1,024,901

# PATENT SPECIFICATION

NO DRAWINGS

1,024,901

*Date of Application and filing Complete Specification: March 21, 1963.*
*No. 11168/63.*
*Application made in Switzerland (No. 3386) on March 21, 1962.*
*Complete Specification Published: April 6, 1966.*
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**Index at acceptance:**—C2 C(2B48C4, 2B48G3, 3A7V3A4, 3A7V3E2, 3A7V3J3, 3A13C7, 3A13C10F, 3A13C10H)

**Int. Cl.:**—C 07 d

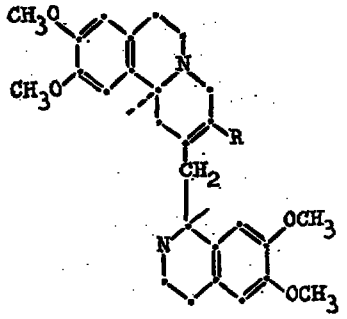
COMPLETE SPECIFICATION

## A process for the manufacture of Dehydro-Emetines and Analogues thereof

We, F. HOFFMANN-LA ROCHE & Co. Aktiengesellschaft, a Swiss Company of 124—184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

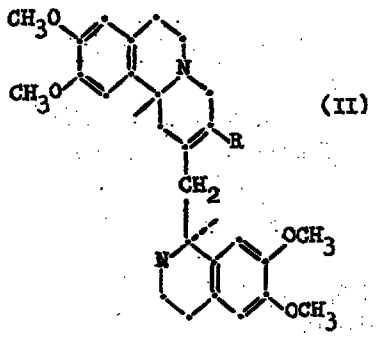
The present invention is concerned with a process for the manufacture of dehydro-emetines and analogues thereof.

The compound known as 2-dehydro-emetine represents an extremely useful chemotherapeutic agent for the treatment of amoebiasis and bilharziasis. It possesses two asymmetric carbon atoms and, when obtained according to known methods, it is in the form of a racemate. The racemate consists of equal parts of (−) 2-dehydro-emetine and (+) 2-dehydro-emetine and it has now been found that only the (−) 2-dehydro-emetine has the desired chemotherapeutic properties while the (+) 2-dehydro-emetine is inactive. These may be respectively formulated thus:



(I)

(−) series
Ia : R = ethyl
Ib : R = lower-alkyl other than ethyl



(II)

(+) series
IIa : R = ethyl
IIb : R = lower-alkyl other than ethyl

It will be understood that, as used in this description and in the claims appended hereto, the term "lower alkyl" refers to both straight-chain and branched-chain alkyl groups containing not more than four carbon atoms (e.g. methyl, ethyl, propyl, *iso*-propyl, butyl and *iso*butyl). Similarly, the term "lower alkoxy" is used to mean alkoxy groups containing not more than four carbon atoms. When R is the ethyl group, the compounds of the foregoing formulae represent 2-dehydro-emetines and are referred to as Ia and IIa respectively. Where R represents a lower-alkyl group other than ethyl, the compounds will be referred to as Ib and IIb respectively.

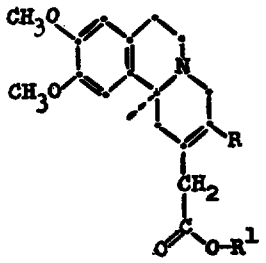
In view of the finding that chemotherapeutic activity is critically dependent on the optical configuration, a stereospecific synthesis of the active isomer is of great interest. Such a method for the synthesis of (−) 2-dehydro-emetine Ia and its 3-(lower alkyl) analogues Ib is one of the objects of this invention.

A known method for the preparation of racemic 2-dehydro-emetine consists in condensing homoveratryl amine with a racemic 2-(loweralkoxycarbonylmethyl)-3-ethyl-9,10-dimethoxy-1,4,6,7-tetrahydro-11bH-benzo[a]quinolizine or (obtained ~~thereform~~ therefrom by hydrolysis) 2-carboxymethyl-3-ethyl-9,10-dimethoxy-1,4,6,7-tetrahydro-11bH-benzo-[a]quinolizine, cyclizing the resulting acid amide and reducing the 2-dehydro-O-methyl psychotrine obtained. When this method is carried out starting from benzo[a]-quinolizines which are substituted in the 3-position by, for example, a methyl, propyl, *iso*propyl, butyl, or *iso*butyl group in place of the ethyl group, there are obtained 3-(lower alkyl) analogues of 2-dehydro-emetine.

It has also been found that the required isomer can readily be obtained by the foregoing process if the (−)-compound present in the racemic starting material is used as the starting material in the process and, further, that the unwanted (+)-compound can be converted into the desired (−)-compound which can be used to supplement the starting material with the (−)-~~compound~~ component.

According to the process provided by the invention, (−) 2-dehydro-emetine and its 3-(lower alkyl) analogues are manufactured by condensing a (−) 2-(lower alkoxy-carbonylmethyl) - 3 - (lower alkyl) - 9,10 - dimethoxy - 1,4,6,7 - tetrahydro - 11bH-benzo[a]quinolizine or the corresponding 2 - carboxymethyl derivative with homo-veratryl amine, cyclising the acid amide obtained, hydrogenating the resulting 2-dehydro - O - methyl - psychotrine or 3 - (lower alkyl) analogue thereof and, if desired, separating the desired (−) - compound from the mixture obtained.

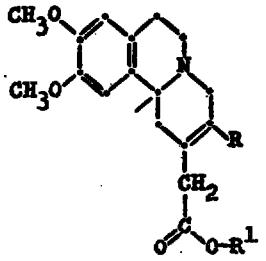
The (−) 2 - (lower alkoxycarbonylmethyl) - 3 - (lower alkyl) - 9,10 - dimethoxy-1,4,6,7 - tetrahydro - 11bH - benzo[a]quinolizines used as starting materials may be formulated thus:



(III)

IIIa : R = $R^1$ = Lower-alkyl
IIIb : R = Lower-alkyl, $R^1$ = hydrogen
IIIc : R = Ethyl, $R^1$ = methyl

The corresponding (+) benzo[a]quinolizines may be formulated thus:—



(IV)

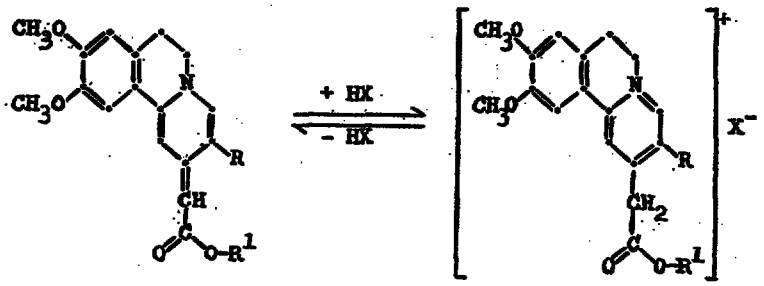
IVa : R = $R^1$ = Lower-alkyl
IVb : R = Lower-alkyl, $R^1$ = hydrogen
IVc : R = Ethyl, $R^1$ = methyl

The invention also includes an extended process which includes the initial step of separating a racemic 2 - (lower alkoxycarbonylmethyl) - 3 - (lower alkyl) - 9,10 - dimethoxy - 1,4,6,7 - tetrahydro - 11bH - benzo[a] - quinolizine into the corresponding (−) and (+) forms, isolating the (−) form from the (+) form, using the former as the starting material and oxidising the latter with a mercuric, cupric or ferric salt, reducing the oxidation product and separating the resulting racemic 2 - (lower alkoxycarbonylmethyl) - 3 - (lower alkyl) - 9,10 - dimethoxy - 1,4,6,7 - tetrahydro - 11bH - benzo[a]quinolizine into the corresponding (−) and (+) forms and supplementing said starting material with the (−) component.

The separation can be carried out, for example, by fractional crystallization of the salts formed between the racemate and a suitable optically active acid such as dibenzoyl D - tartaric acid or L - tartaric acid. A preferred method for the preparation of IIIc from the racemate comprises adding dibenzoyl D - tartaric acid to the racemate and then isolating the dibenzoyl D - tartrate of IVc. The compound IIIc is then obtained from the filtrate by concentration, followed by decomposition with alkali. The compound IIIc can then be purified through the L-tartrate.

The (+)-rotatory enantiomeric base IVa can be reconverted into the racemic form and this can, once again, be separated into its optical antipodes. By this procedure, the total yield of the desired end product is increased. The conversion into the racemate is carried out by oxidizing IVa with a mercuric, cupric or ferric salt, (advantageously with mercuric acetate in acetic acid solution) to form a 2 - (lower alkoxycarbonylmethyl) - 3 - (lower alkyl) - 9,10 - dimethoxy - 6,7 - dihydro - 11bH-benzo[a]quinolizine which can subsequently be reduced.

The oxidation products can be represented by formula V when present in the form of the respective bases, and by formula VI when present as quaternary salts.



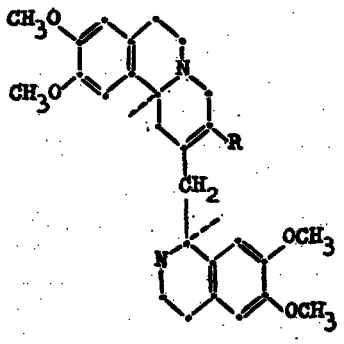
(V) (VI)

In formulae V and VI the symbols R and $R^1$ both represent lower-alkyl groups and $X^-$ represents an anion (e.g. a halogen anion). As can be seen from formulae V and VI tautomerism is involved.

The subsequent reduction can be carried out using suitable reduction systems; for example, potassium borohydride or sodium borohydride in an alkanol containing up to four carbon atoms such as methanol. The reduction can also be carried out by catalytic hydrogenation; for example, by hydrogenation in the presence of platinum oxide.

Prior to the condensation with homoveratryl amine, the (−) 2-(lower alkoxycarbonylmethyl) compound IIIa is advantageously saponified to the carboxymethyl compound IIIb. The saponification can be carried out by acid hydrolysis; for example, by boiling with dilute mineral acid such as dilute hydrochloric acid. The acid amide formation and the cyclization to (−) 2-dehydro-O-methyl-psychotrine or a 3-(lower alkyl) analogue thereof can be carried out according to methods known *per se*. The homoveratryl amide is formed, for example, by heating IIIb with homoveratryl amine in an inert organic water immiscible solvent (preferably an aromatic hydrocarbon such as benzene, toluene or xylene) during which the aqueous azeotrope formed is removed. The cyclization is suitably effected by introducing into the mixture a phosphorus cyclization agent (such as phosphorus oxychloride or phosphorus pentoxide) in an inert solvent (such as benzene) at an elevated temperature (e.g. at the boiling point of the mixture).

The subsequent reduction of the cyclization product proceeds to a stereoisomeric mixture consisting of I and VII via the formation of a new asymmetric centre at the carbon atom 1′ of the *iso*quinoline ring.



(VII)

(−) *iso* series
VIIa : R = ethyl

The reduction can be carried out, for example, catalytically or by means of an alkali metal-metal hydride such as lithium borohydride, lithium aluminium hydride, or sodium borohydride. Where (−) 2-dehydro-O-methyl-psychotrine is reduced there is obtained not only the desired (−) 2-dehydro-emetine Ia but also (−) 2-dehydro-isoemetine VIIIa.

The compounds of the (−) 2-dehydro-isoemetine series can be separated from

the compounds of the (−) 2-dehydroemetine series; for example, by fractional crystallization. The separation can be carried out, for example, by fractional crystallization of the mineral acid salts such as the hydrohalide salts (e.g. the dihydrochlorides and dihydrobromides).

The (−) and the (+) 2-(lower alkoxycarbonylmethyl)-3-(lower alkyl)-9,10-dimethoxy-1,4,6,7-tetrahydro-11bH-benzo[a]quinolizines mentioned earlier are claimed *per se* in the specification of our copending application for Letters Patent No. 11454/65 (now serial no: 1024902).

The oxidation products, namely, the compounds of formulae V and VI hereinbefore are claimed *per se* in the specification of our copending application for Letters Patent No. 11454/65 (now serial no: 1024902).

The homoveratryl amides aforesaid are claimed *per se* in the specification of our copending application for Letters Patent No. 43797/65 (now serial no: 1024903).

The cyclisation products, namely, 2 - dehydro - O - methyl - psychotrine and its 3 - (lower alkyl) analogues, and their acid addition salts are claimed *per se* in the specification of our copending application for Letters Patent No. 43798/65 (now serial no: 1024904).

Again, the (−) 2 - dehydro - emetine and its 3 - (lower alkyl) analogues of formula I manufactured according to the process of this invention, are new compounds with valuable chemotherapeutic properties (e.g. amoebicidal properties) and are accordingly useful as chemotherapeutics in the treatment of amoebiasis. The compounds of formula I are basic in nature and form acid addition salts with both organic and inorganic acids. They form pharmaceutically acceptable acid addition salts with medicinally acceptable acids such as the hydrohalic acids (e.g. hydrochloric acid, hydrobromic acid) nitric acid, sulphuric acid, phosphoric acid and *para*toluenesulphonic acid. Both the compounds and their salts can be used, for example, in the form of conventional pharmaceutical preparations in which either a base of formula I or a pharmaceutically acceptable acid addition salt thereof can be incorporated. For example, said active agent can be employed in admixture with a compatible pharmaceutical organic or inorganic inert carrier materials suitable for enteral or parenteral application; for example, water, gelatin, starch, magnesium stearate, talc, vegetable oils, gums, polyalkylene glycols and petroleum jelly. The pharmaceutical preparations can be in conventional solid form (such as tablets, dragées, suppositories and capsules) or in conventional liquid form (such as solutions, suspensions or emulsions). They can be subjected to conventional pharmaceutical procedures such as sterilization, and can contain conventional pharmaceutical excipients or adjuvants such as preservatives, wetting agents, emulsifying agents, salts for adjusting osmotic pressure or buffers. They can also contain other chemotherapeutically valuable agents.

The following Examples illustrate the processes of the invention.

## EXAMPLE 1

82 g of 2-methoxycarbonylmethyl-3-ethyl-9,10-dimethoxy-1,4,6,7-tetrahydro-11bH-benzo[a]quinolizine were dissolved in 100 ml of methanol. To this solution there was then added gradually, with stirring, a solution of 90 g of dibenzoyl D-tartaric acid in 100 ml of methanol. Ether was added to the reaction mixture until turbidity, the mixture then permitted to stand for 2 hours in the cold and the filtrate then separated from the precipitated crystals. The filtrate was worked up to the (−) base as described in the next paragraph. Upon crystallization of the precipitate from 300 ml of methanol there were obtained 63 g of a dibenzoyl D-tartrate which melted at 137° — 148°C; $[\alpha]_D^{22} = +49°$ (c = 1 in methanol). In order to obtain the free base, 58 g of this dibenzoyl D-tartrate were partitioned between ether and dilute aqueous sodium hydroxide, after which the ether solution was separated, dried and concentrated. The residue consisted of 30 g of (+) 2 - methoxycarbonylmethyl - 3 - ethyl - 9,10 - dimethoxy - 1,4,6,7 - tetrahydro - 11bH - benzo[a]quinolizine in the form of an oil. A fraction distilled off in a high vacuum of 0.05 mm Hg and at a bath temperature of 230°C exhibited an optical rotation of $[\alpha]_D^{22} = +249°$ (c = 2.2 in methanol).

In order to isolate the (−) antipode the filtrate mentioned earlier was concentrated to dryness and the residue partitioned between dilute aqueous sodium hydroxide and ether, and the ether solution separated and concentrated. The residue obtained was dissolved in 250 ml of acetone and 23 g of finely pulverized tartaric acid added thereto. The mixture was then warmed until complete solution occurred. The solution was then permitted to stand for *ca* 16 hours whereupon an L-tartrate salt crystallized out and was filtered off. This was then recrystallized from methanol/ether

yielding 50 g of an L-tartrate melting at 103°—105°C; $[\alpha]_D^{22} = -150°$ (c = 1 in methanol). In order to isolate the (−) base, 45 g of this L-tartrate were partitioned between sodium hydroxide and ether. The ether solution was then dried and concentrated, yielding 30 g of (−) 2 - methoxycarbonylmethyl - 3 - ethyl - 9,10 - dimethoxy - 1,4,6,7 - tetrahydro - 11bH - benzo[a]quinolizine in the form of an oil. A sample obtained by distillation in a high vacuum at 0.01 mm Hg and at a bath temperature of 230°C exhibited an optical rotation of $[\alpha]_D^{22} = -255°$ (c = 2 in methanol).

30 g of (−) 2 - methoxycarbonylmethyl - 3 - ethyl - 9,10 - dimethoxy - 1,4,6,7-tetrahydro - 11bH - benzo[a]quinolizine were dissolved in 500 ml of 3 - *N* hydrochloric acid, the resulting mixture was boiled at reflux for 1 hour, then concentrated in a water jet vacuum and the residue dissolved in sodium hydroxide. The ether-soluble part was then removed by extraction with ether and the sodium hydroxide phase adjusted to pH 6.5 by the addition of acetic acid. Solid sodium chloride was then added thereto until saturation and the mixture was then extracted with chloroform. The combined chloroform phases were concentrated and the residue was dissolved in ethyl acetate. The ethyl acetate solution was partially concentrated and then permitted to stand until crystallization occurred. There were obtained by this method, 23 g of (−) 2 - carboxymethyl - 3 - ethyl - 9,10 - dimethoxy - 1,4,6,7 - tetrahydro - 11bH - benzo[a]quinolizine melting at 141° — 143°C; $[\alpha]_D^{22} = -244°$ (c = 1 in methanol).

22 g of the compound obtained were then suspended in 200 ml of xylene, 22 g of homoveratryl amine added thereto and the reaction mixture heated at reflux for 16 hours, during which time the water formed was removed from the reaction mixture by azeotropic distillation. The reaction mixture was then concentrated *in vacuo* and the residue treated with ether until crystallization occurred. The resulting mixture was then filtered off and crystallized from ethyl acetate yielding 26 g of the (−) homoveratryl amide of 2 - carboxymethyl - 3 - ethyl - 9,10 - dimethoxy - 1,4,6,7 - tetrahydro - 11bH - benzo[a]quinolizine melting at 155° — 157°C; $[\alpha]_D^{22} = -189°$ (c = 1 in methanol). 25 g of the (−) homoveratryl amide obtained were dissolved in 260 ml of benzene and 12 ml of phosphorus oxychloride added to the solution. The mixture was then warmed for 1 hour at 80°C and subsequently concentrated *in vacuo*. The residue was dissolved in water, the aqueous phase rendered alkaline by the addition of dilute sodium hydroxide and the free base then extracted with ethyl acetate. The ethyl acetate solution was then dried and concentrated and the residue dissolved in acetone. Methanolic hydrochloric acid was then added thereto, and the resulting mixture diluted with ether until turbidity had set in. After allowing to stand, the resulting crystals were filtered off and recrystallized from methanol/ether (90:10), yielding 12 g of (−) 2-dehydro-O-methyl-psychotrine dihydrochloride in the form of a hydrate with 3.5 mol of water of crystallization. The hydrate was in the form of a reddish-brown product which melted at 178° — 180°C; $[\alpha]_D^{22} = -100°$ (c = 1 in water). Ultraviolet absorption maxima at 235, 289, 305 and 359 mμ, ε = 17,700, 8,500, 8,900 and 8,200 (in ethanol).

9 g of the free base obtained from the foregoing dihydrochloride by treatment with ammonia solution and the customary working up, were dissolved in 100 ml of methanol and treated portionwise with 2 g of sodium borohydride. After standing for 12 hours it was dried, the residue partitioned between water and ether and the ether solution separated and concentrated. The basic mixture was then taken up in aqueous hydrobromic acid and permitted to stand, whereupon 4 g of (−) 2 - dehydro-isoemetine crystallized as a dihydrobromide hydrate which melted at 258° — 260°C after recrystallization from methanol; $[\alpha]_D^{22} = -107°$ (c = 1 in methanol). Ultraviolet absorption maxima in ethanol at λ = 282 mμ, ε = 7,300. In order to effect isolation of (−) 2 - dehydro - emetine, the hydrobromic acid filtrate was first concentrated to dryness, the residue dissolved in methanol and the resulting solution then treated with ether until turbidity. After allowing to stand, the solution was filtered, yielding 2 g of (−) 2 - dehydro - emetine dihydrobromide hemihydrate which, after recrystallization from methanol/ether melted at 243° — 245°C; $[\alpha]_D^{22} = -94°$ (c = 1 in methanol). Ultraviolet absorption maxima in ethanol at λ = 282 mμ, ε = 7,300. The (−) 2 - dehydro - emetine was obtained as the free base by decomposition of the hemihydrate with dilute alkali. The free base melted at 93° — 95°C, after recrystallization from *iso*propyl ether/ether, $[\alpha]_D^{22} = -183°$ (c = 1 in methanol).

The same diastereoisomeric mixture was also obtained by the catalytic hydrogenation of (−) 2 - dehydro - O - methyl - psychotrine and was separated by the same procedure as described earlier in this example.

(−) 2 - Dehydro - emetine dihydrochloride can be obtained in a similar manner to that just described for the dihydrobromide. It is obtained in the form of a white powder decomposing at 235°C and with an ultraviolet absorption maximum in ethanol at 232 and 284 mμ (ε = 15,300 and 7,300).

EXAMPLE 2

10 g of (+) 2 - methoxycarbonylmethyl - 3 - ethyl - 9,10 - dimethoxy - 1,4,6,7 - tetrahydro - 11bH - benzo[a]quinolizine (obtained according to the procedure described in Example 1) were dissolved in 500 ml of 10% aqueous acetic acid. 39.6 g of mercuric acetate were added to this solution, the reaction mixture was heated for 20 hours at 40°C, filtered free of the mercurous acetate formed, the filtrate warmed at about 40°C and hydrogen sulphide added over the course of 10 minutes. After the reaction mixture had been cooled, mercurous sulphide was filtered off and the filtrate concentrated to about 120 ml. in a water-jet vacuum at 40°C.

The concentrate was made alkaline by adding aqueous sodium hydroxide thereto, whereafter the mixture was extracted with 200 ml of chloroform. The chloroform extract was concentrated under reduced pressure, whereupon there were obtained 3.1 g of a residue which, after recrystallization, gave 1.72 g of 2 - methoxycarbonylmethylidene - 3 - ethyl - 9,10 - dimethoxy - 6,7 - dihydro - 2H - benzo[a]quinolizine melting at 213° — 214°C; Ultraviolet maxima in .01 - *N* alcoholic sodium hydroxide solution at 243, 293, 318 and 389 mμ (ε = 22,400, 11,470, 16,900 and 27,000). In the infrared spectrum the carbonyl band was found at 6.02 μ.

By reaction with ethanolic hydrogen chloride and addition of ether, 2 - methoxycarbonylmethyl - 3 - ethyl - 9,10 - dimethoxy - 6,7 - dihydrobenzo[a]quinolizinium chloride of melting point 204°C (with decomposition) was obtained; ultraviolet maxima in rectified alcohol at 232 (shoulder), 269 (shoulder), 286 and 365 mμ (ε = 11,900, 9,400, 13,700 and 12,300). The carbonyl band was found in the infrared spectrum at 5.79 μ.

1 g of 2 - methoxycarbonylmethylidene - 3 - ethyl - 9,10 - dimethoxy - 6,7 - dihydro - 2H - benzo[a]quinolizine was suspended in 10 ml of methanol, whereafter 0.5 g of sodium borohydride was added to the suspension in portions with slight cooling so as to prevent the temperature from rising above 25°C. After 3 hours, the reaction mixture was concentrated under reduced pressure to about one third of the original volume, the concentrate diluted with water and extracted with chloroform. The residue left upon concentration of the chloroform extract was converted into the hydrochloride using methanolic hydrogen chloride. Crystallization, which was induced by the addition of acetone and ether, gave 0.65 g of racemic 2 - methoxycarbonylmethyl - 3 - ethyl - 1,4,6,7 - tetrahydro - 9,10 - dimethoxy - 11bH - benzo[a]quinolizine hydrochloride. This compound can be separated into the optical antipodes as described in Example 1. The (−) antipode can be converted into (−) dehydro - emetine according to the procedure described in Example 1.

EXAMPLE 3

2.0 g of (+) 2 - methoxycarbonylmethyl - 3 - ethyl - 1,4,6,7 - tetrahydro - 9,10 - dimethoxy - 11bH - benzo[a]quinolizine were dissolved in 300 ml of methanol. By adding 32.5 g of mercuric acetate there was formed a suspension which was heated under reflux with stirring for 20 hours. The suspension was filtered, hydrogen sulphide was introduced into the filtrate and the mercurous sulphide formed was removed by filtration.

The residue obtained by concentration of the filtrate was converted to the hydrochloride using ~~methanolic~~ methanolic hydrogen chloride. Crystallization was induced by adding ether. There were thus obtained 4.05 g of 2 - methoxycarbonylmethyl - 3 - ethyl - 6,7 - dihydro - 9,10 - dimethoxy - benzo[a]quinolizinium chloride melting at 204°C (with decomposition). An additional 0.5 g of this chloride was obtained from the mother liquors. By reduction of the chloride according to Example 2, racemic 2-methoxycarbonylmethyl - 3 - ethyl - 1,4,6,7 - tetrahydro - 9,10 - dimethoxy - 11bH - benzo[a]quinolizine was obtained and was separated into the optical antipodes as described in Example 1. The (−) antipode can be converted into (−) 2 - dehydro-emetine according to the procedure described in Example 1.

The following Examples illustrate pharmaceutical preparations containing the compounds provided by the invention:

EXAMPLE A

Tablets, each weighing 110 mg, were prepared containing (−) 2 - dehydro - emetine dihydrobromide hemihydrate as the active substance. The composition of said tablets was as follows:

| | |
|---|---|
| active substance | 10 mg |
| lactose | 80 mg |
| corn starch | 2 mg |
| gelatin | 2 mg |
| talc | 16 mg |

EXAMPLE B

A sterile aqueous solution for injection purposes was prepared in the usual manner; said solution containing 10 mg of (−) 2 - dehydro - emetine dihydrobromide and 0.8 mg of methyl *p* - hydroxy - benzoate per ml.

WHAT WE CLAIM IS:—

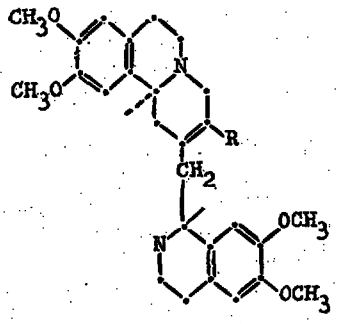
1) A process for the manufacture of (−) 2 - dehydroemetine and its 3 - (lower alkyl) analogues, which process comprises condensing a (−) 2 - (lower alkoxycarbonylmethyl) - 3 - (lower alkyl) - 9,10 - dimethoxy - 1,4,6,7 - tetrahydro - 11bH - benzo[a]quinolizine or the corresponding 2 - carboxymethyl derivative with homoveratryl amine, cyclising the acid amide obtained, reducing the resulting 2 - dehydro - O - methyl - psychotrine or 3 - (lower alkyl) analogue thereof and, if desired, separating the desired (−) - compound from the mixture obtained.

2) A process in accordance with claim 1, wherein (−) 2 - methoxycarbonylmethyl-3 - ethyl - 9,10 - dimethoxy - 1,4,6,7 - tetrahydro - 11bH - benzo[a]quinolizine is used as the starting material.

3) A process in accordance claim 1 or claim 2, which process includes the further and initial step of separating a racemic 2 - (lower alkoxycarbonylmethyl) - 3 - (lower alkyl) - 9,10 - dimethoxy - 1,4,6,7 - tetrahydro - 11bH - benzo[a]quinolizine into the corresponding (−) and (+) forms, isolating the (−) form from the (+) form, using the former as the starting material and oxidising the latter with a mercuric, cupric or ferric salt, reducing the oxidation product and separating the resulting racemic 2 - (lower alkoxycarbonylmethyl) - 3 - (lower alkyl) - 9,10 - dimethoxy - 1,4,6,7 - tetrahydro - 11bH - benzo[a]quinolizine into the corresponding (−) and (+) forms and supplementing said starting material with the (−) component.

4) A process for the manufacture of (−) 2 - dehydro - emetine and its 3 - (lower alkyl) analogues, substantially as described with reference to Examples 1 to 3.

5) (−) Compounds of the formula




wherein R represents a lower-alkyl group, and acid addition salts thereof.

6) (−) 2 - dehydro - emetine and acid addition salts thereof.

7) (−) 2 - dehydro - emetine dihydrobromide.

8) (−) 2 - dehydro - emetine dihydrochloride.

EXAMPLE A

Tablets, each weighing 110 mg, were prepared containing (—) 2 - dehydro - emetine dihydrobromide hemihydrate as the active substance. The composition of said tablets was as follows:

| | |
|---|---|
| active substance | 10 mg |
| lactose | 80 mg |
| corn starch | 2 mg |
| gelatin | 2 mg |
| talc | 16 mg |

EXAMPLE B

A sterile aqueous solution for injection purposes was prepared in the usual manner; said solution containing 10 mg of (—) 2 - dehydro - emetine dihydrobromide and 0.8 mg of methyl *p* - hydroxy - benzoate per ml.

WHAT WE CLAIM IS:—

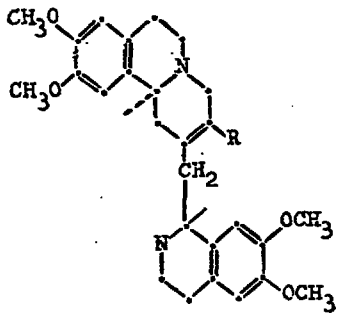
1) A process for the manufacture of (—) 2 - dehydroemetine and its 3 - (lower alkyl) analogues, which process comprises condensing a (—) 2 - (lower alkoxycarbonylmethyl) - 3 - (lower alkyl) - 9,10 - dimethoxy - 1,4,6,7 - tetrahydro - 11bH - benzo[a]quinolizine or the corresponding 2 - carboxymethyl derivative with homoveratryl amine, cyclising the acid amide obtained, reducing the resulting 2 - dehydro - O - methyl - psychotrine or 3 - (lower alkyl) analogue thereof and, if desired, separating the desired (—) - compound from the mixture obtained.

2) A process in accordance with claim 1, wherein (—) 2 - methoxycarbonylmethyl-3 - ethyl - 9,10 - dimethoxy - 1,4,6,7 - tetrahydro - 11bH - benzo[a]quinolizine is used as the starting material.

3) A process in accordance claim 1 or claim 2, which process includes the further and initial step of separating a racemic 2 - (lower alkoxycarbonylmethyl) - 3 - (lower alkyl) - 9,10 - dimethoxy - 1,4,6,7 - tetrahydro - 11bH - benzo[a]quinolizine into the corresponding (—) and (+) forms, isolating the (—) form from the (+) form, using the former as the starting material and oxidising the latter with a mercuric, cupric or ferric salt, reducing the oxidation product and separating the resulting racemic 2 - (lower alkoxycarbonylmethyl) - 3 - (lower alkyl) - 9,10 - dimethoxy - 1,4,6,7 - tetrahydro - 11bH - benzo[a]quinolizine into the corresponding (—) and (+) forms and supplementing said starting material with the (—) component.

4) A process for the manufacture of (—) 2 - dehydro - emetine and its 3 - (lower alkyl) analogues, substantially as described with reference to Examples 1 to 3.

5) (—) Compounds of the formula




wherein R represents a lower-alkyl group, and acid addition salts thereof.

6) (—) 2 - dehydro - emetine and acid addition salts thereof.

7) (—) 2 - dehydro - emetine dihydrobromide.

8) (—) 2 - dehydro - emetine dihydrochloride.

* C L M S *

9) A pharmaceutical composition comprising a (−) - compound as claimed in claim 5, or a pharmaceutically acceptable acid addition salt thereof, in association with a compatible pharmaceutical carrier.

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Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press (Leamington) Ltd.—1966. Published by The Patent Office, 25 Southampton Buildings, London, W.C.2, from which copies may be obtained.

