RESERVE COPY.

PATENT SPECIFICATION

NO DRAWINGS

937,214

Inventor: KENNETH WALTER BENTLEY

Date of filing Complete Specification: March 26, 1962.

Application Date: June 2, 1961. No. 20029/61.

Complete Specification Published: Sept. 18, 1963.

© Crown Copyright 1963.

Index at acceptance:—Class 2(3), C3A7V1(A4:E2:G2:J1:P), C3A13C(1C:9:10F:10H).

International Classification:—C07d.

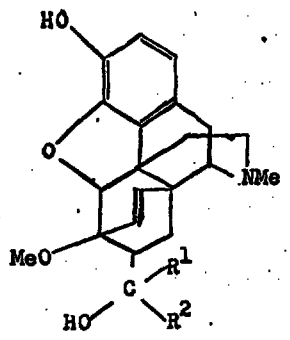
COMPLETE SPECIFICATION

Oripavine Derivatives

We, J. F. MACFARLAN & COMPANY LIMITED, a British Company, of 17, Throgmorton Avenue, London, E.C.2, 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:—

This invention relates to novel derivatives of oripavine and to a process for their preparation.

The present invention provides compounds of the general formula



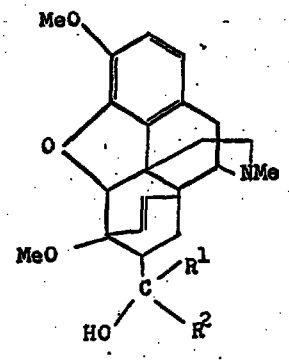
in which formula R^1 represents a hydrogen atom, an alkyl group containing from 1 to 3 carbon atoms or an aryl group, and R^2 represents a hydrogen atom, an alkyl, or alkenyl group containing up to 8 carbon atoms, which group may be substituted on carbon atoms 1 to 5 by an alicyclic or aryl group, or an alicyclic group containing 5, 6 or 7 carbon atoms which may be unsubstituted or substituted by an alkyl group containing 1 to 3 carbon atoms, provided that R^2 does not contain the system —CH—aryl or —CH—C=C attached to the carbon atom bearing the alcoholic hydroxyl group.

The invention also provides the 3-acyl esters of the above phenols, in which the phenolic hydroxyl group is esterified with fatty acids $C_nH_{2n+1}COOH$ in which n is 1, 2 or 3, benzoic acid or nicotinic acid.

The invention also relates to the salts of the above bases with pharmaceutically acceptable acids.

The compounds of the invention are therapeutically useful on account of their power to affect the central nervous system, particularly on account of their depressant, analgesic, sedative, antitussive and/or other morphine-like effects.

The present invention also includes a process for the preparation of the novel compounds of the invention wherein a compound of the general formula



in which R^1 and R^2 have the meanings given above (B.P. Application No. 30566/60 Serial No. 925,723), is demethylated by heating with an alkali metal hydroxide in a suitable solvent, such as diethylene glycol, at a temperature preferably slightly above 200° C. (Specification No. 925,723 does not disclose com-

[*Price 4s. 6d.*]

pounds in which R^2 is H. It will be readily appreciated that the systems

—C(OH—CH—aryl

and

—C(OH)—CH—C=C

do not, owing to the ease with which they suffer base-catalysed dehydration, survive such vigorous alkaline conditions.

The esters of the phenols are readily prepared by the usual methods, such as heating with an acid anhydride, or treatment in alkaline solution with acid anhydrides or chlorides.

The invention is further illustrated by the following Examples, in which parts are parts by weight.

EXAMPLE 1.

6,14-*endo*Etheno-7-α(1-hydroxy-1-ethyl)-tetrahydro-oripavine.

6,14 - *endo*Etheno - 7 - α(1 - hydroxy - 1-ethyl)tetrahydrothebaine (8 parts) was added to a solution of potassium hydroxide (60 parts) in diethylene glycol (150 parts) boiling under reflux at a temperature of from 200 to 210° C. The mixture was boiled under reflux with vigorous stirring until a test portion diluted with 10 times its volume of water gave a homogeneous solution. The whole mixture was then diluted with 5 times its volume of water and saturated ammonium chloride was added until precipitation ceased. The precipitated solid was collected, washed well with water and recrystallised from 2-ethoxyethanol, when the base was obtained as white prisms m.p. 298° C. Found: C, 71.2; H, 7.5. $C_{22}H_{27}O_4N$ requires: C, 71.4, H, 7.3%. The hydrochloride, white prisms m.p. 272° C., was obtained from the base and ethanolic hydrogen chloride by the addition of diethyl ether. Found: C, 63.6; H, 7.0. $C_{22}H_{27}O_4N.HCl.\frac{1}{2}H_2O$ requires C, 63.9; H, 6.8%.

The acetyl ester, prepared by refluxing a mixture of the base and acetic anhydride had m.p. 147° C.

EXAMPLE 2.

6.14-*endo*Etheno-7-(2-hydroxy-2-propyl)-tetrahydro-oripavine.

This was prepared essentially as in Example 1 from 6,14-*endo*etheno-7-(2-hydroxy-2-propyl)tetrahydrothebaine. The precipitated base was extracted with ether, the dried extract evaporated and the solid residue recrystallised from aqueous 2-ethoxyethanol, when the base was obtained as white prisms m.p. 266° C. Found: C, 72.4; H, 7.5; N, 3.2. $C_{23}H_{29}O_4N$ requires C, 72.1; H, 7.6; N, 3.6%. The hydrochloride had m.p. 288 to 290° C. with decomposition.

The 3-acetyl ester was precipitated on the addition of acetic anhydride to a solution of the base in aqueous sodium hydroxide. The solid was collected, washed and recrystallised from methanol, when it was obtained as colourless prisms m.p. 191° C. Found: C, 70.6; H, 7.2. $C_{25}H_{31}O_5N$ requires C, 70.5; H, 7.4%. The hydrochloride had m.p. 266° C.

EXAMPLE 3.

6,14-*endo*Etheno-7-α(2-hydroxy-2-butyl)-tetrahydro-oripavine.

This was prepared as in Example 1 from 6,14 - *endo*etheno - 7 - α(2 - hydroxy - 2-butyl)tetrahydrothebaine and the free base was obtained as white prisms m.p. 268° C. from 2-ethoxyethanol. Found: C, 72.5; H, 8.1; $C_{24}H_{31}O_4N$ requires C, 72.6; H, 7.8%. The hydrochloride formed white prisms m.p. 282° C. Found: C, 62.5; H, 7.6;

$C_{24}H_{31}O_4N.HCl.1\frac{1}{2}H_2O$

requires C, 62.6; H, 7.8%.

The 3-acetyl ester, prepared by heating the base under reflux with acetic anhydride, had m.p. 156° C. on recrystallisation from methanol.

EXAMPLE 4.

6,14-*endo*Etheno-7-α(2-hydroxy-2-pentyl)-tetrahydro-oripavine.

This was prepared as in Example 1 from 6,14 - *endo*etheno - 7 - α(2 - hydroxy - 2-pentyl)tetrahydrothebaine, and the free base was obtained as white prisms m.p. 215° C. from aqueous 2-ethoxyethanol. Found C, 70.0; H, 7.9. $C_{25}H_{33}O_4N.H_2O$ requires C, 70.0; H, 8.1%. The hydrochloride formed white prisms m.p. 266—267° C.

The 3-acetyl ester, prepared by the Schotten-Baumen process, was obtained as colourless prisms m.p. 195° C. from methanol. Found C, 71.3; H, 7.7; $C_{27}H_{35}O_5N$ requires C, 71.5; H, 7.7%. The hydrochloride formed white prisms m.p. 206° C.

The 3-propionyl ester, prepared by heating the base under reflux with propionic anhydride, had m.p. 130° C. on recrystallisation from aqueous ethanol.

EXAMPLE 5.

6,14-*endo*Etheno-7-β(2-hydroxy-2-pentyl)-tetrahydro-oripavine.

This was prepared as in Example 1 from 6,14 - *endo*etheno - 7 - β(2 - hydroxy - 2-pentyl)tetrahydrothebaine, and the free base was obtained as off-white prisms m.p. 280° C. on recrystallisation from 2-ethoxyethanol. Found, C, 71.2; H, 7.8; $C_{25}H_{33}O_4N.\frac{1}{2}H_2O$ requires C, 71.4; H, 8.1%. The hydrochloride formed white prisms m.p. 290° C. (dec.) Found: C, 64.8; H, 7.4; $C_{25}H_{33}O_4N.HCl.H_2O$ requires C, 64.5; H, 7.7%.

EXAMPLE 6.

6,14-*endo*Etheno-7-(3-hydroxy-3-pentyl)-tetrahydro-oripavine.

This was prepared as in Example 1 from 6,14 - *endo*etheno - 7 - (3 - hydroxy - 3-pentyl)tetrahydrothebaine and the base was obtained as white prisms m.p. 157° C. on recrystallisation from aqueous 2-ethoxyethanol. Found: C, 71.5; H, 8.1;

$C_{25}H_{33}O_4N.\frac{1}{2}H_2O$

requires C, 71.4; H, 8.1%. The hydrochloride formed white prisms m.p. >290° C. Found:

C, 66.6; H, 7.6; $C_{25}H_{33}O_4N.HCl$ requires C, 66.9; H, 7.6%.

The 3-acetyl ester, prepared by refluxing the base with acetic anhydride was obtained as prisms m.p. 179° C.

EXAMPLE 7.

6,14-*endo*Etheno-7-α(2-hydroxy-2-hexyl)-tetrahydro-oripavine.

Prepared as in Example 1 from 6,14-*endo*-etheno - 7 - α(2 - hydroxy - 2 - hexyl)tetrahydrothebaine, this base was obtained as white prisms m.p. 174° C. from aqueous 2-ethoxyethanol. Found: C, 70.6; H, 8.5. $C_{31}H_{35}O_4N.H_2O$ requires C, 70.4; H, 7.3%. The hydrochloride formed white prisms m.p. 272° C. Found: C, 67.2; H, 8.0. $C_{26}H_{35}O_4N.HCl$ requires C, 67.5; H, 7.8%.

EXAMPLE 8.

6,14-*endo*Etheno-7-α(2-hydroxy-4-methyl-2-pentyl)tetrahydro-oripavine.

Prepared as in Example 1 from 6,14-*endo*-etheno - 7 - α(2 - hydroxy - 4 - methyl - 2-pentyl)tetrahydrothebaine, this base was obtained as off-white prisms m.p. 217° C. on recrystallisation from aqueous 2-ethoxyethanol. Found: C, 70.7; H, 8.4; $C_{26}H_{35}O_4N.H_2O$ requires C, 70.4; H, 8.3%. The hydrochloride formed prisms m.p. 292° C.

The 3-acetyl ester, from the base and acetic anhydride formed white prisms m.p. 151° C. from aqueous ethanol.

EXAMPLE 9.

6,14-*endo*Etheno-7-α(2-hydroxy-2-heptyl)-tetrahydro-oripavine.

Prepared from 6,14-*endo*etheno-7-α(2-hydroxy-2-heptyl)tetrahydro-thebaine as in Example 1 this base was obtained as off-white prisms m.p. 106° C. from aqueous 2-ethoxyethanol. Found: C, 72.6; H, 8.6.

$C_{27}H_{37}O_4N.\frac{1}{2}H_2O$

requires C, 72.3; H, 8.5%. The hydrochloride formed white prisms m.p. 278° C. Found: C, 66.7; H, 8.0. $C_{27}H_{37}O_4N.HCl.\frac{1}{2}H_2O$ requires C, 66.6; H, 8.0%.

EXAMPLE 10.

6,14-*endo*Etheno-7-α(2-hydroxy-5-methyl-2-hexyl)tetrahydro-oripavine.

Prepared from 6,14 - *endo*etheno - 7 - α(2-hydroxy - 5 - methyl - 2 - hexyl)tetrahydro-thebaine as in Example 1 this base was obtained as white prisms m.p. 131° C. from aqueous 2-ethoxyethanol. Found: C, 73.4; H, 8.1; $C_{27}H_{37}O_4N$ requires C, 73.6; H, 8.2%. In this preparation boiling for several hours was necessary for complete demethylation and precipitation of the base was accompanied by the precipitation of a considerable amount of silica (from attack of the glassware by the alkali); the base was freed from this material by filtration of a hot 2-ethoxyethanol suspension.

The hydrochloride had m.p. 258° C. Found: C, 68.0; H, 8.3; $C_{27}H_{37}O_4N.HCl$ requires C, 68.1; H, 8.0%.

The 3-acetyl ester, obtained by the Schotten Baumen process and by heating the base with acetic anhydride, was obtained as white prisms m.p. 126° C. Found: C, 71.9; H, 8.1; $C_{29}H_{39}O_5N$ requires C, 72.3; H, 8.2%.

EXAMPLE 11.

6,14-*endo*Etheno-7-α(2-hydroxy-2-octyl)-tetrahydro-oripavine.

This base was prepared from 6,14-*endo*-etheno - 7 - α(2 - hydroxy - 2 - octyl)tetrahydrothebaine as in Example 1, being obtained as white prisms m.p. 288° C. on recrystallisation from aqueous 2-ethoxyethanol. Found: C, 74.6; H, 8.6; $C_{28}H_{39}O_4N$ requires C, 74.1; H, 8.6%.

EXAMPLE 12.

6,14-*endo*Etheno-7-α(2-hydroxy-2-decyl)-tetrahydro-oripavine.

This base, prepared as in Example 1 from 6,14 - *endo*etheno - 7 - α(2 - hydroxy - 2-decyl)tetrahydrothebaine was obtained as off-white crystals m.p. 275° C. from aqueous 2-ethoxyethanol. Found: C, 74.5; H, 9.5. $C_{30}H_{43}O_4N$ requires C, 74.7; H, 9.4%.

EXAMPLE 13.

6,14-*endo*Etheno-7-α(2-hydroxy-3-methyl-2-butyl)tetrahydro-oripavine.

This base was prepared from 6,14-*endo*-etheno - 7 - α(2 - hydroxy - 3 - methyl - 2-butyl)tetrahydrothebaine as in Example 1, and was obtained as white prisms m.p. 278° C. on recrystallisation from aqueous 2-ethoxyethanol. The hydrochloride was obtained as a white powder m.p. 296° C. Found: C, 64.4; H, 7.5; $C_{25}H_{33}O_4N.HCl$ requires C, 64.5; H, 7.7%.

EXAMPLE 14.

6,14-*endo*Etheno-7-α(1-hydroxy-1-phenyl-1-ethyl)tetrahydro-oripavine.

This base, prepared as in Example 1 from 6,14 - *endo*etheno - 7 - α(1 - hydroxy - 1-phenyl - 1 - ethyl)tetrahydrothebaine was obtained as white prisms m.p. 252° C. from aqueous 2-ethoxyethanol. Found: C, 72.9; H, 7.6; $C_{28}H_{31}O_4N.H_2O$ requires C, 72.7; H, 7.2%. The hydrochloride was obtained as white prisms m.p. 286° C.

EXAMPLE 15.

6,14-*endo*Etheno-7-α(1-hydroxybenzyl)-tetrahydro-oripavine.

This was prepared from 6,14-*endo*Etheno-7-α(1-hydroxybenzyl)tetrahydrothebaine as in Example 1 and was obtained as white prisms m.p. 160° C. Found: C, 72.6; H, 6.7; $C_{27}H_{29}O_4N.H_2O$ requires C, 72.8; H, 6.7%. The hydrochloride had m.p. 300° C.

EXAMPLE 16.

6,14-*endo*Etheno-7-α(1-hydroxy-3-phenyl-1-propyl)tetrahydro-oripavine.

This base, prepared from 6,14-*endo*etheno-7 - α(1 - hydroxy - 3 - phenyl - 1 - propyl)-tetrahydrothebaine was obtained as white prisms m.p. 120° C. on recrystallisation from aqueous 2-ethoxyethanol. Found: C, 75.8; H, 7.3 $C_{29}H_{33}O_4N$ requires C, 75.7; H, 7.2%.

The hydrochloride formed white prisms m.p. 290° C. Found: C, 69.9; H, 7.1; $C_{29}H_{33}O_4N.HCl$ requires C, 70.2; H, 6.9.

EXAMPLE 17.

6,14-*endo*Etheno-7-α(3-hydroxyl-phenyl-3-butyl)tetrahydro-oripavine.

This base was prepared from 6,14-*endo*etheno - 7 - α(3 - hydroxy - 1 - phenyl - 3-butyl)tetrahydrothebaine as in Example 1 and on recrystallisation from aqueous 2-ethoxyethanol was obtained as white prisms m.p. 226° C. Found: C, 75.7; H, 7.6 $C_{30}H_{35}O_4N$ requires C, 76.1; H, 7.5%. The hydrochloride formed white prisms m.p. 255° C. Found: C, 70.6; H, 7.1; $C_{30}H_{35}O_4N.HCl$. requires C, 70.5; H, 7.1%.

EXAMPLE 18.

6,14-*endo*Etheno-7-α(1-hydroxy-1-cyclopentyl-1-ethyl)tetrahydro-oripavine.

This base was prepared from 6,14-*endo*etheno - 7 - α(1 - hydroxy - 1 - cyclopentyl-1-ethyl)tetrahydrothebaine as in Example 1 and on recrystallisation from aqueous 2-ethoxyethanol was obtained as white prisms m.p. 300—302° C. Found: C, 74.0; H, 7.9; $C_{27}H_{35}O_4N$ requires C, 74.1; H, 8.1%. The hydrochloride formed white prisms m.p. 294—296° C. Found: C, 64.6; H, 7.9; $C_{27}H_{35}O_4N.HCl.1\frac{1}{2}H_2O$ requires C, 64.7; H, 7.9%.

EXAMPLE 19.

6,14-*endo*Etheno-7-α(1-hydroxy-1-cyclohexyl-1-ethyl)tetrahydro-oripavine.

This base was prepared from 6,14-*endo*etheno - 7 - α(1 - hydroxy - 1 - cyclohexyl-1-ethyl)tetrahydrothebaine by the general method of Example 1 and was obtained as white prisms m.p. 232° C. on recrystallisation from methanol. Found: C, 69.2; H, 8.4; $C_{28}H_{37}O_4N.2H_2O$ requires C, 69.0; H, 8.4%. The hydrochloride formed white prisms m.p. 248° C. Found: C, 66.1; H, 7.8; $C_{28}H_{37}O_4N.HCl.H_2O$ requires C, 66.4; H, 7.9%.

The 3-acetyl ester, prepared from the base and acetic anhydride was obtained as white prisms m.p. 193° C. Found: C, 70.8; H, 8.2; $C_{30}H_{39}O_5N.H_2O$ requires C, 70.5; H, 8.1%. Hydrochloride m.p. 262° C. Found: C, 67.6; H, 7.6; $C_{30}H_{39}O_5N.HCl$ requires C, 67.9; H, 7.6%.

EXAMPLE 20.

6,14-*endo*Etheno-7-β(1-hydroxy-1-cyclohexyl-1-ethyl)tetrahydro-oripavine.

This base prepared from 6,14-*endo*etheno-7 - β(1 - hydroxy - 1 - cyclohexyl - 1-ethyl)tetrahydrothebaine, as in Example 1, was obtained as white prisms m.p. 242° C. on recrystallisation from methanol. Found: C, 74.2; H, 8.2; $C_{28}H_{37}O_4N$ requires C, 74.5; H, 8.2%.

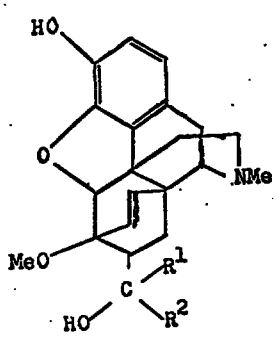
EXAMPLE 21.

6,14-*endo*Etheno-7-(hydroxymethyl)-tetrahydro-oripavine.

This was prepared from 6,14-*endo*etheno-7 - (hydroxymethyl)tetrahydrothebaine as in Example 2, and was obtained, after purification through the hydrochloride (made in ethanol), as white prisms m.p. 218—219° C. the hydrochloride had m.p. 298° C.

WHAT WE CLAIM IS:—

1. Compounds of the general formula



and salts thereof with pharmaceutically acceptable acids in which formula R^1 represents a hydrogen atom, an alkyl group containing from 1 to 3 carbon atoms or an aryl group, and R^2 represents a hydrogen atom, an alkyl, or alkenyl group containing up to 8 carbon atoms, which group may be substituted on carbon atoms 1 to 5 by an alicyclic or aryl group, or an alicyclic group containing 5, 6 or 7 carbon atoms which may be unsubstituted or substituted by an alkyl group containing 1 to 3 carbon atoms, provided R^2 does not contain the system —CH—aryl or —CH—C=C attached to the carbon atom bearing the alcoholic hydroxyl group.

2. 3-Acyl esters of the bases claimed in claim 1 wherein the phenolic hydroxyl group is esterified with a fatty acid of the formula $C_nH_{2n+1}COOH$ in which formula n is 1, 2 or 3 or with benzoic or nicotinic acid.

3. 6,14 - *endo*Etheno - 7 - α(1 - hydroxy-1-ethyl)tetrahydro-oripavine.

4. 6,14 - *endo*Etheno - 7 - α(2 - hydroxy-2-pentyl)tetrahydro-oripavine.

5. 6,14 - *endo*Etheno - 7 - α(2 - hydroxy-2-hexyl)tetrahydro-oripavine.

6. 6,14 - *endo*Etheno - 7 - α(2 - hydroxy-2-heptyl)tetrahydro-oripavine.

7. 6,14 - *endo*Etheno - 7 - α(2 - hydroxy-5-methyl-2-hexyl)tetrahydro-oripavine.

8. 6,14 - *endo*Etheno - 7 - α(3 - hydroxy-1-phenyl-3-butyl)tetrahydro-oripavine.

9. The 3-acetyl ester of 6,14-*endo*Etheno-7 - α(2 - hydroxy - 2 - pentyl)tetrahydro-oripavine.

10. A process for the production of compounds as claimed in claim 1 which comprises demethylating a compound of the general formula

The hydrochloride formed white prisms m.p. 290° C. Found: C, 69.9; H, 7.1; $C_{29}H_{33}O_4N.HCl$ requires C, 70.2; H, 6.9.

EXAMPLE 17.

6,14-*endo*Etheno-7-α(3-hydroxyl-phenyl-3-butyl)tetrahydro-oripavine.

This base was prepared from 6,14-*endo*etheno - 7 - α(3 - hydroxy - 1 - phenyl - 3-butyl)tetrahydrothebaine as in Example 1 and on recrystallisation from aqueous 2-ethoxyethanol was obtained as white prisms m.p. 226° C. Found: C, 75.7; H, 7.6 $C_{30}H_{35}O_4N$ requires C, 76.1; H, 7.5%. The hydrochloride formed white prisms m.p. 255° C. Found: C, 70.6; H, 7.1; $C_{30}H_{35}O_4N.HCl$. requires C, 70.5; H, 7.1%.

EXAMPLE 18.

6,14-*endo*Etheno-7-α(1-hydroxy-1-cyclopentyl-1-ethyl)tetrahydro-oripavine.

This base was prepared from 6,14-*endo*etheno - 7 - α(1 - hydroxy - 1 - cyclopentyl-1-ethyl)tetrahydrothebaine as in Example 1 and on recrystallisation from aqueous 2-ethoxyethanol was obtained as white prisms m.p. 300—302° C. Found: C, 74.0; H, 7.9; $C_{27}H_{33}O_4N$ requires C, 74.1; H, 8.1%. The hydrochloride formed white prisms m.p. 294—296° C. Found: C, 64.6; H, 7.9; $C_{27}H_{35}O_4N.HCl.1\frac{1}{2}H_2O$ requires C, 64.7; H, 7.9%.

EXAMPLE 19.

6,14-*endo*Etheno-7-α(1-hydroxy-1-cyclohexyl-1-ethyl)tetrahydro-oripavine.

This base was prepared from 6,14-*endo*etheno - 7 - α(1 - hydroxy - 1 - cyclohexyl-1-ethyl)tetrahydrothebaine by the general method of Example 1 and was obtained as white prisms m.p. 232° C. on recrystallisation from methanol. Found: C, 69.2; H, 8.4; $C_{28}H_{37}O_4N.2H_2O$ requires C, 69.0; H, 8.4%. The hydrochloride formed white prisms m.p. 248° C. Found: C, 66.1; H, 7.8; $C_{28}H_{37}O_4N.HCl.H_2O$ requires C, 66.4; H, 7.9%.

The 3-acetyl ester, prepared from the base and acetic anhydride was obtained as white prisms m.p. 193° C. Found: C, 70.8; H, 8.2; $C_{30}H_{39}O_5N.H_2O$ requires C, 70.5; H, 8.1%. Hydrochloride m.p. 262° C. Found: C, 67.6; H, 7.6; $C_{30}H_{39}O_5N.HCl$ requires C, 67.9; H, 7.6%.

EXAMPLE 20.

6,14-*endo*Etheno-7-β(1-hydroxy-1-cyclohexyl-1-ethyl)tetrahydro-oripavine.

This base prepared from 6,14-*endo*etheno-7 - β(1 - hydroxy - 1 - cyclohexyl - 1-ethyl)tetrahydrothebaine, as in Example 1, was obtained as white prisms m.p. 242° C. on recrystallisation from methanol. Found: C, 74.2; H, 8.2; $C_{28}H_{37}O_4N$ requires C, 74.5; H, 8.2%.

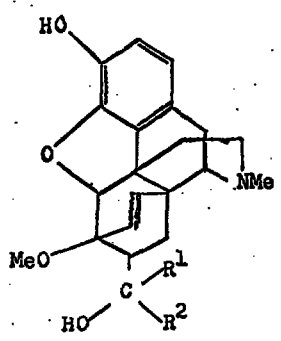
EXAMPLE 21.

6,14-*endo*Etheno-7-(hydroxymethyl)-tetrahydro-oripavine.

This was prepared from 6,14-*endo*etheno-7 - (hydroxymethyl)tetrahydrothebaine as in Example 2, and was obtained, after purification through the hydrochloride (made in ethanol), as white prisms m.p. 218—219° C. the hydrochloride had m.p. 298° C.

WHAT WE CLAIM IS:—

1. Compounds of the general formula



and salts thereof with pharmaceutically acceptable acids in which formula R^1 represents a hydrogen atom, an alkyl group containing from 1 to 3 carbon atoms or an aryl group, and R^2 represents a hydrogen atom, an alkyl, or alkenyl group containing up to 8 carbon atoms, which group may be substituted on carbon atoms 1 to 5 by an alicyclic or aryl group, or an alicyclic group containing 5, 6 or 7 carbon atoms which may be unsubstituted or substituted by an alkyl group containing 1 to 3 carbon atoms, provided R^2 does not contain the system —CH—aryl or —CH—C=C attached to the carbon atom bearing the alcoholic hydroxyl group.

2. 3-Acyl esters of the bases claimed in claim 1 wherein the phenolic hydroxyl group is esterified with a fatty acid of the formula $C_nH_{2n+1}COOH$ in which formula n is 1, 2 or 3 or with benzoic or nicotinic acid.

3. 6,14 - *endo*Etheno - 7 - α(1 - hydroxy-1-ethyl)tetrahydro-oripavine.

4. 6,14 - *endo*Etheno - 7 - α(2 - hydroxy-2-pentyl)tetrahydro-oripavine.

5. 6,14 - *endo*Etheno - 7 - α(2 - hydroxy-2-hexyl)tetrahydro-oripavine.

6. 6,14 - *endo*Etheno - 7 - α(2 - hydroxy-2-heptyl)tetrahydro-oripavine.

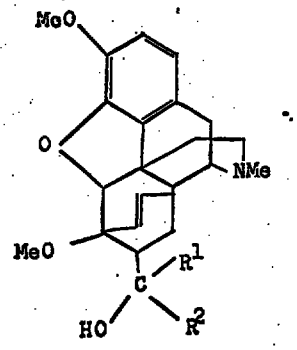
7. 6,14 - *endo*Etheno - 7 - α(2 - hydroxy-5-methyl-2-hexyl)tetrahydro-oripavine.

8. 6,14 - *endo*Etheno - 7 - α(3 - hydroxy-1-phenyl-3-butyl)tetrahydro-oripavine.

9. The 3-acetyl ester of 6,14-*endo*Etheno-7 - α(2 - hydroxy - 2 - pentyl)tetrahydro-oripavine.

10. A process for the production of compounds as claimed in claim 1 which comprises demethylating a compound of the general formula

* C L M S *



by heating with an alkali metal hydroxide in the presence of a suitable solvent.

11. A process as claimed in claim 1 wherein the demethylation is carried out by heating to a temperature of above 200° C. in the presence of an alkali metal hydroxide in solution in diethylene glycol.

12. A process for the production of the 3-acyl esters claimed in claim 2 which comprises reacting a compound as claimed in claim 1 with an acid anhydride or acid chloride.

13. A process for the production of compounds as claimed in claim 1 substantially as described with reference to any of the Examples.

14. Oripavine derivatives when produced by the process claimed in claim 13.

ELKINGTON & FIFE,
Chartered Patent Agents,
Bank Chambers, 329, High Holborn,
London, W.C.1.
Agents for the Applicants.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press (Leamington) Ltd.—1963. Published by The Patent Office, 25 Southampton Buildings, London, W.C.2, from which copies may be obtained.

ERRATUM

SPECIFICATION No. 937,214

Page 2, line 45, *delete* ")" *after* "hydroxy"

THE PATENT OFFICE
29th September 1964

* C L M S *