitrile.

(b) Further refining the technology of ETHAMBUTOL Hydrochloride production to afford both better yields and more efficient recovery of excess (+)-2A1B.

(c) Improving the yields of (+)-2AlB reactions not only with (±)-2AlB but also with L(+)-Tartaric acid.

However, the economic aspects of the studied technology dictate a modified order of importance of the technical priorities as follows:

(a) Further refining of the reaction of (+)-2AlB with Ethylene Dichloride because these materials together account for almost 85 per cent of C_{tp} and 94 per cent of direct material costs (table 4). If the average performer could achieve the conversion efficiency of the ideal performer only in this step, C_{tp} could be reduced by about $US 6.51 or approximately 12 per cent.

(b) Improving the reactive yield of (+)-2AlB from (±)-2AlB which accounts for almost 51 per cent of C_{tp} and over 70 per cent of direct material costs (table 5). Assuming that the maximum indicated improvement were realized, C_{tp} could be reduced by about $US 4.28 or approximately 10 per cent; direct material costs by about 14 per cent.

(c) Upgrading the (±)-2AlB yield from the reaction of Acetonitrile. This could achieve savings of as much as $US 1.96, reducing C_{tp} by more than 5 per cent and direct material costs by over 11 per cent (table 6).

Such calculations may also be utilized in a different approach when the starting point is a desirable ETHAMBUTOL Hydrochloride cost/price. The proportional difference between the desirable price and the C_{tp} is distributed among the intermediates, and the yields to attain the necessary cost reductions are calculated. These desirable yields can then be analyzed to determine whether or not they may be feasible in a commercial operation.

8.4 Estimation of the price of chemical intermediates

The production costs of chemical intermediates such as (+)-2AlB and (±)-2AlB can be estimated if the relevant data in tables 5 and 6 are divided by the appropriate chemical input conversion coefficients from table 2.

Hence, in table 12 it costs the average performer an estimated $US 33.86 to produce his input of one kilo of (+)-2AlB whereas it costs the ideal performer $US 31.72 per kilo. Both production costs are significantly below the $US 46.50 price listed in table 3. Such information can be very useful when negotiating the price of purchased chemicals.

Table 12. Estimation of the production costs of (+)-2-Amino-1-butanol ($US)

Cost element	C_1	C_2	C_1-C_2
(+)-2-Amino-1-butanol	21.50	17.21	4.29
L(+)-Tartaric Acid	6.95	5.42	1.53
Other materials	0.60	0.47	0.13
Tartaric Acid, recovered	-1.89	-1.47	-0.42
Direct material costs	27.16	21.63	5.53
Conversion costs	6.36	5.33	1.03
Production costs	33.52	26.96	6.56
Conversion factor	0.99	0.85	
Estimated unit production cost (kg)	33.86	31.72	2.14

Similar calculations for (±)-2AlB shown in table 13 suggest savings from 23 to 27 per cent over the cost of $US 8.92 per kg shown in table 3. However, the volumes involved may have to be substantial to make this proposition very attractive because the actual dollars realized range from only $US 2.04 to $US 2.44 per kg produced.

Table 13. Estimation of the production costs of (±)-2-Amino-1-butanol ($US)

Cost element	C_1	C_2	C_1-C_2
Acetonitrile	4.22	2.26	1.96
Butene-1	2.26	1.66	0.60
Chlorine	0.73	0.58	0.15
Other materials	0.92	1.24	-0.32
Direct material costs	8.13	5.74	2.39
Conversion costs	8.44	6.76	1.68
Production costs	16.57	12.50	4.07
Conversion factor	2.41	1.93	
Estimated unit production cost (kg)	6.88	6.48	0.40

9. TRENDS AND FORECASTS OF DEMAND FOR ETHAMBUTOL HYDROCHLORIDE AND INTERMEDIATES

9.1 Morbidity trends for tuberculosis

In 1982, almost 1.6 million cases of tuberculosis were reported to the WHO, down from a total of almost 2.2 million in the preceding years; however, rather than reflecting an actual decrease, this simply reflects an incompleteness of returns from member countries. Totals for 1983 are even further from being complete.

Table 14. Number of tuberculosis cases reported in WHO regions, 1967-1983 (in thousands)[a/]

	1967	1971	1975	1979	1980	1981	1982[a/]	1983[b/]
World total	1,160	1,038	1,862	2,109	2,101	2,183	1,596	825
South-East Asia	481	495	727	752	757	894	747	750
E. Mediteranean	...	...	392	491	525	500	422	48
Africa	212	98	30	117	110	193	205	3
W. Pacific	8	11	160	326	278	353	175	1
Americas	168	207	187	213	218	66	32	24
Europe	291	227	306	210	213	175	15	-

a/ Incomplete returns, particularly from the Western Pacific, Americas and European regions.

b/ Incomplete returns from all regions except South-East Asia.

Source: World Health Statistics 1984, WHO, Geneva (1984).

Consequently, judging by the returns from the preceding three years (1979/1981), it appears that the overall number of annually-reported cases may be plateauing, even though there may be significant yearly variations within the individual countries themselves.

The actual number of cases worldwide is, of course, unknown but previously published WHO extrapolations from the registered cases to the total population[15/] suggest that in 1981 there could have been as many as 7.3 million. Other estimates have placed the annual figure of occurence in developing countries as high as ten million, including four to five million very infectious cases of smear-positive tuberculosis and an equal number of less infectious cases; the latter include those positive by culture only as well as culture-negative cases, the most frequent form of pulmonary disease in children.[16/] At least three million (30 per cent) among those reported are believed to die from the infection every year.[17/]

Although the WHO global target envisages that some communicable diseases in the developing countries will be of no greater public health significance in the year 2000 than they were in technically advanced countries in 1980, the current high incidence and the natural history of tuberculosis in man suggest that such a level of control would be extremely difficult to achieve during so short a span, although it is hoped that a substantial reduction in the magnitude of the problem may be achieved.

It must be realized that the decline in tuberculosis in industrialized countries started long before the introduction of chemotherapy and partly should be attributed to improvements in socio-economic conditions.[19/] Consequently, improving the quality and the rate of development of primary health care services as well as the degree of integration of case-finding and treatment in developing countries will aid but will not provide the ultimate solution to the problem. The combination of case-finding and chemotherapy can be a powerful weapon in eliminating sources of infection as well as suffering

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15/ A. Bulla, Tuberculosis Patients - how many now?. WHO Chronicle, 31: 279-286 (1977), Geneva, Switzerland.

16/ Tuberculosis Control, Technical Report Series 671, WHO, Geneva, p. 10 (1982).

17/ Ibid.

18/ Global medium-term programme, programme 13.8: Tuberculosis. WHO, Geneva, p.2 (1983).

and death. However, in areas where poor socio-economic conditions such as overcrowding, poor hygiene and sanitation, malnutrition and illiteracy continue to exist, effective control will be difficult to attain.

Even if the effectiveness of the BCG vaccine - developed in the 1950s and most frequently used to protect children against tuberculosis - should be proven in more widespead populations, it can have only a relatively small epidemiological effect in that it will not contribute signficiantly to the reduction in the overall risk of infection in the community as a whole.19/

Additionally, chemoprophylaxis with isoniazid can prevent the development of tuberculosis in individuals exposed to infection but its impact upon the community will be minimal because it cannot be applied on a mass scale, even in technically advanced countries.20/ Not only would it be unnecessary for many people who, as adults, have long since built up an immunity to the disease but it would be costly and would foster even greater bacterial resistance which is already a problem with the drug.

Consequently, in a majority of the developing countries there has been little, if any, improvement in the epidemiological situation. In fact, there has been an overall increase in the absolute number of tuberculosis cases in these countries during the last three decades because the population has doubled during the period.21/ These increases are most notable within the African, South-East Asian and Eastern Mediterranean regions.

Data from the African region, even with fewer countries reporting, suggest a recent sharp acceleration in the number of identified cases, most notably in Ethiopia. However, this increase more probably reflects improved and/or expanded identification of infected patients and/or more reliable reporting rather than dramatic increase in the incidence of the disease.

19/ Tuberculosis Control, Technical Report Series 671, WHO, Geneva, p. 11 (1982).

20/ Ibid.

21/ Ibid.

Data from the Eastern Mediterranean region indicate a similar pattern. Within this area, Pakistan has accounted for an increasing share of the cases, reaching 77 per cent in 1982.

On the other hand, numbers from South-East Asia, where around 85 per cent of the identified patients are found in India, continue to oscillate around the ten-year average of about 740,000 reported cases a year.

The Western Pacific nations also present an oscillating trend, even though Japan and the Philippines - two of the three countries where the problem has been most acute (the Republic of Korea is the other) - appear to be successfully reducing local incidence.

The Americas also suggest a rather status quo situation with North America (i.e., Canada and the United States) registering about 14 per cent of the total cases; Central America, about ten per cent; the Caribbean about three per cent; and the South American continent upwards of 70 per cent. Brazil, individually, has exhibited an increasing number of identified cases, attaining about one-third of the Americas' total.

Once again, a like profile is evident in the WHO European region where three diverse countries - Turkey, Poland and Morocco - collectively present between 40 and 50 per cent of all yearly cases.

Despite the fact that the technically-advanced countries have achieved very substantial results in the control of tuberculosis through a combination of improved socio-economic conditions and advances in health care and therapy, the disease will occur in these areas - though at a decreasing rate - for many years to come. Specific problems, such as indigenous high-risk groups, refugees and immigrants from high-prevalence areas will continue to require special attention, even though they are unlikely to have a significant long-term effect on the overall tuberculosis situation locally.[22/]

22/ Global medium-term programme for tuberculosis (1984-1989), WHO, Geneva, annex 5:36 (1983).

9.2 ETHAMBUTOL Hydrochloride consumption

The WHO model list of essential drugs contains six pharmaceuticals specifically for use against tuberculosis: ETHAMBUTOL, isoniazide, pyrazinamide, rifampicin, streptomycin and a combination of thioacetazone plus isoniazid.[23/]

Isoniazid, thioacetazone and streptomycin are the drugs most commonly used, followed by rifampicin, ETHAMBUTOL and pyrazinamide. These latter are used only on a limited scale in developing countries, generally being reserved for retreatment because of high cost. Thioacetazone normally is not used alone and is rarely used in industrialized countries. In both industrialized and developing countries, rifampicin and pyrazinamide are used for short-term chemotherapy where it has been introduced.[24/]

For the initial regimen of therapy, a multi-drug approach is usually taken. This is because some may prove bactericidal against the causative bacteria population, some may be only bacteriostatic and some may be completely ineffective.

In the ninth report of the WHO Expert Committee on tuberculosis, two regimens are recommended for use in developing countries: (a) isoniazid plus thioacetazone, often supplemented by streptomycin in the initial intensive daily phase, and (b) a twice-weekly, fully supervised regimen of streptomycin plus isoniazid, preceded wherever possible, by an initial intensive daily phase. The recommended duration of both is 12 months.

As a consequence of all of the above, the demand for ETHAMBUTOL Hydrochloride - which also is rarely used alone - in developing countries has been somewhat constrained. Nevertheless, it has been notable; annual

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23/ The use of essential drugs, WHO Technical Report Series 722, Geneva, 1985, p. 19.

24/ Recent advances in the chemotherapy of tuberculosis, WHO Chronicle, 34:101-103 (1980).

consumption for developing countries accounting for about 40 per cent of the worldwide total of reported tuberculosis cases was estimated (1980/1982) at about 200 metric tons.

Table 15. Estimated annual consumption of ETHAMBUTOL Hydrochloride, 1980/1982 (metric tons)

ASEAN countries	97
India	90
Bangladesh	1
Arab countries including Egypt	10
	198

Source: UNIDO, ID/WG.331/4 of 26 September 1980, The pricing and availability of intermediates and bulk drugs, p. 60.

Assuming that - based upon the number of identified cases - patients in developing countries represent about 85 per cent of the worldwide potential for anti-tubercular drugs, this estimate of 200 metric tons may be projected to about 425 for all developing countries. Further assuming that, based upon table 3, each metric ton has a value of $US 54,000, the current market for ETHAMBUTOL Hydrochloride in developing countries may be about $US 23 million a year.

9.3 Pharmaceutical price trends

Time-series data for the prices of chemical inputs were rarely available from the Chemical Market Reporter and annual $US price indices 1970-1984 were received for selected reactants and ETHAMBUTOL Hydrochloride through correspondence with buyers.

Figure 2 indicates that the $US price index of ETHAMBUTOL Hydrochloride, after peaking in 1974, has experienced a varying trendline but, overall, a rather significant reduction in price. Generally, with the exception of 1975, the price index of its key intermediate, (+)-2A1B, has followed a closely parallel course (figure 3). Some sections of the $US price trend curve of (±)-2A1B resembles those of (+)-2A1B (figure 4).

Figure 2.

$US UNIT PRICE INDEX 1970-1984
ETHAMBUTOL HYDROCHLORIDE

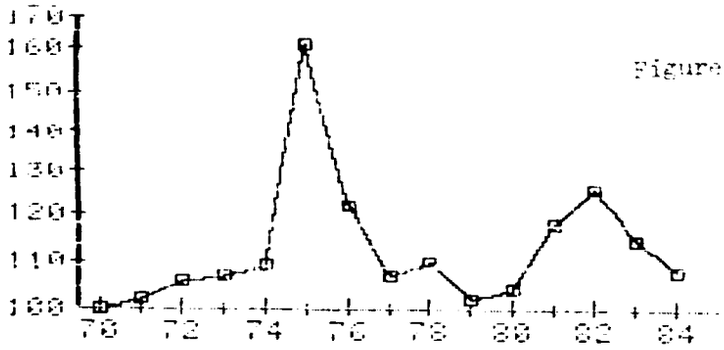


Figure 3.

$US UNIT PRICE INDEX 1970-1984
(+)-2-AMINO-1-BUTANOL

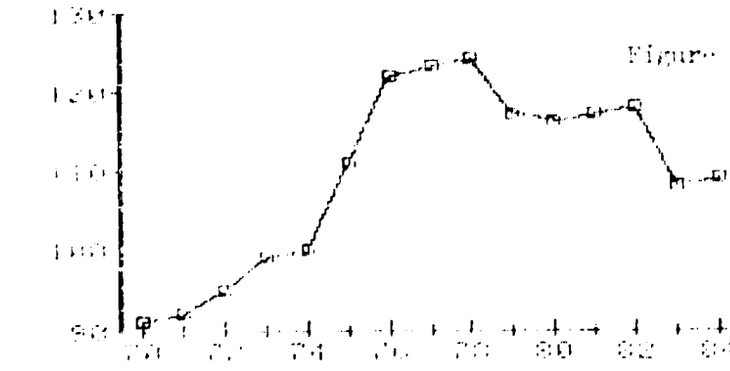


Figure 4.

$US UNIT PRICE INDEX 1970-1984
(+)-2-AMINO-1-BUTANOL

The $US unit price trends of Acetonitrile (figure 5), Chlorine (figure 6), Ethylene Dichloride (figure 7) and Isopropanol (figure 8) have had a gradual, sometimes steep, upward trend. Butene-1 (figure 9) prices peaked in 1981 and show a declining trend during the years 1982-1984. The $US unit price of L(+)-Tartaric Acid (figure 10) fluctuates over a wide range, e.g. jumping from $US 1.25 in 1973 to $US 4.13 in 1974, and shows and overall increasing trend from $US 1.03 in 1970 to $US 2.53 in 1984.

A general conclusion can be inferred from the price trend analysis: the price of the key intermediate, (+)-2A1B, used exclusively in the manufacture of the pharmaceutical chemical moves more or less together with the price of ETHAMBUTOL Hydrochloride (figure 11), whereas there is no correlation between the prices of other input chemicals and that of ETHAMBUTOL Hydrochloride.

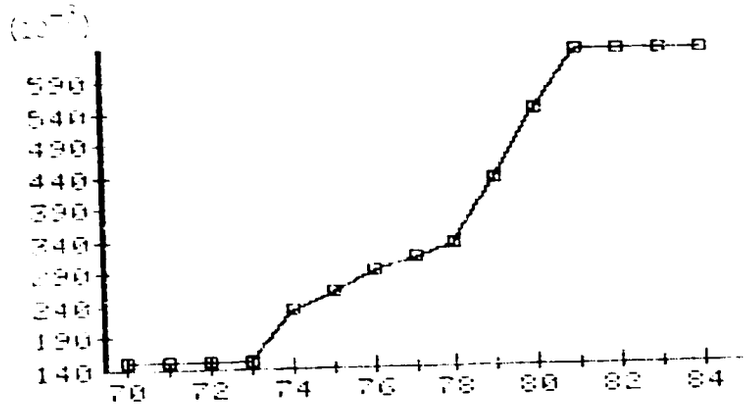
Table 16 provides prices[25/] over the past six years for ETHAMBUTOL Hydrochloride film-coated tablets 400 mg.

Table 16. Prices for ETHAMBUTOL Hydrochloride tablets available in international trade

Year	Price	
	Dfl	$US
1980	52.00	26.16
1981	52.50	21.04
1982	79.00	29.60
1983	69.00	24.18
1984	64.30	20.04
1985	67.50	22.11

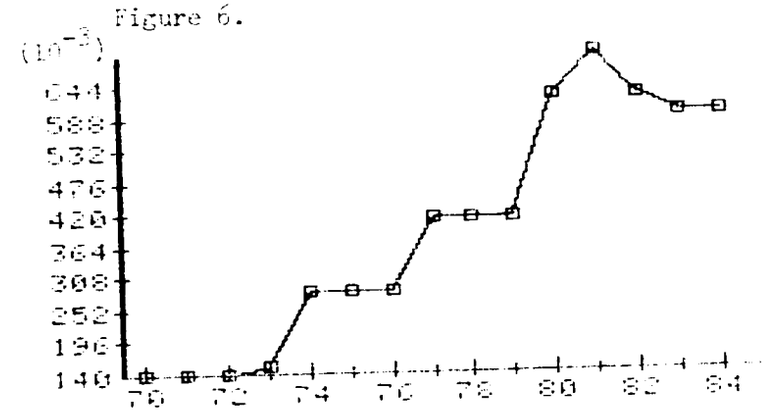
25/ Price Indicators 1980-1985 of IDA International Dispensary Association, Amsterdam.

Figure 5.



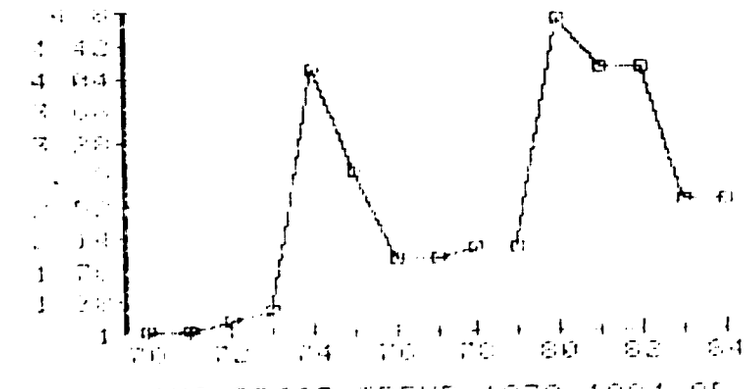
$US UNIT PRICE TREND 1970-1984
ISOPROPANOL

Figure 6.



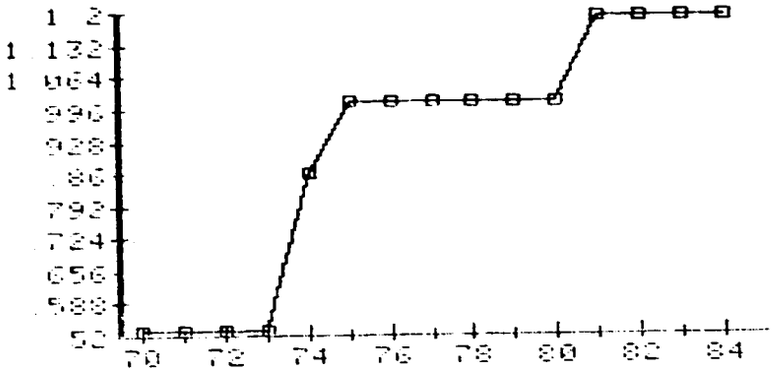
$US PRICE TREND 1970-1984 OF
BUTENE-1

Figure 7.



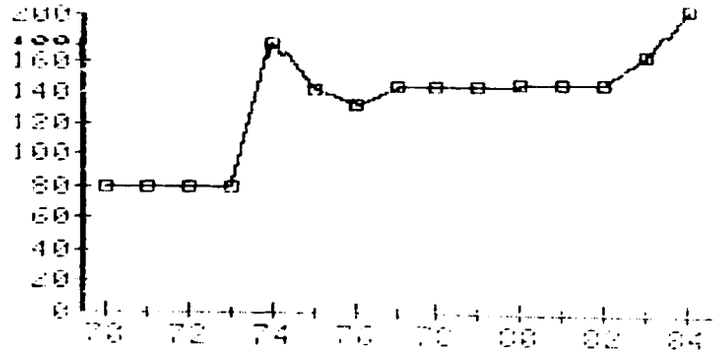
$US PRICE TREND 1970-1984 OF
[illegible]

Figure 8.



$US PRICE TREND 1970-1984 OF ACETONITRILE

(tons) Figure 9.

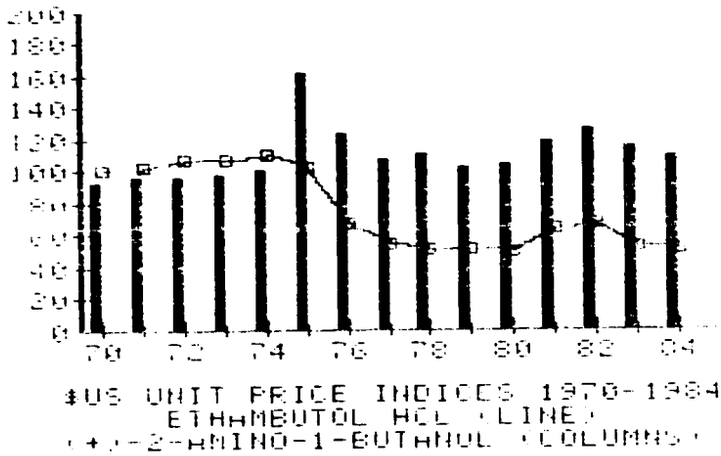


$US UNIT PRICE TREND 1970 1984 CHLORINE

Figure 10.

$US UNIT PRICE TREND 1970-1984 ETHYLENE DICHLORIDE

Figure 11. $US unit price indices 1970-1984



The overall change 1980-1985 shows an increase in the Dfl. price and a decrease in the $US price. Current prices have fluctuated widely during te period. The rise has been about 30 per cent from Dfl. 52.00 to Dfl. 67.50 and the decrease above 15 per cent, from $US 26.16 to $US 22.11 for one thousand film-coated ETHAMBUTOL tablets of 400 mg. The Dfl. price was lowest in 1980, whereas the nadir of the $US price was observed in 1984. This example also implies that price trends in $US might distort the picture of a national market in general, and on the product level in particular.

9.4 Assessment of some external factors affecting ETHAMBUTOL Hydrochloride consumption

9.4.1 Economic competition

Safety, effectiveness and other factors being equal, cost is the major consideration in the selection of the drug of choice in a given therapeutic category. Table 17 illustrates the comparative costs of some of the primary drugs used for the treatment of tuberculosis.

Table 17. Indices of relative daily cost of standard dosages of antitubercular drugs

	Standard daily dose[a]	Relative daily cost[b]
Isoniazid	300 mg	1.00
Isoniazid and thioacetazone	300/150 mg	1.00
Streptomycin (injectable)	1 g 2x wk	2.46[c]
ETHAMBUTOL Hydrochloride	15 mg/kg[d]	5.12
Pyrazinamide	35 mg/kg[d]	18.30
Rifampicin	10 mg/kg[d]	22.80

a/ Expert Commitee on Essential Drugs, Information sheets: Section 7.9, antituberculosis drugs, WHO, Geneva, 1982.

b/ Employing the closest standard dosage sizes and prices listed in the International Dispensary Association (IDA) Price Indicator for February 1985.

c/ Dividing the cost of drug for two administrations equally over seven days.

d/ Assuming 60 kg of body weight.

Admittedly, price relationships of different drugs will vary dependent upon quantity purchased, source from which obtained, country in which acquired and, in some cases, the weight of the patient. Consequently, they should be reassessed based upon the specific situation. However, from the data presented here, it is evident that, on a daily basis, isoniazid or the popular isoniazid plus thioacetazone combination afford the most economical therapies. (Isoniazid is used alone for prophylaxis but rarely by itself for treatment.) Streptomycin costs almost 2.5 times and ETHAMBUTOL Hydrochloride over five times as much. Pyrazinamide and rifampicin are far more expensive than any of the others.

9.4.2 Therapeutic competition

Isoniazid has been categorized as the most effective antitubercular drug available; it is not only the most potent bactericidal agent against actively growing bacilli but it is also the only one effective for prophylaxis. Nevertheless, resistant strains of tubercle bacilli can emerge rapidly and may become dominant unless the drug is used in combination with various other agents.

ETHAMBUTOL Hydrochloride has been shown to suppress the growth of not only isoniazid-resistant but also streptomycin-resistant mycobacteria when the agents have been used together. Resistance to ETHAMBUTOL, itself, appears to develop in vitro very slowly and in a somewhat erratic manner. As a consequence, ETHAMBUTOL plus isoniazid, with or without the addition of streptomycin has frequently been used for initial treatment of tubercular patients. In cases where some resistance appears to have developed or where retreatment is being undertaken, ETHAMBUTOL has also been used in combination with other, mostly second-line antitubercular drugs including p-aminosalicylic acid, cycloserine, ethionamide, pyrazinamide and viomycin.

Generally speaking, all of the primary antitubercular agents discussed in this paper are well tolerated and notable adverse effects will occur in less than five per cent of all patients; reportedly, these may vary from country to country and patient to patient. However, the number of patients in which treatment has to be discontinued permanently is usually lower than three per cent.[26/]

The most notable adverse effect resulting from ETHAMBUTOL therapy is some loss of visual acuity. Isoniazid has been known to cause hepatitis and streptomycin ototoxicity. The latter may be potentiated by the concurrent use of thioacetazone.

In programming an effective therapy, ideally the drugs should be chosen for their specific activity against various types of bacterial population present in lesions. On large populations of bacilli actively multiplying at neutral pH on the wall of pulmonary caverns the effect of isoniazid, streptomycin and rifampicin is bactericidal; ETHAMBUTOL is bacteriostatic; and pyrazinamide is inactive. Against the small bacterial population that multiplies slowly in an acid medium inside macrophages (phagocytes), pyrazinamide is most effective followed by isoniazid plus rifampicin;

26/ Recent advances in the chemotherapy of tuberculosis, WHO Chronicle, 34:101-103 (1980).

streptomycin is inactive. Against bacilli in solid caseous lesions which multiply intermittently, only rifampicin is bactericidal, all others being inactive.[27/]

Two regimens recommended by the WHO for use in developing countries have already been given in section 9.2.

For short-term therapy, from the bacteriological standpoint, the rifampicin-isoniazid combination in both the initial and continuation phases[28/] has been strongly recommended as optimum therapy for all forms of the disease including those caused by more sensitive strains. These drugs are usually supplemented - at least, in the initial phases - with one or two others such as ETHAMBUTOL or streptomycin. Overall, courses of short-term therapy usually run from six to nine months.

Short-course chemotherapy regimens (6-months duration) are gradually being introduced as standard treatment in control programmes; in the region of the Americas they are already given to almost 50 per cent of the newly reported cases. However, the regimens of one year's duration will remain the basic chemotherapy for the tuberculosis programmes in many countries unless further substantial reductions are made in the cost of the drugs for short-term use, particularly rifampicin and pyrazinamide.[29/]

9.4.3 Other factors affecting ETHAMBUTOL Hydrochloride use

Although, worldwide, the overall total number of tuberculosis cases reported appears to be plateauing, it has been recognized that the majority of those existing now go unreported, either because they are unidentified or because of deficiencies in reporting systems. Programmes are underway aimed at improving both of these situations.

27/ Op. cit.

28/ Op. cit.

29/ Global medium-term programme, programme 13.8: Tuberculosi, WHO, Geneva, p. 3 (1983).

Nevertheless, poor socio-economic conditions in some countries, further aggravated by population growth and various economic constraints, cannot only foster further spread of the condition but also impede the progress of the proper diagnosis and treatment.

Therefore, it is anticipated that there will be a very significant market for anti-tubercular drugs in developing countries for some time to come.

9.5 Future prospects

As noted in section 9.4.2, ETHAMBUTOL Hydrochloride is a good complementary drug to isoniazid because it can offset the rapid build-up of bacterial resistance. Nevertheless, as long as the price remains high, it follows that it will be used very selectively in developing countries.

Conceivably, this situation may change. Local production of the drug is already underway in three of these countries - India, Brazil and the Republic of Korea - which together account for over 40 per cent of all reported tuberculosis cases, as well as in several European markets. These efforts, together with the expirations of the various product and process patents, mostly relating to intermediates, should all serve to stimulate competition and eventually reduce prices.

9.6 Short-term forecasts of ETHAMBUTOL Hydrocholoride demand to 1990

Time series of ETHAMBUTOL Hydrochloride consumption has not been available, hence historical growth rate cannot be calculated.

The market for developing countries, which can be taken equal to the world market in practical terms, was estimated at about 425 tons in 1982.

In the absence of a better method, we might assume that the growth rate 1982-1990 of ETHAMBUTOL Hydrochloride consumption will be 2.2 per cent, i.e. equal to the estimated average annual percentage change for population growth in all developing countries.

The estimates in table 18 show the 1990 demands of ETHAMBUTOL Hydrochloride and intermediates, based on the conversion efficiencies of the average and ideal performers.

Table 18. Current and future world-wide consumption estimates of ETHAMBUTOL Hydrochloride and intermediates (tons)

Chemical	1982 (estimated)	1990 (forecast)
ETHAMBUTOL Hydrochloride	425	495
(+)-2-Amino-1-butanol	360-420	420-490
(±)-2-Amino-1-butanol	820-1,025	955-1,190

In the Asian region, Indian integrated manufacturers probably cover the national demand by local production. Latin America and Africa are net importers to-day although, demand - as judged by morbidity figures - would justify local production of ETHAMBUTOL Hydrochloride and key intermediates in both regions.

Demand for (±)-2-Amino-1-butanol would justify consideration of local production in all regions, particularly if other industrial uses of the chemical were also taken into account.

9.7 Long-term forecasts of ETHAMBUTOL Hydrochloride demand to 2000

The environment of the antituberculosis drug market is very complex and the circumstances surrounding the situation by the year 2000 cannot be predicted. It can be said with confidence, however, that ETHAMBUTOL Hydrochloride is an essential drug in the treatment of tuberculosis and its consumption is estimated to grow moderately on the global level. This situation is not expected to change during the forthcoming years, because ETHAMBUTOL Hydrochloride cannot be replaced with other antituberculosis drugs in those cases when its use is indicated. The present spectrum of

antituberculosis drugs is good and no large scale research is reported for new therapies or new drugs. Hence, no turning point or descending trend is expected in the life cycle curve of ETHAMBUTOL Hydrochloride in the forthcoming decade.

10. CONCLUSIONS AND RECOMMENDATIONS

10.1 Major conclusions of the techno-economic analysis

Backward integration degrees I-III are technically feasible and all the chemical reactions involved can be carried out, utilizing equipment generally available in pharmaceutical chemical plants. However, as pointed out earlier, commercial-scale technology for backward integration III may prove difficult to obtain.

Nevertheless, significant cost advantages may be realized in initiating production with (+)-2A1B (backward integration II) even though final yields may not be quite as high as those achieved when employing only backward integration I.

None of the three processes result in environmental pollution unusual with pharmaceutical chemical plants. The effluents of the production do not require specific treatment. Ordinarily little solvent recovery is required but calcium tartrate or calcium sulfate might be formed as solid waste.[30/] It should be mentioned, however, that calcium tartrate can be sold to tartaric acid manufacturers. Where this is the case, calcium tartrate is rather a co-product than a wate.

It appears that no unusual labour or safety regulations need be instituted, but extreme caution must be exercised in the handling and use of the hydrogen chloride gas required in backward integration I because of the toxicity to humans and the possibility of air pollution. Additionally, the chemicals utilized in backward integration III must be treated with great care. Acetonitirile is easily oxidized and unstable and presents a severe explosion hazard when exposed to heat or flame; Butene-1 can also present a very dangerous fire hazard.

30/ UNIDO/IS.387, 6 June 1983.

Although stainless steel equipment is generally recommended for carrying out the syntheses, some manufacturers have indicated a preference for glass based vehicles for certain steps.

Water, steam, electricity and cold energy requirements are not unusual.

The economies gained by optimum recovery of excess (+)-2AlB as well as Tartaric Acid have been shown; these are important points to consider when evaluating and/or buying production know-how.

The economic feasibility of ETHAMBUTOL Hydrochloride production is equally influenced by the price and conversion efficiency of the key intermediates which are dominant elements of the C_{tp} in both backward integration degrees I and II. However, conversion costs also contribute significantly in degree II and become dominant in degree III, requiring an even greater level of technical expertise to satisfactorily carry out this particular synthesis.

In view of the possible difficulty in obtaining the commercial-scale technology, the more complex nature of the process and the increased level of competence and direction required to satisfactorily handle the chemicals involved and profitably pursue backward-integration III, it would appear that backward integration II may be the most appropriate one to undertake. Not only could it deliver significant gains in gross profit and convertible currency savings over backward integration I but if carried out very successfully - that is, at least approaching the accomplishments demonstrated for the ideal performer - it appears that this method could deliver about 70 per cent of the gross gain and 64 per cent of the convertible currency saving which it might be possible to achieve by employing the more complex backward integration III (table 7). With backward integration II, gross profits range from $US 11.78 to $US 20.00 per kilo with a concurrent convertible currency saving somewhere between $US 23.59 and $US 30.01.

10.2 Alternative strategies

10.2.1 Total backward integration

This strategy makes the ETHAMBUTOL Hydrochloride manufacture completely independent from the two expensive key intermediates employed in backward integration I or II. However, such local production of (+)-2AlB requires the presence of a developed inorganic chemical and petrochemical industry; Butene-1 and chlorine must be and Acetonitrile should preferably be produced domestically.

Assuming that the commercial-scale production technology can be obtained, its technical level is relatively high, its overall process is more complex, and its basic chemicals are somewhat more dangerous to handle. Additionally, production of (+)-2AlB requires some special equipment and all reactions cannot be carried out economically in a multipurpose batch reactor.

As a consequence of all of the above, the economic feasibility of the (+)-2AlB production depends heavily upon the volume anticipated or required as well as - far more than backward integration I or II - upon the technical knowledge and abilities of not only plant management but also all of the personnel directly involved.

Such total backward integration would also require continuing support from research and development activities, principally directed at improving and maintaining the efficiency of the syntheses.

Energy requirements are somewhat higher than usual but other utility needs are customary.

Environmental pollution problems are not envisaged from the patent descriptions and there is no need for special effluent treatment.

Gross profits resulting from this process could range from $US 16.71 to $US 24.70; convertible currency savings have been figured at between $US 36.96 and $US 41.47. However, an undetermined amount of this may be offset by the need to upgrade both facilities and personnel.

10.2.2 Advanced backward integration

This alternative assumes that (±)-2A1B is purchased and resolved by L(+)-Tartartic Acid to obtain (+)-2A1B for further chemical conversion.

This technical alternative offers a very good economic feasibility, because unit gross profit ranges from $US 11.78 to $US 20.00, i.e. about 28 per cent and 59 per cent over C_{tp}, whereas the unit convertible currency saving is between $US 23.59 and $US 30.01.

The chemical operations can be carried out in multipurpose batch reactors. Neither labour safety nor environment protection considerations differ much from those of minimum backward integration.

The disadvantage of this alternative is mainly the high level of technological discipline required to carry out efficiently the resolution of (±)-2A1B and the recovery of L(+)-Tartaric Acid.

10.2.3 Minimum backward integration

In this alternative, the most expensive intermediate, (+)-2A1B is purchased and reacted with Ethylene Dichloride to produce ETHAMBUTOL Hydrochloride.

The advantage of this is that production is technically relatively simple and little investment is required. The economic feasibility depends mainly on the efficiency of (+)-2A1B recovery.

The main disadvantage is that the production for the average performer is unprofitable and convertible currency savings, depending upon volume, may be relatively minimal.

Additionally, process economics are very sensitive to the supply and cost of (+)-2A1B which can account for well over 80 per cent of C_{tp}.

However, it is conceivable that this step could be regarded as the initial step of advanced backward integration.

10.2.4 Purchase of ETHAMBUTOL Hydrochloride in bulk

The strategic alternatives would not be complete without considering the purchase of ETHAMBUTOL Hydrochloride on the world market for finishing and packaging locally and to use such investment resources as may be available towards the production of a pharmaceutical bulk substance which may have greater local demand and/or more limited availability and/or better economic feasibility.

10.2.5 Some factors affecting the alternative strategies

Procurement

There are two possible variations on all the alternative strategies:

(i) Long-term purchasing agreement, or

(ii) Buying at spot prices on the world market of ETHAMBUTOL Hydrochloride and intermediates.

The benefits of variation (i) include the guaranteed supply and independence from increases of the market prices; the main risk is that no profit can be realized from the eventual decreases of the spot prices.

The advantage of variation (ii) is the possibility of making extra profit from the decreased spot prices; the principal risk is that the production costs, particularly in backward integration I, are very sensitive to the increases of spot prices and there might also be availability problems if the balance of demand and supply is disturbed to an unusual extent.

It must be stressed, however, that the procurement efficiency plays an eminent role in process economics, because direct materials are dominant cost elements and their share in C_{tp} depends on prices and conversion efficiency to the same extent.

Technology

A decision should also be made whether to establish one's own R & D programme, or to buy technical improvements also in the future. At the early stages, co-operation with the technology supplier seems to be the most expedient decision, but the medium-term objective should be the establishment of one's own research apparatus, however modest, capable of developing the existing production technologies.

Management

The more advanced is the vertical integration, the more dominant is the share of conversion costs in the total production costs.

The conversion costs could not be analysed in this study in detail for lack of break-down figures and also because cost components such as depreciation, interest on investment loans and working capital, taxes, insurances, royalties, overheads, etc. vary from country to country and even from manufacturer to manufacturer within the same country.

The reduction of conversion costs needs effective management of all resources and sales activities. Once all practical reserves in technical development have been exhausted, management becomes the only dominant element of the total production costs and the decisive factor of competition.

10.3 Market analysis

One of the major attributes of ETHAMBUTOL Hydrochloride is that it can be produced in multi-purpose batch reactors and, consequently, can be produced in relatively small quantities if there is little demand. Unfortunately, the economies of scale would have to be carefully considered since the intermittent production of small quanitities may add significantly to the product's cost.

Rough calculations suggest that - predicated upon a daily dosage of two 400 mg tablets - one metric ton would provide enough chemical to treat about 3,400 people for one year. Consequently, 100 tons could provide enough medication for about 340,000 patients or about one-sixth of all of the case which have been reported to the WHO annually over the last few years.

However, it is acknowledged that the number of cases reported to the WHO represent only a fraction of the actual number worldwide and projections of recent consumption (section 9.2) suggest that the developing countries could consume as much 425 tons of the chemical a year. Thus, there should be some opportunities for ETHAMBUTOL production in developing countries, particularly in Africa where no such facilities currently exist and where a largely unquantified need undoubtedly does exist.

10.4 Recommendations

Developing countries at various stages in the development of the pharmaceutical industry have been summarily reviewed with respect to their possibilities to implement the various degrees of backward integration.

The minimum backward integration is technically feasible, but economically not attractive. Local production can be considered primarily in those countries where the short-term objective is to gain experience in and to train skilled staff for the pharmaceutical chemical industry.

The advanced backward integration of the manufacture of ETHAMBUTOL Hydrochloride is technically feasible and economically attractive. Therefore, it is worth considering the making of in-depth studies on its marketing, engineering and financial aspects, aiming at establishing the production of the drug or its intermediates, either within an existing plant or as a contribution to the rationale for establishing a new multi-purpose plant.

The maxiumum degree of backward integration shows further savings in both total production costs and convertible currency. Integrated ETHAMBUTOL Hydrochloride manufacturers, particularly with petrochemical production facilities, might also be interested in the preparation of a pre-feasibility study for the manufacture of (+)-2AlB.

The prospects for establishing a new manufacturing operation solely for the production of ETHAMBUTOL Hydrochloride generally do not appear to be economically feasible although, as better tuberculosis morbidity figures become available, this concept could change.

An interesting finding of the study is that recovery of (+)-2AlB, L(+)-Tartaric Acid and to a lesser extent Isopropanol, plays an important role in the process economics.

Annex 1 to the

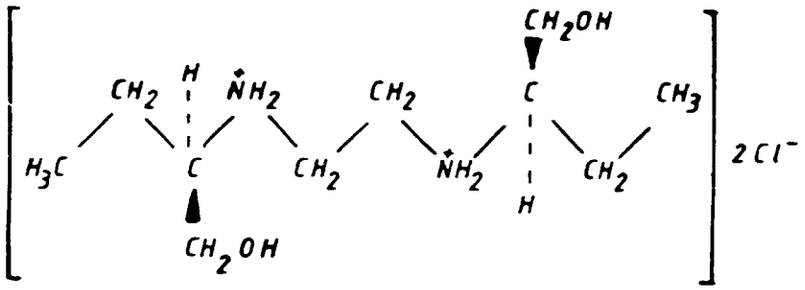
Technical and Economic Analysis of the Manufacture of ETHAMBUTOL Hydrochloride

Chemical Synthesis of ETHAMBUTOL Hydrochloride

A. BASIC DATA OF THE PHARMACEUTICAL CHEMICAL

1. International non-proprietary name: ETHAMBUTOL Hydrochloride[31/]

2. Graphic formula:



3. Chemical formula: $C_{10}H_{26}Cl_2N_2O_2$

4. Molecular weight: 277.23

5. Chemical abstracts index name: [R-(R*,R*)]-2,2'-(1,2-Ethanediyldiimino)-bis-(1-butanol)-dihydrochloride

6. Cas registry number: [1070-11-7]

7. Other forms: ETHAMBUTOL Base [74-55-5], which is not used in the preparation sub-sector of the pharmaceutical industries.

8. Basic patent: U.S. Pat. 3,176,040, Wilkinson [illegible]rd: Novel 2,2'-(Ethylendiimino)-di-Butanols (1965 to Am[illegible]o.)

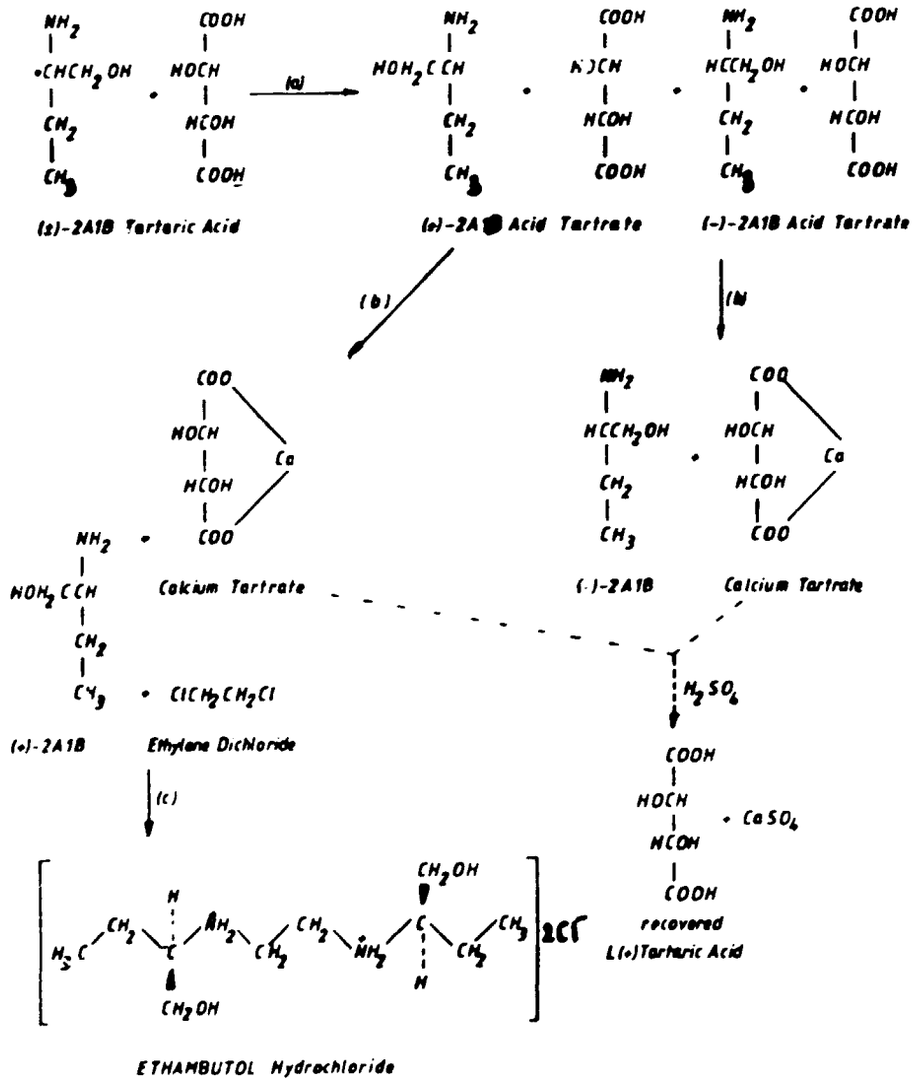
31/ The use of essential drugs, WHO Technical [illegible]ries 722, Geneva (1983), p. 19.

B. BRIEF DESCRIPTION OF THE PRODUCTION PROCESSES

Most bulk substance manufacturers in the pharmaceutical industry produce ETHAMBUTOL starting from (+)2-Amino-1-butanol, which is resolved with L(+)-Tartaric Acid and the isolated (+)-2A1B enantiomer is condensed with Ethylene Dichloride to yield ETHAMBUTOL Hydrochloride.

1. Chemical synthesis of ETHAMBUTOL Hydrochloride

1.1 Schematic illustration of the synthesis



Backward integration I

(+)-2A1B and a fraction of Ethylene Dichloride (reaction (c) below) are heated to a temperature from 45° to 65°C to initiate the condensation. Further quantities of Ethylene Dichloride are added at such a rate that the exothermic reaction maintains the temperature at around 130°C. (+)-2A1B is used in a large - five- to eight-fold - excess in order to depress side reactions.

The excess (+)-2A1B is distilled off under vacuum of less than 20 mmHg.

The distillation residue is dissolved, usually in Isopropanol, and ETHAMBUTOL is precipitated as the Hydrochloride from the clear filrate by the addition of dry hydrochloric acid gas. The obtained white crystals are centrifuged, washed with solvent and dried.

Backward integration II

(±)-2A1B is resolved with L(+)-Tartaric acid in two steps.

The fist step is the formation of (+)-2A1B and (-)-2A1B acid tartrates (reaction (a) below), in which (±)-2A1B is added to the methanolic solution of L(+)-Tartaric acid at a rate to maintain the temperature below 55°C. The reaction mixture is subsequently refluxed, cooled to 15° to 20°C and the (+)-2A1B acid L(+)-tartrate is allowed to crystallize, whereas the (-)-2A1B acid L(+)-tartrate remains in solution. The crystals are centrifuged and washed with cold methanol.

The second step consists of the decomposition of (+)-2A1B acid L(+)-tartrate and the subsequent recovery of (+)-2A1B (reaction (b) below). First (+)-2A1B acid L(+)-tartrate is dissolved in water and this aqueous solution is added to a calcium hydroxide suspension at a rate to keep the temperature below 60°C. The reaction mixture is cooled down, the precipitated calcium tartrate is removed by filtration, and both (+)-2A1B and the solvent are recovered from the filtrate by fractionated vacuum distillation.

Other methods also exist for the production of (+)-2AlB, e.g., the racemate can also be resolved with L(+)-Mandelic Acid.[32/]

In an interesting new method,[33/] (+)-2-Amino-1-butanol is produced by the asymmetric hydrolisis of (±)-Acylamino-1-butanol with a microbe that decomposes only the (+)-acyl derivative. The reaction is carried out at a pH of 6.0, a temperature of 37°C, and the obtained (+)-2AlB is recovered by adsorption to a weak anion-exchange resin. The yield of (+)-2AlB with 98 per cent purity was near to 100 per cent.

Backward integration III

This will be discussed in more detail in annex II.

1.2 Chemical reactions

(a) $2C_4H_{11}NO + 2C_4H_6O_6 = C_8H_{17}NO_7 + C_8H_{17}NO_7$

178.28 300.18 239.23 239.23

(b) $C_8H_{17}NO_7 + Ca(OH)_2 = C_4H_{11}NO + C_4H_4CaO_6 + 2H_2O$

239.23 74.09 89.14 188.15 36.04

(c) $2C_4H_{11}NO + C_2H_4Cl_2 = C_{10}H_{26}Cl_2N_2O_2$

178.28 98.96 277.25

1.3 Combined equation of the synthesis

$4C_4H_{11}NO + 4C_4H_6O_6 + 2Ca(OH)_2 + C_2H_4Cl_2 =$

356.56 600.36 148.18 98.96

$C_{10}H_{24}N_2O_2 \cdot 2HCl + C_4H_4CaO_4 + C_8H_{17}NO_7 + 4H_2O$

277.23 72.92 376.30 478.46 72.08

32/ Czech. Pat. CS 208913 B, 1 November 1982.

33/ Japan Pat. 58/198296 A2, 18 November 1983.

1.4 Chemical input conversion coefficients

The various expressions of the conversion efficiency available from the studied sources were converted to chemical input conversion/consumption coefficients to refer to the manufacture of one kg of ETHAMBUTOL Hydrochloride and were summarized in table A.1. If the material input consumption coefficients in the literature were given with reference to an intermediate, such as (+)-2AlB or (±)-2AlB, the original figures were given in brackets behind the derived overall consumption coefficient. Publications which describe the chemical conversion efficiency of different steps of backward integration but came from different sources were not included in the table but they were used for the evaluation of the quality of the data from other sources.

With a few exceptions, only the conversion efficiencies of principal reactants were given in the literature and the consumption of less important chemicals and/or auxiliary materials was expressed as a value under the collective term other materials, if at all. The scarce information was included in table A.1, because it is qualitatively useful and could be used to estimate roughtly the value of other materials.

Those sources were disregarded when quantitative data were available for the inputs but the ETHAMBUTOL Hydrochloride yield was not given.[34/]

1.5 Other information

A chapter was devoted to the wastes and waste water treatment of chemicals produced by organic synthesis, and a simplified flow sheet for the manufacture of ETHAMBUTOL Hydrochloride by a process similar to that of backward-integration degree II was described in a UNIDO document.[35/] The

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34/ Pharmaceutical Manufacturing Encyclopedia, Noyes Data Corporation, Park Ridge, New Jersey, U.S.A., (1979), p. 116

35/ UNIDO/IS.387 of 6 June 1983: Water use and effluent treatment practices for the manufacture of the 26 priority drugs in the UNIDO illustrative list.

Table A.1. Chemical input conversion coefficients in the manufacture of ETHAMBUTOL Hydrochloride

Name	Source											
	1	2	3	4	5	6	7	8	9	10	11	12
Backward integration I												
(+)-2-Amino-1-butanol	1.53	0.90	0.92-1.60	1.10	0.90	0.85	0.90	0.86	0.88			
Ethylene dichloride	...	0.55	...	0.45	0.45	0.45	0.45	...	0.50			
Hydrochloric acid gas	...	...	...	...	...	...	...	...	0.26			
Isopropanol				3.52	5.30	3.00	2.36	2.40	...			
Sulphuric acid				2.69	2.10	...	...	...	...			
Ethanol									1.37			
Sodium hydroxide				0.72	0.38	0.20	...	...	0.28			
Methanol									0.31			
Charcoal				...	...	...	0.10	...	...			
Other materials, $/kg				0.98	...	...	...	1.78	...			
Backward integration II												
(±)-2-Amino-1-butanol									(2.49)	2.54		1.93 (2.27)
L(+) Tartaric acid									3.21 (4.14)	4.15		4.17
Backward integration III												
Butene-1										2.68 (1.39)	1.66	
Acetonitrile										2.26 (1.17)	2.43	
Chlorine										3.40 (1.76)	1.78	

1 Wilkinson, Shepherd et al. J. Am. Chem. Soc. 83, 2212 (1961)
2 UNIDO unpublished working paper
3 UNIDO/ID/WG.304/6 (1979)
4 UNIDO/ID/WG.331/4 (1980)
5-6 UNIDO/PC.14 (1981)
7 Unpublished country project proposal
8 UNIDO/PC.52 (1982)
9 UNIDO correspondence
10 U.S. pat. 3,553,257 and 3,944,617
11 U.S. pat. 3,855,300
12 UNIDO correspondence

analysis of the described operations concluded that effluents of the production do not require specific treatment. Ordinarily, little if any solvent recovery is required but calcium tartrate or calcium sulfate might be formed as solid waste. Calcium tartrate becomes a waste only if L(+)-Tartaric acid is not recovered, which is the exception rather than the rule.

Although it appears that no unusual labour or safety regulations need be instituted, extreme caution must be exercised in the handling and use of hydrochloric acid gas required in backward integration I because of the toxicity to humans and the possibility of air pollution.

Information in the literature and analysis of the process descriptions showed that steam, water, brine, inert gas, process water, distilled water and electricity requirements were not unusual in synthetic pharmaceutical chemical plants.

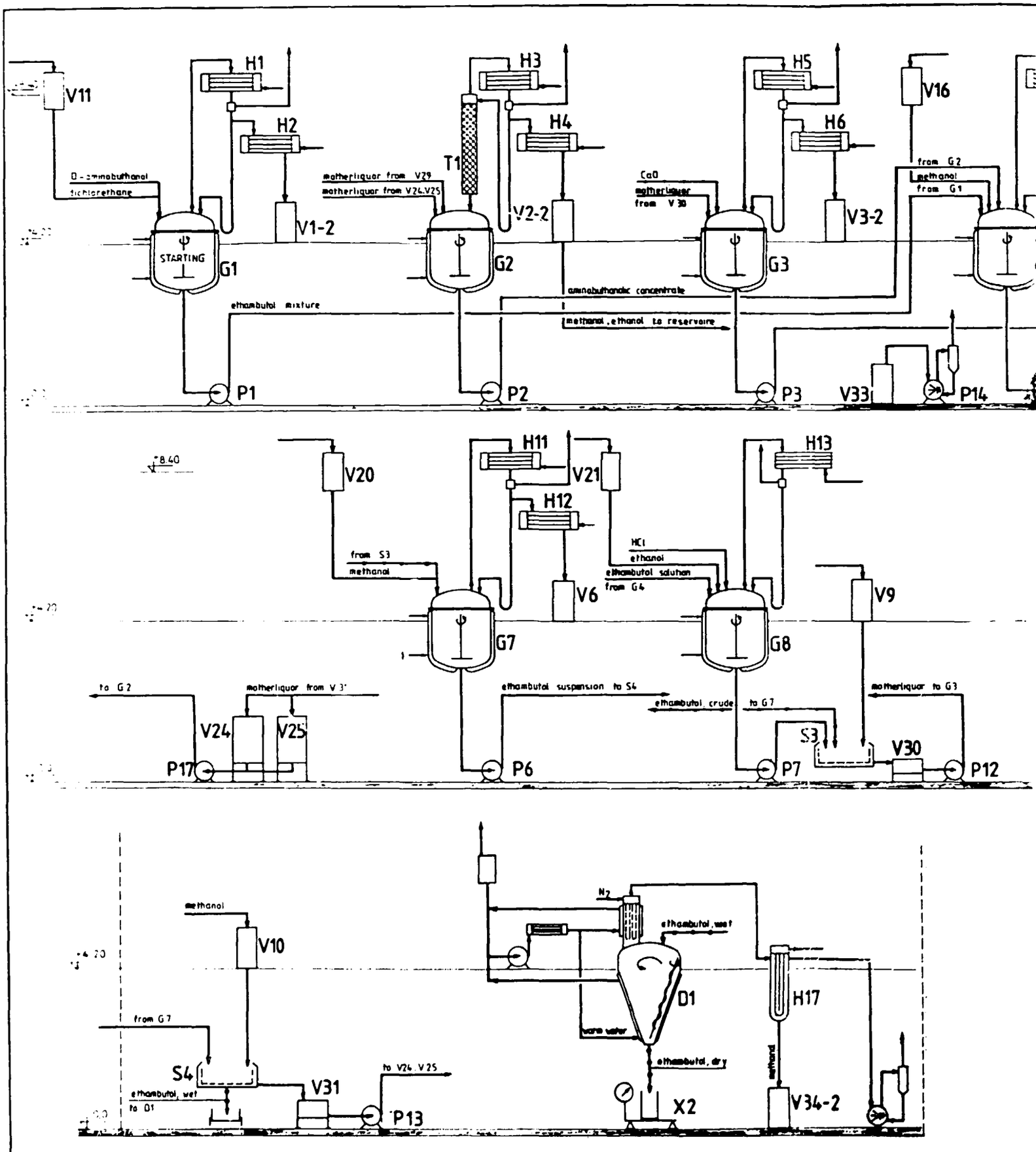
The principal apparatus used in backward integration I of the manufacturing process was described in several papers, and none of the listed equipment unusual in pharmaceutical chemical plants. Table A.2 describes the machinery and equipment illustrated in figure A.1.

Although stainless steel equipment is generally recommended for carrying out syntheses, some manufacturers have indicated a preference for glass-based vehicles for certain steps, because of the high corrosivity of ETHAMBUTOL Hydrochloride solutions.

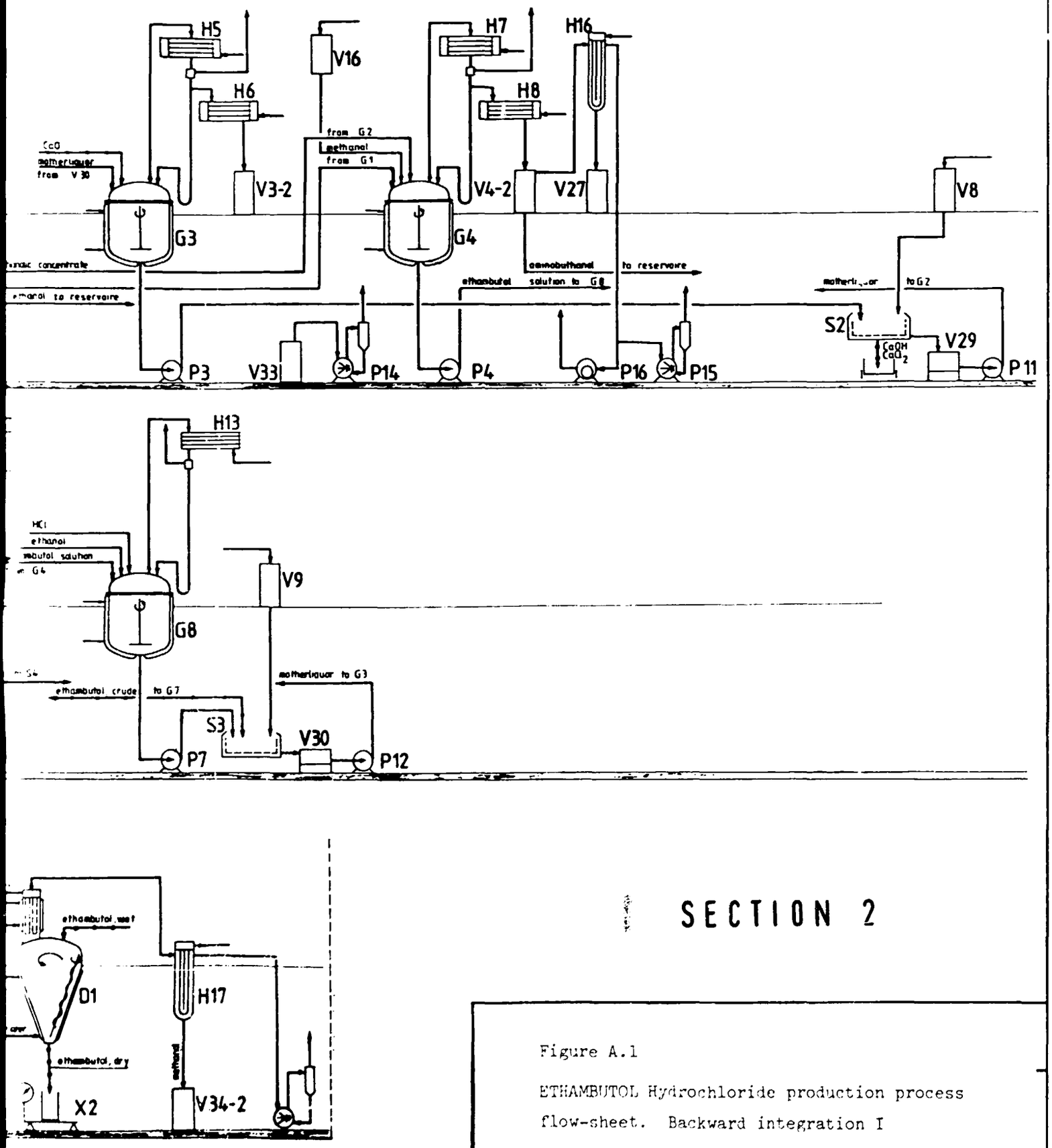
It is essential that all materials used contain as little water as possible; because of the high solubility of ETHAMBUTOL Hydrochloride in water, excessive amounts of the liquid could reduce the yields.

The process flow sheet and the related list of main equipment for backward integration degree I of ETHAMBUTOL Hydrochloride production is given in the following pages.[36/]

36/ Multipurpose plant, VEGYTERV Hungarian Chemical Industries Engineering Centre document (1983).


V11
H1
H2
H3
H4
H5
H6
V16
T1
D-aminobuthanol
trichlorethane
matheriquor from V29
matheriquor from V24.V25
CaO
matheriquor
from V 30
from G2
methanol
from G1
V1-2
V2-2
V3-2
STARTING
G1
G2
G3
aminobuthanolic concentrate
ethambutol mixture
methanol, ethanol to reservoire
P1
P2
P3
V33
P14
V20
H11
V21
H12
H13
from S3
methanol
HCl
ethanol
ethambutol saluhan
from G4
V6
V9
G7
G8
to G2
matheriquor from V 3
V24
V25
P17
ethambutol suspension to S4
ethambutol crude
to G7
matheriquor to G3
S3
V30
P6
P7
P12
methanol
V10
N2
ethambutol, wet
D1
H17
from G7
S4
V31
to V24 V25
ethambutol, wet
to D1
P13
ethambutol, dry
X2
V34-2

SECTION 1



SECTION 2

Figure A.1

ETHAMBUTOL Hydrochloride production process flow-sheet. Backward integration I

Table A.2. List of main equipment for the production of ETHAMBUTOL Hydrochloride - Backward integration I

Code	Number	Name	Material
D1	1	2.0 m^3 vacuum drier	Stainless steel
G1, G2		3.0 m^3 jacketed batch	
G3, G7	4	reactor	Enamelled steel
G4	1	3.0 m^3 jacketed batch	
		reactor	Stainless steel
G8	1	6.3 m^3 jacketed batch	
		reactor	Enamelled steel
H1, H3, H5			
H7, H11	5	16 m^2 condenser	Stainless steel
H2, H4, H6			
H8, H12	5	16 m^2 cooler	Stainless steel
H13	1	25 m^2 condenser	Artificial carbon
H16, H17	2	4.0 m^2 vacuum condenser	Stainless steel
P1, P3, P4			
P6, P11,P13	6	100 l/min centrifugal pump	Stainless steel
P2, P7, P12	3	100 l/min centrifugal pump	Enamelled steel
P14, P15	2	60 m^3/h waterring vacuum pump	Steel
P16	1	60 m^3/h oilring vacuum pump	Steel
P17	1	200 l/min centrifugal pump	Stainless steel
S2, S3,	2	1000-mm diameter centrifuge	Stainless steel
S4		1000-mm diameter centrifuge	Rubber-coated steel
T1	1	250-mm diameter distillation	
		column	Stainless steel
V1/2, V2/2,			
V3/2, V4/2,			
V6	5	0.63 m^3 receiver tank	Stainless steel
V8, V9,V10	3	0.63 m^3 washing medium	
		feeding tank	Stainless steel
V11, V16,			
V20, V21	4	0.63 m^3 feeding tank	Stainless steel
V24, V25,	2	2 m^3 receiver tank	Stainless steel

Table A.2. List of main equipment for the production of ETHAMBUTOL Hydrochloride - Backward integration I (cont'd)

Code	Number	Name	Material
V27	1	0.25 m^3 receiver tank	Stainless steel
V29, V31	2	0.5 m^3 filtrate receiver tank	Stainless steel
V30	1	0.5 m^3 filtrate receiver tank	Rubber-coated steel
V33	1	0.25 m^3 feeding tank	Steel
V34/2	1	0.25 m^3 receiver tank	Steel
X2	1	500-kg balance	Steel

Annex 2 to the

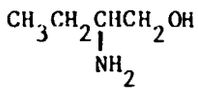
Technical Economic Analysis of the Manufacture of ETHAMBUTOL Hydrochloride

Chemical Synthesis of (±)-2-Amino-1-butanol

A. BASIC DATA OF THE KEY INTERMEDIATE

1. Common names: 2-Aminobutanol, d,l-2-amino-1-butanol, 2-amino-n-butanol

2. Graphic formula:



3. Chemical formula: $C_4H_{11}NO$

4. Molecular weight: 89.14

5. Chemical abstract index name: 2-Amino-n-butyl alcohol

6. CAS Registry Number: [96-20-8]

7. Brief history of the product: The compound has been known since 1902. (±)-2-Amino-1-butanol is an intermediate in the synthesis of surface active agents, vulcanization accelerators, drugs, and other fine chemicals. The discovery of the antituberculotic agent ETHAMBUTOL has increased the importance of the chemical, as evidenced by all patents granted in the early 1970s.

8. Basic patent: Originally, (±)-2-Amino-1-butanol was prepared from nitropropane. The processes used nowadays are described in recently expired and expiring patents, e.g., Takahashi et al. 3,944,700 (1974 to Sankyo Chemical Industries), and Singh, US Pat. 3,944,617 (1976 to American Cyanamide Co.) which use Butene-1 as starting material.

B. BRIEF DESCRIPTION OF THE PRODUCTION PROCESSES

Two important manufacturing processes are described in details in the literature for the commercial production of (±)-2-Amino-1-butanol.

1. Synthesis of (±)-2-Amino-1-butanol starting from Nitropropane - Route A

1-nitropropane is reacted with formaldehyde to yield (±)-2-nitro-1-aminobutanol, which is reduced by catalytic hydrogenation to (±)-2-Amino-1-butanol.

1.1 Schematic illustration of the synthesis

$CH_3CH_2CH_2NO_2$ + HCHO $\xrightarrow[\text{(a) addition}]{}$

nitropropane formaldehyde

$CH_3CH_2\overset{\bullet}{C}\underset{NO_2}{H}CH_2OH$ $\xrightarrow[\text{(b) catalytic hydrogenation}]{H_2}$

(±)-2-nitro-1-butanol

$CH_3CH_2\overset{\bullet}{C}\underset{NH_2}{H}CH_2OH$

(±)2-AMINO-1-BUTANOL

1.2 Chemical reactions

(a) $C_3H_7NO_2$ + CH_2O = $C_4H_9NO_3$

89.09 30.03 119.12

(b) $C_4H_9NO_3$ + $3\ H_2$ = $C_4H_{11}NO$ + $2\ H_2O$

119.12 6.05 89.14 36.03

1.3 Combined equation of the synthesis

$C_3H_7NO_2$ + CH_2O + $3\ H_2$ = $C_4H_{11}NO$ + $2\ H_2O$

89.09 30.03 6.05 89.14 36.03

1.4 Chemical consumption coefficients

In the absence of industrial information, the data of patent DT 2,603,076 (1976 to Société Chimique de la Grande Paroisse Azote et Produits Chimiques) are used for analysis. In this process, a quaternary ammonium salt or a tertiary amine is used as a phase transfer catalyst in order to improve the yield as well as to avoid the formation of undesirable by-products. Example 1 uses Raney-nickel for catalytic hydrogenation and does not include purification before this step, whereas in example 2, a mixed platinum-palladium catalyst is used for hydrogenation and the unreacted nitropentane is recovered by fractionated vacuum distilation. During this operation, by-products are also removed. Table A.3 shows the relevant chemical parameters.

Table A.3. Chemical consumption coefficients (kg/kg) and yields (per cent) of (±)-2-Amino-1-butanol synthesis - Route A

Reactants	Material input consumption coefficients			Yields	
	F	f_1	f_2	y_1	y_2
1-nitropropane	0.999	1.610	1.352	62.0	74.0
formaldehyde	0.337	0.543	0.546	62.0	61.7

Commercial scale yields should usually be better than those described in table A.3 and the patent description gives no information on the life and regeneration of the catalyst. The production costs of the nitropropane process are not analysed partly for this reason, partly because the alternative process starting from Butene-1 is less dangerous and the starting material is a readily available industrial chemical. Another disadvantage of route A is that the catalytic hydrogenation step cannot be carried out in multipurpose batch reactors.

2. Synthesis of (±)-2-Amino-1-butanol starting from Butene-1 - Route B

2.1 Schematic illustration of the synthesis

$$CH_3CH_2CH = CH_2 + Cl_2 + CH_3CN \longrightarrow CH_3CH_2\underset{\underset{N=CClCH_3}{|}}{CH}CH_2Cl$$

butene-1 chlorine acetonitrile N-[(1-chloromethyl)propyl]-acetimidoyl chloride

$$\xrightarrow{\text{(a) hydrolysis}} \quad CH_3CH_2\underset{\underset{NHCOCH_3}{|}}{\overset{\bullet}{C}}HCH_2Cl \quad \xrightarrow{\text{(b) hydrolysis}}$$

N - [(1-chloromethyl) propyl] - acetamide

$$CH_3CH_2\underset{\underset{NH_2}{|}}{\overset{\bullet}{C}}HCH_2OH$$

(±)-2-AMINO-1-BUTANOL

2.2 Chemical reactions

(a) $C_4H_8 + Cl_2 + C_2H_3N = C_6H_{11}Cl_2N$

56.11 70.9 41.05 168.07

(b) $C_6H_{11}Cl_2N + H_2O = C_6H_{12}ClNO + HCl$

168.07 18.02 149.63 36.46

(c) $C_6H_{12}ClNO + 2H_2O = C_4H_{11}NO + HCl + C_2H_4O_2$

149.63 36.04 89.14 36.46 60.05

2.3 Combined equation of the synthesis

$$C_4H_8 + Cl_2 + C_2H_3N + 3H_2O = C_4H_{11}NO + C_2H_4O_2 + 2HCl$$

56.11 70.91 41.05 54.06 89.14 60.05 72.92

2.4 Chemical consumption coefficients

Data for the analysis of the process are available only from patent descriptions.[37/38/] f_1, y_1 and f_2, y_2 values were calculated from these patents.

Table A.4. Chemical consumption coefficients (kg/kg) and yields (per cent) of (±)-2-Amino-1-butanol synthesis - Route B

Reactants	Material input consumption coefficients			Yields	
	F	f_1	f_2	y_1	y_2
Butene-1	0.63	1.66	1.39	38	45
Acetonitrile	0.46	2.43	1.17	19	39
Chlorine	0.80	1.78	1.76	45	45

These patents were granted in the middle of 1970s and commercial scale yields are probably much better to-day. The techno-economic feasibility of the process can further be improved, if the purification of (±)-2AlB is combined with resolution, the next step of synthesis.

2.5 Other information

Local production of (±)-2AlB is linked to the existence of a developed chemical and petrochemical industry, because Butene-1 and Chlorine must be produced domestically.

The technical level of the production technology of (±)-2AlB is relatively high and steady performance requires skilled staff and good technical management.

37/ Takahashi et al., U.S. Pat. 3,855,300 (1974 to Sankyo Chemical Industries Ltd.)

38/ Singh, U.S. Pat. 3,944,617 (1976 to American Cyanamide).

In route B, (+)-2AlB can be produced in a multipurpose batch reactor.

The energy requirement of the production is somewhat higher than usual. Other utilities are customary.

Environment pollution problems are not envisaged from the patent descriptions. There is no need for special effluent treatment.

(+)-2AlB production from nitropropane is more dangerous (explosion) than that from Butene-1. The nitropropane process requires special equipment as well.

Annex 3 to the

Technical and Economic Analysis of the Manufacture of ETHAMBUTOL Hydrochloride

Patent Information on ETHAMBUTOL Hydrochloride manufacturing processes[39/]

US 3,176,040 1965.03.30

Novel 2,2'-(Ethylenediimino)-di-1-butanols
Wilkinson, Shepherd
American Cyanamid Co.

OS 243,774 1965.11.25

Verfahren zur Herstellung von neuen Hydroxydiaminen
Wilkinson, Shepherd
American Cyanamid Co.

US 3,271,450 1966.09.06

2,2'-(Ethylenediimino)-Di-1-Butanols
Wilkinson, Shepherd
American Cyanamid Co.

US 3,297,707 1967.01.10

Pyridylesters of 2,2'-(Ethylenediimino)-di-1-butanols and non-toxic acid addition salts thereof
Wilkinson, Shepherd
American Cyanamid Co.

OS 252,890 1967.03.10

Verfahren zur Herstellung von neuen Hydroxydiaminen
Wilkinson, Shepherd
American Cyanamid Co.

BDR 1,251,770 1967.10.12

Verfahren zur Herstellung von aliphatischen Hydroxydiaminen und deren Säureadditionssalzen
Wilkinson, Shepherd
American Cyanamid Co.

OS 281,786 1970.06.10

Verfahren zur Herstellung von sehr reinem (+)2,2'-(äthylendiimino)-di-1-butanol hydrochloride
Zoja
Laboratorio Clinico-Farmaceutico Giorgio Zoja S.P.A.

39/ Collection from secondary sources.

US 3,553,257 1971

Preparation of d-2-Amino-1-butanol salts
Halmos, Ricketts
American Cyanamid Co.

HU 162,518 1972.10.28

Eljárás d,d'-2,2'-(etiléndiimino)-di-1-butanol-dihidroklorid elöállítására
Kazan
American Cyanamid Co.

OS 309,395 1973.08.10

Verfahren zur Herstellung von sehr reinem (+)2,2'-(äthylendiimino)-di-1-butanol hydrochloride
Portelli, Cervato
Zamban S.P.A.

US 3,769,347 1973.10.30

Production of d,d'-2,2'-(ethylenediimino)-di-1-butanol hydrochloride
Kazan
American Cyanamid Co.

OS 320,604 1975.02.25

Verfahren zur Herstellung von (+)2,2'-(äthylendiimino)-di-butan-1-ol
Bernardi, Foglio, Temperilli
Società Farmaceutici Italia

OS 323,122 1974.09.15

Verfahren zur Herstellung von d-N,N'-bis-(1-hydroxymethylpropyl)-Athylendiamin in dessen hydrochlorid
Butula, Gordana
Pliva

OS 324,290 1974.11.15

Verfahren zur Herstellung von N,N'-bis-(alpha-hydroxyalkyl)-diaminen
Butula, Gordana
Pliva

US 3,855,300 1974.12.17

Process for the production of 2-Amino-1-butanol
Takahashi, Shiaya, Kobayashi, Fujii, Nishimura
Sankyo Chemical Industries Ltd.

US 3,944,617 1976.03.16

Synthesis of dl-2-Amino-1-butanol
Singh
American Cyanamid Co.

US 3,944,619 1976.03.16

Synthesis of d-2-Amino-1-butanol
Singh
American Cyanamid Co.

US 3,944,618 1976.03.16

Synthesis of Ethambutol
Singh
American Cyanamid Co.

OS 328,419 1976.03.25

Verfahren zur Herstellung von (+)-2,2'-(Athylendiimino)-di-1-butanol and seinen Salzen
Mitsui Toatsu Chemicals, Mitsui Pharmaceuticals

EDR 2,603,076 1976.08.05

Verfahren zur Herstellung von 2-aminobutan-1-ol
Adrian, Guj, Marcel-Xavier, Donai, Benattan, André
Société Chimique de la Grande Paroisse Azote et Produits Chimiques S.A.

HU 170,394 1976.12.28

Eljárás N,N'-bisz-(1-hidroxibutil-2-)-etiléndiamin elöállitására
Ecsery, dr. Hermanné, Török et al.
Chinoin

Annex 4 to the

Technical and Economic Analysis of the Manufacture of ETHAMBUTOL Hydrochloride

Patent information of (+)-2-Amino-1-butanol manufacturing processes[40/]

CA: 75(9)63452t
Optically active N(1-phenylethyl)-carbamyl carboxylic acids for optically resolving racemic basis
Inventor (author): Ernst Felder; Davide Pitre
Assignée: Bracco Industria Chimica S.P.A.
Patent: United States; US 3576854 Date: 1971.04.27
Application: Switerzland Date: 1968.03.15

CA: 75(5)35119w
Dextrorotatory 2,2'-(ethylenediimino)-di-1-butanol
Inventor (author): Giorgio Zoja
Assignée: Laboratorio Chimico Farmaceutico Giorgio Zoja S.P.A.
Patent: United States; US 3579586 Date: 1971.05.18
Application: Germany Date: 1968.06.05

CA: 74(17)87369b
(+)-2,2'-(Ethylenediimino)-di-1-butanol having antituberculosis activity
Assignée: Antonio Gallardo, S.A.
Patent: Spain; ES 357033 Date: 1970.03.01
Application: Spain Date: 1968.08.08

CA: 74(15)76008g
Resolution of 2-aminobutanol
Inventor (author): Géza Tóth
Assignée: Chinoin Gyógyszer és Vegyészeti Termékek Gyára Rt.
Patent: Hungary Teljes; HU 667 Date: 1970.07.24
Application: Hungary Date: 1968.12.28

CA: 74(13)63960s
Simultaneous preparation of 2-amino-1-butanol and 2-amino-2-ethyl-1,3-propanediol
Inventor (author): John B. Tindall
Assignée: Commercial Solvents Corp.
Patent: Germany Offen.; DE 2026538 Date: 1970.12.10
Application: United States Date: 1969.06.06

CA: 74(3)12600m
Pharmaceutically suitable dichlorohydrate of D-2,2'-(ethylenediimino)-di-1-butanol
Assignée: Laboratorio Chimico Farmaceutico Giorgio Zoja S.P.A.
Patent: France Demande; FR 2014155 Date: 1970.04.17
Application: Germany Date: 1968.08.06

40/ Results of the computer search in all issues of Chemical Abstracts published between 1 January 1967 and 31 December 1984.

CA: 73(7)34782d
d-2-Aminobutanol
Inventor (author): Jenö Seres; Klára Daróczi, János Lengyel
Assignée: Chinoin Gyógyszer és Vegyészeti Termékek Gyára Rt.
Patent: Hungary; HU 157225 Date: 1970.04.08
Application: Hungary Date: 1968.06.23

CA: 73(5)24902d
d-2-Amino-1-butanol
Inventor (author): Imre A. Halmos, Thomas E. Ricketts
Assignée: American Cyanamid Co.
Patent: Britain; GB 1188185 Date: 1970.04.15
Application: United States Date: 1966.09.16

CA: 87(7)53255q
2-Amino-1-alcohols
Inventor (author): Walter Himmele, Leopold Hupfer, Herbert Toussaint, Gerhard Paul
Assignée: BASF A.-G.
Patent: Germany Offen.; DE 2547654 Date: 1977.04.28
Application: Germany; DE 2547645 Date: 1975.10.24

CA: 86(1)4928g
2-Amino-1-butanol
Inventor (author): Guy Adrian, Marcel X. Sion, Andre Benattar
Assignée: Société Chimique de la Grande Paroisse, Azote et Produits Chimiques
Patent: Germany Offen.; DE 2603076 Date: 1976.08.05
Application: France; FR 753431 Date: 1975.02.04

CA: 91(19)157248p
Synthesis of dl-2-amino-1-butanol hydrochloride and derivatives thereof
Inventor (author): Balwant Singh
Assignée: American Cyanamid Co.
Patent: Britain; GB 1541290 Date: 1979.02.28
Application: Britain; GB 765023 Date: 1976.02.09

CA: 91(9)74598b
3-Acyl-4-ethyl-2-oxazolones and oxazolidinones
Inventor (author): Balwant Singh
Assignée: American Cyanamid Co.
Patent: United States; US 4150030 Date: 1979.04.17
Application: United States; US 642944 Date: 1975.12.22

CA: 91(3)19897y
Amino alcohols
Inventor (author): Yataro Ichikawa, Eishin Yoshisato, Koji Nakagawa
Assignée: Teijin Ltd.
Patent: United States; US 4151204 Date: 1979.04.24
Application: United States; US 590945 Date: 1975.06.27

CA: 90(11)86723f
2-Aminobutanol
Inventor (author): Czeslaw Belzecki, Witold Tomasik, Jerzy Trojnar
Assignée: Instytut Chemii Organicznej
Patent: Poland; PL 86547 Date: 1977.12.31
Application: Poland; PL 161371 Date: 1973.03.20

CA: 88(25)190067q
2-Amino-1-butanol
Inventor (author): Iustin Alexandru Mihai Pihuleac, Ioan Bradescu, Thea Panaitescu, Steliana Cilianu, Mariana Ionescu
Assignée: Institutul de Cercetari Chimico-Farmaceutice
Patent: Romania; RO 60029 Date: 1976.02.16
Application: Romania; RO 71101 Date: 1972.06.01

CA: 88(13)89089y
Resolution of racemic organic amines
Inventor (author): Masahiko Saito, Yoshiki Sato, Kenzo Watanabe, Toshio Wakabayashi
Assignée: Teijin Ltd.
Patent: Japan Kokai Tokkyo Koho; JP 77139001 Date: 1977.11.19
Application: Japan; JP 7655279 Date: 1976.05.17

CA: 88(3)22136t
Synthesis of dl-2-amino-1-butanol
Assignée: American Cyanamid Co.
Patent: Belgium; BE 838764 Date: 1976.08.20
Application: Belgium; BE 838764 Date: 1976.02.20

CA: 87(23)183977n
Synthesis of D-2-amino-1-butanol
Inventor (author): Balwant Singh
Assignée: American Cyanamid Co.
Patent: South Africa; ZA 7600577 Date: 1976.11.24
Application: South Africa; ZA 76577 Date: 1976.02.02

CA: 87(9)67960c
2,6-Dinitroaniline herbicides
Inventor (author): Albert William Lutz, Robert Eugene Diehl
Assignée: American Cyanamid Co.
Patent: United States; US 4025538 Date: 1977.05.24
Application: United States; US 174938 Date: 1971.08.25

CA: 95(11)97030g
Optically active 2-aminobutanol and its salts with acids
Inventor (author): László Magdányi, Lajos Kovács
Assignée: Finomvegyszer Szövetkezet
Patent: Hungary Teljes; HU 19359 Date: 1981.01.28
Application: Hungary; HU 79FI695 Date: 1979.01.31

CA: 94(11)82201u
Amino alcohols
Assignée: Denki Kagaku Kogyo K.K.
Patent: Japan Kokai Tokkyo Koho; JP 80138389 Date: 1980.10.29
Application: Japan; JP 7945899 Date: 1979.04.14

CA: 99(1)5191s
(+)-2-Amino-1-butanol by resolution of racemic aminobutanol
Inventor (author): Alois Krajicek, Eduard Spicak, Adolf Imnr, Antonin Xerny, Miroslav Semonsky
Patent: Czechoslovakia; CS 208913 B Date: 1982.11.01
Application: CS 718822 Date: 1971.12.20

CA: 97(21)181716j
d-2-Amino-1-butanol
Inventor (author): Péter Lónyai
Patent: Hungary Teljes; HU 21828 O Date: 1982.02.27
Application: HU 79LO430 Date: 1979.01.27

CA: 100(15)119354s
Microbial production of d-2-aminobutanol
Assignée: Chisso Corp.
Patent: Japan Kokai Tokkyo Koho; JP 58/198296 A2 Date: 1983.11.18
Application: Japan; JP 82/79699 Date: 1982.05.12

Annex 5 to the

Technical and Economic Analysis of the Manufacture of ETHAMBUTOL Hydrochloride

Manufacturers and Suppliers of ETHAMBUTOL Hydrochloride

1.1 Integrated manufacturers

AMERICAN CYANAMID CO.
Medical Division
One Cyanamid Plaza
Wayne, NJ 07470

Telex: 130400
FAX: 201-831-1106
Phone: 201-831-2000

BORGE PHARMACEUTICALS
9929 Hibert Street, Suite A
San Diego, CA 92131
United States of America

Telex: 295104 BORGE UR
Phone: (619) 578-5400

CHINOIN PHARMACEUTICAL AND CHEMICAL WORKS LTD.
P.O. Box 110
1325 Budapest
Hungary
Represented by:
MEDIMPEX
Hungarian Trading Company for Pharmaceutical Products
Vörösmarty tér 4
H-1808 Budapest V.
Hungary

LUPIN LABORATORIES PVT. LTD.
159 CST Road, Kalina, Santacruz East
Bombay-400 098
India

Telex: 011-71587 LUPN IN
Cable: LUPINLAB

RAPTAKOS BRETT & CO. LTD.
47 Dr Anni Besant Road
Worli, Bombay 400 025
India

Telex: 2579 RUIA IN
Cable: CALCINOLL
Phone: 49 34 251

SIEMGLUSS AND SON
P.O. Box 105624
D-2000 Hamburg 1
Federal Republic of Germany

Telex: 216 2667
Cable: VITACHEMIE HAMBURG
Phone: 040/23 21 21-29

THEMIS PHARMACEUTICALS
38 Suren Road, Andheri (East)
Bombay 400 098
India

Telex: 011 3603
Cable: THEMIS
Phone: 575631

1.2 Non-integrated manufacturers

LABORATORIO CHIMICO
Farmaceutico Giorgio Zoja SpA
Viale Lombardia 20
I-20131 Milano
Italy

Telex:
Cable: ZOJAFARMA
Phone: 2.361.041/2/3

1.3 International trading houses

ARCHEMIA S.
Via E. Pagliano 21
20149 Milan
Italy

Telex: 331238 ARCHEMI
Cable: ARCHEMIA
Phone: (02) 4988211/212/213

AVRACHEM AG
Gartenstrasse 12
6340 Baar
Switzerland

Telex: 864996
Phone: (042) 31 83 55

DANGSCHAT AUSSENHANDELSGMBH
P.O. Box 101224
D-2000 Hamburg 1
Federal Republic of Germany

Telex: 2 12 501 dong d
Cable: DONGSCHATTRADO
Phone: (040) 23 30 41

KARL O. HELM AKTIENGESELLSCHAFT
Nordkanalstrasse 28
P.O. Box 103060
D-2000 Hamburg 1
Federal Republic of Germany

Telex: 2170150
Cable: HELMPHARMA
Phone: (040) 2375-1422

MARSING AND CO. LTD. A/S
Sjaellandsbroen 6
DK-2450 Copenhagen SV
Denmark

Telex: 19925 marco dh
Cable: MARSINGCO
Phone: (01) 164444

Annex 6 to the

Technical and Economic Analysis of the Manufacture of ETHAMBUTOL Hydrochloride

Manufacturers and Suppliers of Intermediates for the Production of ETHAMBUTOL Hydrochloride

1. (+)-2-Amino-1-butanol

ALDRICH CHEMICAL COMPANY
940 West Saint Paul Ave.
Milwaukee, WI 53233

Phone: 414-273-3850

BASF AKTIENGESELLSCHAFT
Carl-Bosch-Strasse 38
D-6700 Ludwigshafen
Federal Republic of Germany

CHEMICAL DYNAMICS CORPORATION
Post Office Box 395
South Plainfield, NJ 07080

FLUKA CHEMICAL CORPORATION
255 Oser Ave.
Hauppauge, NY 11787

Phone: 516-273-0110

K & K LABORATORIES
Division of ICN Biochemicals, Inc.
121 Express St.
Plainview, NY 11803

Phone: 516-433-6262

2. (±)-2-Amino-1-butanol

CHEMICAL DYNAMICS CORPORATION
Post Office Box 395
South Plainfield, NJ 07080

FLUKA CHEMICAL CORPORATION
255 Oser Ave.
Hauppauge, NY 11787

Phone: 516-273-0110

PFALTZ & BAUER, INC.
Division of Aceto Chemical
172 East Aurora St.
Waterbury, CT 06708

3. Ethylene Dichloride

THE ASSOCIATED OCTEL COMPANY LTD.
P.O. Box
Oil Sites Road
Ellesmere Part
South Wirral L65 4HF
London W1X 6DT
United Kingdom

Telex: 629384
Cable: OCTEL...
Phone: 051-355-3611

4. L(+) Tartaric acid

CHEMISCHE FABRIK UETIKON
Seestrasse
CH-8707 Uetikon-am-See
Switzerland

Telex: 875 675
Cable: CHEMIE UETIKON
Phone: 01-922 11 41

PAHI, S.L.
Avenida de Madrid, 66
Barcelona - 28
Spain

Telex: 51883 PAHIE
Cable: PAHI BARCELONA
Phone: 656 2409

SOCIETE CHIMIQUE DE LA GRANDE PAROISSE SA
9, avenue Robert Schumann
F-75007 Paris
France

Telex: 260872F
Phone: (1)555-4430

VINAL SpA
Via Emilia, 3
I-270456 Santa Giulietta PV
Italy

Telex: 321116 VINAL I
Phone: 0383-89340/89120

Résumé

Cette étude a été preparée par le Service des études sectorielles de l'ONUDI comme apport à un modèle global de prise de décision dans le choix de produits pharmaceutiques et intermédiaires susceptibles d'être fabriqués localement par synthèse chimique organique.

L'économie de procédé dans la fabrication de l'hydrochloride d'ETHAMBUTOL a été évaluée en tenant compte du coût des intermédiaires-clés, des entrées directes de matériel, de même que du coût de conversion. Les données techniques et économiques utilisées dans l'étude ont été tirées de publications ou fournies par les fabricants ou les maisons de commerce eux-mêmes.

La situation des pays parvenus à divers stages de développement y est passée brièvement en revue par rapport aux possibilités de réaliser divers degrés d'intégration verticale.

L'intégration verticale minimum est techniquement réalisable mais peu intéressante au point de vue économique. Une production locale peut être envisagée avant tout dans les pays où l'objectif à court-terme serait d'acquérir de l'expérience dans le domaine de l'industrie pharmaceutique et d'y former un personnel qualifié.

L'intégration verticale avancée de fabrication de l'hydrochloride d'ETHAMBUTOL peut être techniquement réalisée et est économiquement attractive. La préparation d'une étude de perspectives à l'investissement portant sur les aspects de marketing, d'ingénierie et de financement se justifie surtout dans les pays où la consommation de l'hydrochloride d'ETHAMBUTOL est importante comme dans ceux qui visent à établir ou à augmenter leur production de produits pharmaceutiques et d'intermédiaires, soit dans une usine existante, soit comme une composante dans une usine polyvalente.

L'intégration verticale maximum présente une économie accrue à la fois dans le coût total de production et dans les devises convertibles. Les fabricants intégrés d'hydrochloride d'ETHAMBUTOL, en particulier ceux qui possèdent une production pétrochimique, trouveront intérêt à préparer une étude de perspectives à l'investissement pour la fabrication du (+)-2-amino-1-butanol.

Fait à signaler enfin, il ressort de cette étude que la récupération du (+)-2-amino-1-butanol, du L(+)-acide tartarique, et à un moindre degré de l'Isopropanol, affecte largement l'économie de procédé de fabrication de l'ETHAMBUTOL.

Resumen

El presente estudio fue realizado por la Subdivisión de Estudios Sectoriales de la ONUDI como parte de un modelo sectorial de toma de decisiones adecuado para seleccionar productos químicos e intermedios para fabricación local por síntesis orgánica.

La economía del proceso de la producción de Clohidrato de ETAMBUTOL se evaluó teniendo en cuenta los costos de intermedios claves, los costos de insumos materiales directos y los costos de conversión. Los datos técnicos y económicos usados en el estudio se tomaron de fuentes publicadas o se obtuvieron por correspondencia con casas productoras y proveedoras.

Países en desarrollo en etapas distintas de desarrollo de la industria farmacéutica fueron revisados brevemente con respecto a la implementación de los varios grados de la integración vertical.

El grado mínimo de integración vertical es técnicamente viable, pero no lo es económicamente. Producción local puede considerarse prioritaria en aquellos países donde el objetivo a corto plazo es ganar experiencia en y entrenar personal para la industria farmacoquímica.

El grado avanzado de la integración vertical es técnicamente viable y económicamente atractivo. La preparación de un estudio de previabilidad sobre los aspectos detallados de ingeniería, financieros y de mercado es justificada, particularmente en países con demanda alta de Clorhidrato de ETAMBUTOL y en aquéllos que tienen como meta el establecimiento o expansión de la producción de substancias

farmacoquímicas e intermedias en plantas existentes o como contribución a la racionalidad para el establecimiento de una planta multipropósito nueva.

El grado máximo de integración vertical ofrece ventajas económicas adicionales con respecto tanto a la rentabilidad como al ahorro en moneda convertible. Productores integrados de Clorhidrato de ETAMBUTOL, particularmente los con plantas petroquímicas de producción, podrían estar interesados también en la preparación de un estudio de previabilidad sobre la producción de (+)-2-Amino-1-butanol.

Es un hecho interesante que la regeneración de (+)-2-Amino-1-butanol, Acido L(+)-Tartárico y en grado menor, Isopropanol, desempeña un papel importante en la economía del proceso.

ТЕХНИЧЕСКИЙ И ЭКОНОМИЧЕСКИЙ АНАЛИЗ ПРОИЗВОДСТВА ХЛОРГИДРАТА ЭТАМБУТОЛА

КРАТКОЕ СОДЕРЖАНИЕ

Настоящее исследование подготовлено Отделением секторальных исследований ЮНИДО в качестве вклада в создание общей модели принятия решений о выборе фармацевтических химических веществ и промежуточных соединений для местного производства методом органического химического синтеза.

В ходе исследования произведена оценка экономических показателей технологии производства хлоргидрата этамбутола с учетом стоимости основных промежуточных соединений, прямых материальных затрат и затрат на преобразование веществ. Технико-экономические данные, положенные в основу исследования, взяты из публикаций или получены от производителей и поставщиков.

Проведен общий обзор развивающихся стран, имеющих фармацевтическую промышленность на различных этапах развития, для изучения их возможностей обеспечения различной степени обратной интеграции.

Минимальная обратная интеграция является технически целесообразной, но экономически нерентабельной. На местное производство можно рассчитывать в первую очередь в тех странах, в которых ближайшей задачей является приобретение опыта и подготовка квалифицированного персонала в области фармацевтической промышленности.

Технически целесообразна и экономически рентабельна более высокая обратная интеграция производства хлоргидрата этамбутола.

Подготовка предварительного технико-экономического обоснования, касающегося сбыта и технических и финансовых аспектов, оправдана особенно в тех странах, которые отличаются высоким спросом на хлоргидрат этамбутола, и может быть направлена на создание/расширение производства фармацевтических химических веществ и промежуточных соединений либо в рамках имеющегося предприятия, либо в качестве вклада в обоснование целесообразности создания нового многоцелевого предприятия.

Максимальная степень обратной интеграции к тому же дает экономию как в плане общих издержек, так и конвертируемой валюты. Производители хлоргидрата этамбутола в рамках интегрированного производства, особенно если они располагают нефтехимическими мощностями, могут также проявить интерес к подготовке предварительного технико-экономического обоснования производства (±)-2-амино-1-бутанола.

В результате исследования был получен интересный вывод, а именно, что на экономических показателях технологии производства серьезно сказывается извлечение (+)-2-амино-1-бутанола, L(+)-винной кислоты и в меньшей степени изопропанола.

For the guidance of our publications programme in order to assist in our publication activities, we would appreciate your completing the questionnaire below and returning it to UNIDO, Division for Industrial Studies, D-2119, P.O. Box 300, A-1400 Vienna, Austria

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Q U E S T I O N N A I R E

Technical and economic analysis of the manufacture of ETHAMBUTOL Hydrochloride

	(please check appropriate box) yes	no
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(3) Was the information provided new?	/_/	/_/
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(5) Did you find the recommendations sound?	/_/	/_/
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