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COMPLETE SPECIFICATION

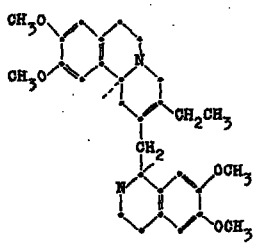
A process for the manufacture of 2-Dehydroemetines

L & Co.

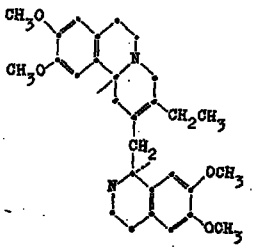
We, F. HOFFMANN-LA ROCHE & AKTIENGESELLSCHAFT, a Swiss Company, of 124—184, Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following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

The present invention is concerned with a process for the manufacture of 2-dehydro-emetines and with novel compounds occurring therein.

The compound known as 2-dehydro-emetine represents an extremely useful chemotherapeutic agent for the treatment of amoebiasis and bilharziasis. When obtained according to known methods it is in the form of a mixture of stereoisomers which contains 2-dehydro-emetines and 2-dehydro-isoemetines. These may be respectively formulated thus:

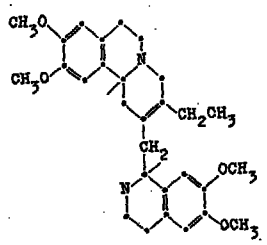


Ia

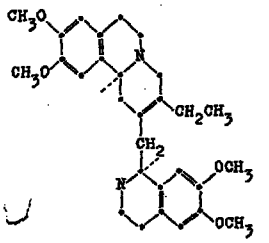


Ib

2-dehydro-emetines



IIa



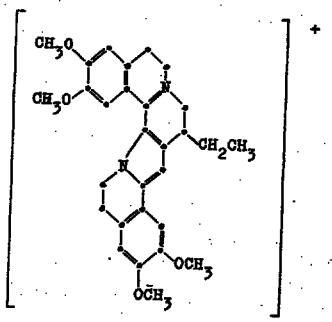
IIb

2-dehydro-isoemetines

It will be appreciated that the formulæ have been drawn as if there were no free rotation of the cyclic portions of the molecules about the bonds joining them to the methylene group linking them, since the relative configurations of the asymmetric centres 1[1] and 11b can then be shown as well as each pair of optical isomers.

These stereoisomers can be readily separated from one another. Chemotherapeutic investigations have shown that only the 2-dehydro-emetines possess the desired activity, whereas the 2-dehydro-isoemetines are inactive. In order to obtain an increased total yield of the active substance, it is therefore desirable to convert the 2-dehydro-isoemetines into 2-dehydro-emetines. The object of the present invention is to provide such a conversion.

It is known that emetine is converted into an oxidation product by treatment with mercuric acetate in acetic acid solution. This product is called rubremetine and has the following formula:



III

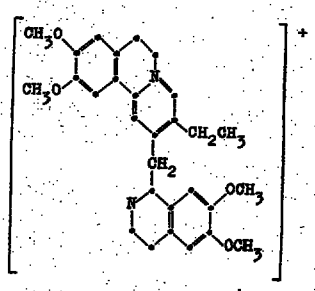
As is evident, this compound possesses a complicated hexacyclic structure and, moreover, cannot be reconverted into emetine by any known method. It was to be expected therefore that the corresponding oxidation in the dehydro-emetine series would lead ~~to~~ a similar oxidation product, no longer subject to reconversion into dehydro-emetine. Surprisingly, this is not the case. Rather, it has been found on the one hand that 2-dehydro-isoemetines yield an oxidation product of formula IV which can easily be reduced to the desired dehydro-emetine substance and, on the other hand, that N-acyl derivatives thereof can also be similarly converted—"acyl" referring especially to the carbonyl moieties of carboxylic acids (for example, alkanoyl radicals such as lower-alkanoyl—particularly acetyl, and aroyl radicals such as benzoyl).

The present invention accordingly provides a process which essentially consists in the conversion of 2-dehydro-isoemetines or their N-acyl derivatives into 2-dehydro-emetines or their N-acyl derivatives by oxidation with a mercuric salt and the subsequent reduction of the resulting oxidation product.

A particularly useful embodiment of the process comprises oxidizing a racemic or optically active 2-dehydro-isoemetine or an N-acyl derivative thereof with a mercuric salt, reducing the oxidation product so obtained, isolating the desired racemic or optically active 2-dehydro-emetine or an N-acyl derivative thereof from the resulting stereoisomeric mixture consisting of a racemic or optically active 2-dehydro-emetine and a racemic or optically active 2-dehydro-isoemetine or N-acyl derivative of either and, if desired, separating any racemates into their enantiomers and, if desired, removing any acyl groups.

As stated earlier, N-acyl derivatives can also be used as starting materials. Such N-substituted compounds can easily be prepared from a 2-dehydro-isoemetine by reaction with a suitable acylating agent. N-(lower alkanoyl) derivatives are obtained, for example, by reacting a 2-dehydro-isoemetine with a lower-alkanoyl halide or anhydride. For example, N-acetyl-2-dehydro-isoemetine can be prepared by reacting 2-dehydro-isoemetine with acetic anhydride. Other suitable acyl moieties are aroyl groups (for example, benzoyl).

The treatment of a 2-dehydro-isoemetine or N-acyl derivative thereof with a mercuric salt destroys the asymmetric centre at the 11b-carbon atom by dehydrogenation, whereupon there is obtained an oxidation product. This oxidation product is a trisdehydro-emetine compound which contains a cation of the following formula:



IV

or an N-acyl derivative thereof in association with an anion derived from a compatible inorganic or organic acid, and acid addition salts thereof.

The anion of the trisdehydro-emetine compound of formula IV is the anionic moiety of an organic or inorganic acid. Such anions are, for example, the anions of inorganic acids (such as the hydrohalic acids and perchloric acid) or of organic acids (such as acetic acid and oxalic acid). The chloride anion is especially preferred. In order to be compatible with the cation, the anion should be that of an acid which does not degrade the cationic structure.

The anion of the mercuric salt used can be either inorganic or organic. Moreover, it can be the anion of a strong or weak acid. Preferably, the mercuric salt used should be one which is soluble in the reaction medium.

A mercuric salt which is especially useful as the oxidizing agent is mercuric acetate. Mercuric salts of other acids such as, for example, mercuric nitrate, as well as the complexes of mercuric salts with ethylenediamine tetraacetic acid are also suitable. The use of mercuric acetate in dilute acid (for example, aqueous acetic acid) is especially advantageous. The oxidation proceeds best at elevated temperatures, preferably at between about 30° C and 60° C, but can be carried out at room temperature if desired. The

mercurous acetate, for example, which precipitates after the oxidation can be separated and easily regenerated to form mercuric acetate. It is suitable to remove the mercury salt residues present in the solution before carrying out the reduction. The removal can suitably be effected by introducing hydrogen sulphide into the acid solution.

The oxidation product of the 2-dehydro-isoemetine or N-acyl derivative thereof, is advantageously isolated as salts of strong organic or inorganic acids after the oxidation. As such, there can be used common strong inorganic acids (such as for example, hydrochloric acid, hydrobromic acid, and perchloric acid) or common strong organic acids (such as oxalic acid). Hydrochloric acid is especially preferred. Some acids degrade the cationic trisdehydro-emetine structure and, obviously, the acid used should not be one of these; for example, it should not be one of the hypohalous acids.

The trisdehydro-emetine cation of formula IV as well as N-acyl derivatives thereof have been found to decompose upon warming in acid or alkali solution. It is therefore important to exercise close control during the working up of the oxidation product to make sure that the trisdehydro-emetine is not heated for an unnecessary length of time. Suitably, temperatures over 60° C should be avoided.

In the second step of the process of the invention, the oxidation products are subjected to reduction. Suitable reducing agents are, for example alkaline-earth-metal hydrides such as, for example, calcium hydride, alkali-metal metal hydrides such as alkali-metal borohydrides or alkali-metal aluminium hydrides, especially sodium borohydride—preferably in aqueous methanol. The alkali-metal metal hydrides are conveniently used in a suitable solvent. The choice of a suitable solvent depends on the solubility of the reducing agent, of the substance being reduced and of the reduction product. Suitable solvents are, for example, water or organic solvents such as dioxan, tetrahydro-furan, N,N-dimethyl-formamide and lower-alkanols (e.g., methanol or ethanol). It is often advantageous to use an organic solvent in an aqueous medium. Carrying out the reduction in aqueous methanol is especially suitable. The reduction can also be effected in a hydrogen atmosphere in the presence of a hydrogenation catalyst (e.g., platinum oxide, platinum, palladium or RANEY-nickel) suitably in an alcoholic solution and at a low temperature. As a rule, any N-substituent must be removed by subsequent hydrolysis if it is desired that the nitrogen atom of the *iso*quinoline ring be unsubstituted in the end product.

The bases obtained after the reduction of the trisdehydro-emetine of formula IV or an N-acyl derivative thereof are in the form of isomeric mixtures of a 2-dehydro-emetine and a 2-dehydro-isoemetine or of their N-acyl derivatives as the case may be. These can be separated according to known methods, for example, by fractional crystallization, advantageously by way of their salts (the oxalates are especially suitable for this purpose), into a 2-dehydro-emetine and a 2-dehydro-isoemetine or an N-acyl derivative of either. The 2-dehydro-isoemetine obtained can then be converted into a 2-dehydro-emetine by being again submitted to the process of this invention.

After carrying out the oxidation and reduction, any N-substituent is suitably removed; for example, by acid hydrolysis. Thus, an N-acetyl-2-dehydro-emetine can be converted into a 2-dehydro-emetine; for example, by boiling in dilute hydrochloric acid. In the case where the process proceeds through an N-benzoyl derivative, the benzoyl moiety can be converted into a benzyl moiety during the reduction step. This occurs, for example, when the reduction is carried out with a reducing agent such as lithium aluminium hydride. The benzyl moiety can be subsequently removed by hydrogenolysis in the presence of a selective hydrogenation catalyst (for example, palladium/carbon in acetic acid solution).

According to a variant process provided by the invention, a 2-dehydro-isoemetine is used as the starting material and is subjected to acylation between the oxidation and reduction steps.

It will be appreciated that racemic as well as optically active starting materials can be employed. When a racemic starting material is employed the racemate obtained after the oxidation and reduction can, if desired, be separated into its enantiomers.

The following Examples illustrate the invention.

EXAMPLE 1.

80 g of racemic 2-dehydro-isoemetine were dissolved in 3.2 litres of 10% aqueous acetic acid, mixed with 250 g of mercuric acetate and the resulting mixture was maintained at 40° C for 15 hours. The resultant mercurous acetate was filtered off, the excess mercuric salt removed as the sulphide, and the filtered solution concentrated at 40° C (bath temperature) *in vacuo*. The residual product was converted to its hydrochloride with methanolic hydrochloric acid and this was crystallized at *ca* 20° C from methanol/ether. 80 g of trisdehydro-emetine chloride hydrochloride of melting point 176°—178° C were thus obtained. Treatment of the methanolic solution of the hydrochloride with 60% aqueous perchloric acid yielded trisdehydro-emetine diperchlorate melting at 162°—163° C; ultraviolet maxima of the hydrochloride in alcohol at 232 mμ (shoulder), 285 mμ and 365 mμ, ϵ=23,200, 18,300 and 15,800.

A solution of 4.4 g of sodium borohydride in 25 ml of water was added, in the course

of 0.25 hours with cooling to 20°—25° C, to a solution of 15 g of trisdehydro-emetine chloride hydrochloride in 150 ml of methanol. The resulting mixture was stirred for 2 hours, the methanol removed *in vacuo*, the residue extracted with chloroform and the chloroform solution concentrated to dryness.

The residue obtained from the concentration procedure was dissolved in 50 ml of methanol and 4.9 g of anhydrous oxalic acid added thereto. On standing for *ca* 16 hours at 5° C, 7.75 g of racemic 2-dehydro-isoemetine in the form of its acid oxalate melting at 176°—178° C crystallized out. This substance was in all ways identical with an authentic specimen. It can be again subjected to the oxidation and reduction steps described earlier. After the removal by filtration of the crude oxalate of racemic 2-dehydro-isoemetine, the filtrate was concentrated *in vacuo*. The residue was then partitioned between aqueous sodium hydroxide and chloroform. The chloroform solution was concentrated and the residue consisted of 7.6 g of crude 2-dehydro-emetine base. This was dissolved in 50 ml of 80% methanol and 8—*N* methanolic hydrochloric acid was added thereto in slight excess. ~~Either~~ was added to the resulting solution until turbidity occurred and the dispersion was then permitted to stand for *ca* 16 hours at 5° C. As a result there were obtained 5.6 g of 2-dehydro-emetine dihydrochloride in the form of a hydrate melting at 245°—247° C (decomposition) which, in all respects, was identical with an authentic sample. The filtrate contained a mixture of the hydrochloride of 2-dehydro-isoemetine and 2-dehydro-emetine. By repeating the separation described earlier there were obtained a further 2.05 g of 2-dehydro-isoemetine oxalate and 0.4 g of 2-dehydro-emetine dihydrochloride.

EXAMPLE 2.

2.6 g of racemic N-acetyl-2-dehydro-isometine (melting at 153°—154° C) were dissolved in 150 ml of 10% aqueous acetic acid. To this solution were added 6.4 g. of mercuric acetate and the mixture was stirred for 12 hours at 40° C in a nitrogen atmosphere. After working up the reaction mixture according to the method described in example 1, there was obtained N-acetyl-trisdehydro-emetine perchlorate which, upon recrystallization from methanol/ether, melted at 233°—234° C and exhibited ultraviolet-maxima at 232 mμ (shoulder), 268 mμ (shoulder), 282 mμ and 367 mμ. [N-acetyl-trisdehydro-emetine perchlorate can also be prepared by the following method: 3 g of trisdehydro-emetine chloride hydrochloride in 20 ml of pyridine and 12 ml of acetic anhydride was permitted to stand for 20 hours at *ca* 20° C. The reaction mixture was then concentrated *in vacuo* and the residue dissolved in dilute hydrochloric acid. This was then extracted with chloroform. The residue obtained on concentration of the chloroform solution consisted of crude N-acetyl-trisdehydro-emetine chloride. This crude product was dissolved in methanol and converted into its perchlorate by the addition of perchloric acid. There were thus obtained 2.85 g of N-acetyl-trisdehydro-emetine perchlorate which was identical with the product obtained by the procedure already described].

A solution of 0.5 g of racemic N-acetyl-trisdehydro-emetine perchlorate in 5 ml of N,N-dimethyl-formamide was added in the course of 20 minutes to a solution of 0.5 g of sodium borohydride in 2.5 ml of water. Towards the end of the reaction, an additional 0.2 g of sodium borohydride was added. The reaction mixture was stirred for a further 1.5 hours, then treated with dilute sodium hydroxide and extracted with chloroform. The residue from the chloroform extract was fractionally crystallized from methanol. There was thus obtained 0.15 g of racemic N-acetyl-2-dehydro-emetine melting at 188° C and then 0.1 g of racemic N-acetyl-2-dehydro-isoemetine melting at 150° C. Both of these compounds were identical with authentic samples.

Racemic 2-dehydro-emetine was obtained from racemic N-acetyl-2-dehydro-emetine by hydrolysis; for example, by treating the N-acetyl compound for 4 hours at reflux with 20% aqueous hydrochloric acid. By the conventional working up procedure and crystallization via the oxalate there was obtained racemic 2-dehydro-emetine. The hydrolysis of the N-acetyl group was also effected prior to the separation of the mixture containing racemic N-acetyl-2-dehydro-emetine and racemic N-acetyl-2-dehydro-isoemetine.

EXAMPLE 3.

1. *The oxidation step.*

a) 3.64 g of disodium ethylenediamine-N,N,N¹,N¹-tetraacetic acid and 3.08 g of mercuric acetate were added to a solution of 2.39 g of 2-dehydro-isoemetine in 50 ml of 10% acetic acid. The resulting mixture was then warmed for 2.5 hours at 40° C and then concentrated *in vacuo* at a water-bath temperature of 40° C. The residue was then taken up in ethanol and treated with alcoholic hydrochloric acid. The insoluble mercury salts were removed by filtration and the filtrate was treated with ether, whereupon 1.25 g of trisdehydro-emetine chloride hydrochloride crystallized out.

b) 8.57 g of mercuric nitrate were added to a solution of 2.39 g of 2-dehydro-isoemetine in 100 ml of water and 1.05 ml of 65% nitric acid. The resulting mixture was warmed for 20 hours at 40° C and yielded trisdehydro-emetine nitrate.

c) 0.5 g of (−) 2-dehydro-isoemetine dihydrobromide was dissolved in water. The solution was made alkaline with sodium

hydroxide and then extracted with chloroform. The chloroform was evaporated and the resulting (−) 2-dehydro-isoemetine was dissolved in 25 ml of 10% acetic acid and heated with 1.6 g of mercuric acetate for 15 hours at 40° C. After working up in the method described in example 1, the reaction product was dissolved in 15 ml of methanol and treated with 60% perchloric acid. 0.45 g of (+)-trisdehydro-emetine diperchlorate crystallized out and, upon recrystallization from acetone/ether, melted at 170°—171° C; $[\alpha]_D^{25}$= +48° (0.1% in methanol).

2. *The reduction step.*

This can be carried out after the manner shown in example 1 or example 2.

WHAT WE CLAIM IS:—

1) A process for the conversion of 2-dehydro-isoemetines or their N-acyl derivatives into 2-dehydro-emetines or their N-acyl derivatives which comprises oxidizing them with a mercuric salt and subsequently reducing the oxidation product.

2) A process in accordance with claim 1 insofar as it comprises oxidizing a racemic or optically active 2-dehydro-isoemetine or an N-acyl derivative thereof with a mercuric salt and reducing the oxidation product so obtained, which process includes the step or steps of isolating the desired racemic or optically active 2-dehydro-emetine or an N-acyl derivative thereof from the resulting stereoisomeric mixture consisting of a racemic or optically active 2-dehydro-emetine and a racemic or optically active 2-dehydro-isoemetine or N-acyl derivative of either and, if desired, separating any racemates into their enantiomers and, if desired, removing any acyl groups.

3) A variation of the process set forth in claim 1 or claim 2 insofar as a 2-dehydro-isoemetine is used as the starting material, which variation comprises the inclusion of the further step of acylation between the oxidation and reduction steps.

4) A process in accordance with claim 1, claim 2 or claim 3, wherein the mercuric salt used is mercuric acetate.

5) A process in accordance with any one of claims 1 to 4 inclusive wherein the reduction is effected using an alkaline-earth-metal hydride or an alkali-metal metal hydride.

6) A process in accordance with claim 5, wherein the reduction is effected using sodium borohydride.

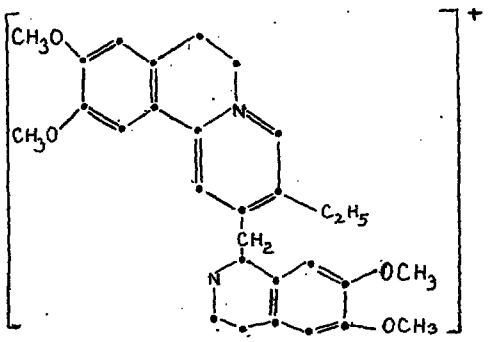
7) A process in accordance with any one of the preceding claims insofar as an acyl derivative or an acylation step is used, wherein said derivative is an acetyl derivative and said step is an acetylation.

8) A process in accordance with any one of claims 1 to 7 inclusive, wherein the 2-dehydro-isoemetine or N-acetyl-2-dehydro-isoemetine is oxidized with mercuric acetate in dilute aqueous acetic acid solution and the resulting trisdehydro-emetine or N-acetyl-trisdehydro-emetine subsequently reduced.

9) A process in accordance with claim 8, wherein the reduction is effected by using sodium borohydride in aqueous methanol.

10) A process for the manufacture of 2-dehydro-emetines substantially as described with reference to the Examples.

11) A compound containing a cation of the formula



or an N-acyl derivative thereof in association with an anion derived from an inorganic or organic acid (other than an acid having a degradative effect on said cation), and acid addition salts of same.

12) Trisdehydro-emetine chloride hydrochloride.

13) Trisdehydro-emetine diperchlorate.

14) N-acetyl-trisdehydro-emetine perchlorate.

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hydroxide and then extracted with chloroform. The chloroform was evaporated and the resulting (−) 2-dehydro-isoemetine was dissolved in 25 ml of 10% acetic acid and heated with 1.6 g of mercuric acetate for 15 hours at 40° C. After working up in the method described in example 1, the reaction product was dissolved in 15 ml of methanol and treated with 60% perchloric acid. 0.45 g of (+) trisdehydro-emetine diperchlorate crystallized out and, upon recrystallization from acetone/ether, melted at 170°—171° C; $[\alpha]_D^{25}$= +48° (0.1% in methanol).

2. *The reduction step.*

This can be carried out after the manner shown in example 1 or example 2.

WHAT WE CLAIM IS:—

1) A process for the conversion of 2-dehydro-isoemetines or their N-acyl derivatives into 2-dehydro-emetines or their N-acyl derivatives which comprises oxidizing them with a mercuric salt and subsequently reducing the oxidation product.

2) A process in accordance with claim 1 insofar as it comprises oxidizing a racemic or optically active 2-dehydro-isoemetine or an N-acyl derivative thereof with a mercuric salt and reducing the oxidation product so obtained, which process includes the step or steps of isolating the desired racemic or optically active 2-dehydro-emetine or an N-acyl derivative thereof from the resulting stereoisomeric mixture consisting of a racemic or optically active 2-dehydro-emetine and a racemic or optically active 2-dehydro-isoemetine or N-acyl derivative of either and, if desired, separating any racemates into their enantiomers and, if desired, removing any acyl groups.

3) A variation of the process set forth in claim 1 or claim 2 insofar as a 2-dehydro-isoemetine is used as the starting material, which variation comprises the inclusion of the further step of acylation between the oxidation and reduction steps.

4) A process in accordance with claim 1, claim 2 or claim 3, wherein the mercuric salt used is mercuric acetate.

5) A process in accordance with any one of claims 1 to 4 inclusive wherein the reduction is effected using an alkaline-earth-metal hydride or an alkali-metal metal hydride.

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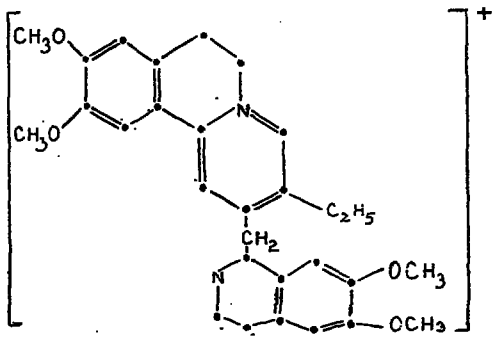
7) A process in accordance with any one of the preceding claims insofar as an acyl derivative or an acylation step is used, wherein said derivative is an acetyl derivative and said step is an acetylation.

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9) A process in accordance with claim 8, wherein the reduction is effected by using sodium borohydride in aqueous methanol.

10) A process for the manufacture of 2-dehydro-emetines substantially as described with reference to the Examples.

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13) Trisdehydro-emetine diperchlorate.

14) N-acetyl-trisdehydro-emetine perchlorate.

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* C L M S *