969,263

PATENT SPECIFICATION

NO DRAWINGS

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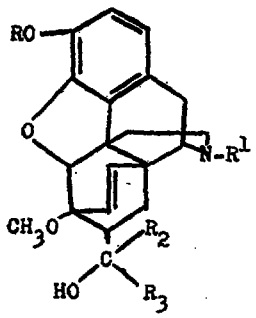
COMPLETE SPECIFICATION

Novel Derivatives of Thebaine and Oripavine

We, J. F. MACFARLAN & CO. 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 it is to be performed, to be particularly described in and by the following statement:—

This invention relates to novel compounds of thebaine oripavine and to processes for their production.

The novel compounds of the invention are compounds of the formula I



(I)

in which formula R represents a hydrogen atom a methyl group, or an acyl group of composition $C_nH_{2n+1}CO-$ wherein n is an integer, R^1 represents a hydrogen atom or an alkyl or alkenyl group containing 2 to 8 carbon atoms, or a propargyl, cyclopropylmethyl, methyl cyclopropylmethyl or a dimethylcyclopropyl methyl group, R^2 represents a hydrogen atom, or alkyl group containing up to 3 carbon atoms or an aryl group, and R^3 represents a hydrogen atom, an alicyclic group containing 5, 6 or 7 carbon atoms or an alkyl or alkenyl group containing up to 8 carbon atoms which may be substituted on carbon atoms 1 to 4 by an alicyclic, aryl, alkoxy or aryloxy group, or by a heterocyclic group containing oxygen, provided that when R represents a hydrogen atom or an acyl group or when R^1 represents a hydrogen atom, a cyclopropyl methyl, methyl cyclopropyl methyl or dimethyl-cyclopropylmethyl group, R^3 does not contain the system —CH—aryl or —CH—C=C attached directly to the carbon atom bearing the alcoholic hydroxyl group, and salts of these bases with pharmaceutically acceptable acids.

The compounds of the invention are therapeutically useful because of their power to affect the central nervous system, particularly through their analgesic, sedative and antitussive effects, and, in those compounds where R^1 is other than a hydrogen atom, for their power to antagonise the effect of narcotic drugs.

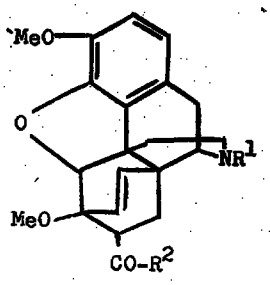
The invention provides also a process for the preparation of the novel compounds in which the group R^3 does not contain the system —CH—aryl or —CH—C=C linked directly to the carbon atom bearing the alcoholic hydroxyl group, in which a tertiary base of structure (I), in which R and R^1 are methyl groups (see British Patent Specification No. 925723), is treated with cyanogen bromide and the resulting N-cyano-compound (R^1=CN) is heated with an alkali metal hydroxide or alkoxide in a suitable solvent, such as diethylene glycol at temperatures up to 180° C, advantageously at 170° C (to give compounds in which R is a methyl group) or at temperatures above 180° C, advantageously 210° C (to give compounds in which R is a hydrogen atom) the group R^1 in both cases being a hydrogen atom. If required, the

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secondary base so formed is converted into the tertiary base by treatment with an alkyl, alkenyl or cycloalkyl halide R^1X, R^1 being for example one of the following groups: *n*-propyl, isobutyl, allyl, methylallyl, dimethylallyl and propargyl; or by acylation, for example, with cyclopropyl- or a substituted cyclopropyl-carbonyl chloride followed by reduction with lithium aluminium hydride.

Demethylation to give phenolic compounds need not necessarily take place at the stage of the secondary base since compounds in which R is a hydrogen atom may be prepared from the bases in which R is a methyl group and R^1 has the meaning given above by heating with an alkali metal hydroxide or alkoxide in a suitable solvent, such as diethylene glycol, at a temperature above 180° C, advantageously at 210° C and this method of preparation is clearly part of the same general process. It will be appreciated that the systems —C(OH)—CH—aryl and —CH(OH)—CH—C=C cannot survive the vigorous alkaline conditions inherent in one stage of this process because of the ease with which they suffer base-catalysed dehydration.

The invention includes also a process for the preparation of those compounds of structure (I) in which R is a methyl group, R^1 is one of the following; *n*-propyl, isobutyl, allyl, methylallyl, dimethylallyl and propargyl and R^2 and R^3 have the meanings given above in which bases of the structure (II)



(II)

are treated with a Grignard reagent R^3MgX, in which R^3 has the full meaning given above and X represents halogen. The ketones required for this process are conveniently prepared from bases of the above ketonic structure (II) in which R^1 is a methyl group (e.g. see British Patent No. 902,659) by treatment successively with cyanogen bromide, dilute mineral acid preferably dilute hydrochloric acid, sodium nitrite and finally with appropriate halide R^2X as sent out in example No. 3(b).

The 3-acyl esters of the phenolic members of the series are conveniently prepared from those compounds of structure (I) in which R is a hydrogen atom by standard methods of acylation, e.g. by heating under reflux with an acid anhydride and the sodium salt of the corresponding acid or by treatment with an aqueous solution of an alkali metal hydroxide and an acid anhydride or halide.

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

EXAMPLE 1.

6, 14 - *endo*etheno - 7 - (2 - hydroxy - 2 - propyl) - terahydronorthebaine

A mixture of cyanogen bromide (4 parts), chloroform (25 parts) and 6, 14 *endo* - etheno - 7 - (2 - hydroxy - 2 - propyl) - tetrahydrothebaine (9 parts) was kept at room temperature overnight and extracted with 2*N* hydrochloric acid. The chloroform layer was separated, dried over sodium sulphate and evaporated. The residue was triturated with methanol and N - cyano - 6, 14 - *endo*etheno - 7 - (2 - hydroxy - 2 - propyl) tetrahydro - northebaine (8.5 parts) m.p. 228° C was obtained. This N - cyano - compound (57 parts) was added to a solution of potassium hydroxide (57 parts) in diethylene glycol (400 parts) and the mixture was stirred at 170° C for 30 minutes, during which time ammonia was evolved. The mixture was then poured into stirred ice-water and the precipitated needles (m.p. 77° C) were collected. This base, on recrystallisation from water, had m.p. 78° C. The hydrochloride, prepared in methanolic hydrogen chloride and recrystallised from methanol had m.p. 290° C (dec.)

EXAMPLE 2.

(a) 6, 14 - *endo*etheno - 7 - (2 - hydroxy - 2 - propyl) - tetrahydronororipavine

N - cyano - 6, 14 - *endo*etheno - 7 - (2 - hydroxy - 2 - propyl) - tetrahydronorthebaine (as prepared in Example 1) (100 parts) was added to potassium hydroxide (250 parts) in diethylene glycol (1200 parts) at 180 to 190° C and the mixture was stirred at 210 to 220° C for 30 minutes and then poured into ice-water. The aqueous solution so obtained was saturated with ammonium chloride and the precipitated phenolic base was collected and washed well with water. The crude material (80 parts) had m.p. 280 to 282° C, raised to 284° C by recrystallisation from methanol. A further quantity (7 parts) of the phenolic base was obtained by extraction of the aqueous filtrate with chloroform.

Hydrolysis conditions intermediate in vigour (alkali content and temperature) between those given above and those used in example 1 gave a mixture of the phenol and its methyl ether; the latter was precipitated when the reaction mixture was poured into ice-water and could be removed by filtration; subsequent saturation of the filtrate with ammonium chloride liberated the phenol, which could be collected or extracted with chloroform.

(b) 6, 14 - *endo*etheno - 7 - (2 - hydroxy - 2 - propyl) - tetrahydronorthebaine (29 parts) was demethylated by heating for 30 minutes with stirring at 210° C in a solution of potas-

sium hydroxide (90 parts) and diethylene glycol (500 parts) preheated to that temperature. The product, m.p. 284° C (20 parts), was isolated as in example 2(a). The hydrochloride, prepared in ethanolic hydrogen chloride, and recrystallised from ethanol, had m.p. 208° C (dec.).

EXAMPLE 3.

N - Allyl - 6, 14 - *endo*etheno - 7 - (2 - hydroxy - 2 - propyl) - tetrahydro - northebaine

(a) 6, 14 - *endo*etheno - 7 - (2 - hydroxy - 2 - propyl) - tetrahydronorthebaine (3.4 parts), allyl bromide (1 part) and sodium carbonate (2 parts) in ethanol were boiled under reflux for 24 hours. The mixture was filtered and evaporated, leaving a viscous gum that crystallised on standing. On recrystallisation from light petroleum (b.p. 40 to 60° C), the product was obtained as prisms m.p. 104° C.

(b) 6, 14 - *endo*etheno - 7 - acetyltetra - hydrothebaine (British Patent Application No. 4020/61) (Serial No. 902659), (25 parts) and cyanogen bromide (8 parts) in chloroform (75 parts) were kept at room temperature overnight. The chloroform was evaporated and the residue was triturated with methanol. The resulting crystalline N - cyano - 6, 14 - *endo*etheno - 7 - acetyltetrahydronorthebaine (23 parts), m.p. 236° C, was collected.

The N-cyano-compound so obtained (10 parts) was finely powdered and boiled with 2*N* hydrochloric acid (100 parts) until almost all of the solid matter had dissolved (about 2 hours). The almost-insoluble N-cyano-compound was wetted by the aqueous acid only with difficulty and at first frothing was troublesome; this was minimised by adding a few drops of a neutral wetting agent such as "Stergene" (a Registered Trade Mark). The hot mixture was filtered from a small amount of insoluble matter, and cooled to 0° C. An aqueous solution of sodium nitrite (2 parts) was then added with stirring to the mixture containing the substituted urea resulting from partial hydrolysis of the N-cyano-compound. When gas evolution ceased the reaction mixture was made alkaline with ammonia solution and the base was extracted with chloroform; evaporation of the solvent afforded 6, 14 - endoetheno - 7 - acetyltetrahydronorthebaine (6 parts) as a hard glass. The base gave a crystalline hydrochloride, m.p. 350° C, recrystallisable from hot water, when treated with aqueous hydrochloric acid or methanolic hydrogen chloride. The picrate had m.p. 270° C (dec).

6, 14 - *endo*etheno - 7 - acetyltetrahydro - northebaine thus obtained (20 parts) was boiled with allyl bromide (6 parts) in ethanol (100 parts) in the presence of anhydrous sodium carbonate (10 parts) for 20 hours. The mixture was cooled and filtered and the filtrate was evaporated leaving N - allyl - 6, 14 - *endo*etheno - 7 - acetyltetrahydro - northebaine as an uncrystallisable glass, that gave a hydrochloride which crystallised as plates from ethanol m.p. 233° C (14 parts).

A solution of N - allyl - 6, 14 - *endo* - etheno - 7 - acetyltetrahydronorthebaine base so obtained (13 parts) in ether (50 parts) was added to a boiling stirred solution of methylmagnesium iodide prepared from magnesium (3.8 parts) methyl iodide (22.5 parts) and ether (100 parts). The mixture was stirred and heated under reflux for two hours and then poured into a saturated aqueous solution of ammonium chloride. The ethereal layer was separated, dried and evaporated, leaving a viscous residue that crystallised on standing. On recrystallisation from light petroleum (b.p. 40 to 60° C) the product was obtained as prisms m.p. 104° C.

EXAMPLE 4.

N - Allyl - 6, 14 - *endo*etheno - 7 - (2 - hydroxy - 2 - propyl) - tetrahydro - nororipavine

(a) 6, 14 - *endo*etheno - 7 - (2 - hydroxy - 2 - propyl) - tetrahydronororipavine (from example 2) (3.4 parts) was boiled in ethanol (80) parts with allyl bromide (1 part) and anhydrous sodium carbonate (2 parts) for 20 hours. The mixture was cooled and filtered and the filtrate was evaporated. Treatment of the residue with methanol gave the desired N-allyl base (1.5 parts) which on recrystallisation from methanol was obtained as prisms, m.p. 120° C on slow heating, 210° C if inserted in a melting point bath at 200° C. The hydrochloride prepared in and recrystallised from ethanol, had m.p. 248° C (dec).

The 3-acetyl ester was prepared by treating the base (1 part) in acetic anhydride (1 part) under reflux for 10 minutes. The mixture was poured into water, the base was liberated with aqueous sodium carbonate and isolated by ether extraction. This ester was an oil which gave a crystalline hydrochloride m.p. 236° C.

(b) N - Allyl - 6, 14 - *endo*etheno - 7 - (2 - hydroxy - 2 - propyl) - tetrahydro - northebaine was dimethylated by heating it with potassium hydroxide (40 parts) and diethylene glycol (150 parts) at 200° C until a text portion gave a homogeneous solution when diluted with 10 parts of water. The mixture was then poured into 8 times its volume of water and the phenolic base was precipitated by adding saturated aqueous ammonium chloride. The precipitate was extracted with ether and the ethereal solution was dried and evaporated leaving the solid base which was recrystallised from methanol, when it was obtained as prisms m.p. 120° C on slow heating, 210° C if inserted into a melting point bath at 200° C, both melting points were undepressed on mixing with material prepared as in Example 4(a).

EXAMPLE 5.

N - Cyclopropylmethyl - 6, 14 - *endo* - etheno - 7 - (2 - hydroxy - 2 - propyl) - tetrahydronorthebaine.

6, 14 - *endo*Etheno - 7 - (2 - hydroxy - 2 - propyl) - tetrahydronorthebaine (5 parts) was stirred in dry ether with anhydrous potassium carbonate (5 parts) and cyclopropylcarbonylchloride (1.4 parts) was added. After 6 hours water and dilute hydrochloric acid were added and the ethereal layer was separated. On drying and evaporation this afforded the nonbasic amide N - cyclopropylcarbonyl - 6, 14 - *endo*etheno - 7 - (2 - hydroxy - 2 - propyl) - tetrahydronorthebaine as prisms m.p. 214° C when recrystallised from methanol. This amide (2 parts) was dissolved in tetrahydrofuran (20 parts) and reduced under reflux for 5 hours with lithium aluminium hydride. Water (8 parts) was then added. The mixture was filtered and the residue was washed with ether. The combined washings and filtrate were shaken with dilute hydrochloric acid. The aqueous acid solution was made alkaline with ammonia, and the precipitated base isolated by ether extraction when N - cyclopropylmethyl - 6, 14 - *endo*etheno - 7 - (2 - hydroxy - 2 - propyl) - tetrahydronorthebaine was obtained as a viscous gum that formed a crystalline hydrochloride m.p. 266° C.

EXAMPLE 6.

N - Cyclopropylmethyl - 6, 14 - *endo* - etheno - 7 - (2 - hydroxy - 2 - propyl) - tetrahydronororipavine.

This was prepared as in Example 5 from (a) 6, 14 - *endo*etheno - 7 - (2 - hydroxy - 2 - propyl) - tetrahydronororipavine (5-parts) and cyclopropylcarbonyl chloride (2.4 parts); (b) lithium aluminium hydride (2.15 parts) and tetrahydrofuran (100 parts). The intermediate *amide* had m.p. 290° C and the desired final base m.p. 234° C.

EXAMPLE 7.

N - Propargyl - 6, 14 - *endo*etheno - 7 - (2 - hydroxy - 2 - propyl) - tetra - hydronorthebaine

This base was prepared by the method of Example 3(a) from 6, 14 - *endo*etheno - 7 - (2 - hydroxy - 2 - propyl) - tetrahydro - northebaine (5 parts), propargyl bromide (1.2 parts) and anhydrous sodium carbonate (5 parts) in ethanol. The mixture was filtered and the desired base precipitated with water. On recrystallisation from aqueous ethanol it had m.p. 163° C.

EXAMPLE 8.

N - *n* - Propyl - 6, 14 - *endo*etheno - 7 - (2 - hydroxy - 2 - propyl) tetrahydronorthebaine.

This base was prepared from 6, 14 - *endo* - etheno - 7 - (2 - hydroxy - 2 - propyl) tetra - hydronorthebaine (5 parts), *n*-propyl iodide (5 parts) and anhydrous sodium carbonate (5 parts) by the method of Example 3 (a), on recrystallisation from ethanol it was obtained as colourless needles, m.p. 157° C, hydrochloride m.p. 286° C (dec).

EXAMPLE 9.

N - Isobutyl - 6, 14 - *endo*etheno - 7 - (2 - hydroxy - 2 - propyl) tetrahydronorthebaine.

This base was prepared from 6, 14 - *endo* - etheno - 7 - (2 - hydroxy - 2 - propyl) tetra - hydronorthebaine (5 parts), isobutyl bromide (2 parts) and anhydrous sodium carbonate (5 parts). Recrystallisation from ethanol gave prisms, m.p. 76° C, hydrochloride m.p. 294° C.

EXAMPLE 10.

N - 2 - Methylallyl - 6, 14 - *endo*etheno - 7 - (2 - hydroxy - 2 - propyl) tetrahydronorthebaine.

This base was prepared as in Example 3 (a) from 6, 14 - *endo*etheno - 7 (2 - hydroxy - 2 - propyl) - tetrahydronorthebaine (5 parts) 2-methylallyl bromide (1.5 parts) and anhydrous sodium carbonate (5 parts); the base so obtained was non-crystalline but formed a crystalline hydrochloride, m.p. 248° C.

EXAMPLE 11.

N - 3, 3 - Dimethylallyl - 6, 14 - *endo* - etheno - 7 - (2 - hydroxy - 2 - propyl) - tetrahydronorthebaine.

This base was prepared as in Example 3 (a) from 6, 14 - *endo*etheno - 7 (2 - hydroxy - 2 - propyl) - tetrahydronorthebaine (5 parts), 3, 3 - dimethylallyl bromide (1.5 parts) and anhydrous sodium carbonate (5 parts) but using acetone as a solvent. It was obtained as prisms, m.p. 110° C hydrochloride m.p. 172° C.

EXAMPLE 12.

N - Propargyl - 6, 14 - *endo*etheno - 7 - (2 - hydroxy - 2 - propyl) tetrahydronororipavine.

This base was prepared as in Example 4 (a) from 6, 14 - *endo*etheno - 7 - (2 - hydroxy - 2 - propyl) tetrahydronororipavine (5 parts), propargyl bromide (1.5 parts) and anhydrous sodium carbonate (5 parts), and so obtained it had m.p. 120° C, hydrochloride, m.p. 240° C.

EXAMPLE 13.

N - 3, 3 - Dimethylallyl - 6, 14 - *endo* - etheno - 7 - (2 - hydroxy - 2 - propyl) - tetrahydronororipavine.

This base was prepared as in Example 4 (a) from 6, 14 - *endo*etheno - 7 - (2 - hydroxy - 2 - propyl) tetrahydronororipavine (5 parts), 3, 3 - dimethylallyl bromide (1.5 parts) and anhydrous sodium carbonate (5 parts) but using acetone as solvent. In this way it was obtained as a non-crystalline gum

but formed a crystalline hydrochloride, m.p. 212° C.

EXAMPLE 14.

6, 14 - *endo*etheno - 7 - hydroxymethyl - nororipavine.

This base was prepared as in Examples 1 and 2 from 6, 14 - *endo*etheno - 7 - acetoxy - methyltetrahydrothebaine and cyanogen bromide, followed by hydrolysis at 210° C. The intermediate N - cyano - compound had m.p. 190° C and the secondary base was non-crystalline, but gave a crystalline hydrochloride, m.p. 264° C.

EXAMPLE 15.

N - Allyl - 6, 14 - *endo*etheno - 7 - hydroxymethylnororipavine

This base was prepared as in Example 4 (a) from 6, 14 *endo*etheno - 7 - hydroxy - methyltetrahydronororipavine (5 parts), allyl bromide (1.5 parts) and anhydrous sodium carbonate (5 parts); it was non-crystalline, but gave a crystalline hydrochloride m.p. 281° C.

EXAMPLE 16.

6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - butyl) - tetrahydronorthebaine.

This was prepared as in Example 1 from 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - butyl) - tetrahydrothebaine, cyanogen bromide and chloroform, followed by hydrolysis at 170° C. The intermediate N - cyano - compound had m.p. 198° C and the secondary base had m.p. 96° C.

EXAMPLE 17.

N - Allyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - butyl) - tetra - hydronorthebaine.

This base was prepared as in Example 3 (a) from 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - butyl) - tetrahydrothebaine (5 parts), allyl bromide (1.5 parts) and anhydrous sodium carbonate (5 parts). The base was non-crystalline, but gave a crystalline hydrochloride m.p. 286° C.

EXAMPLE 18.

N - *n* - Propyl - 6, 14 *endo*etheno - 7α - (2 - hydroxy - 2 - butyl) - tetra - hydronorthebaine.

The base was prepared as in Example 3 (a) from 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - butyl) - tetrahydronorthebaine (5 parts), *n*-propyl bromide (1.5 parts) and anhydrous sodium carbonate (5 parts), it had m.p. 142° C.

EXAMPLE 19.

N - Propargyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - butyl) - tetra - hydronorthebaine.

The base was prepared as in Example 3 (a) from 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - butyl) - tetrahydronorthebaine (5 parts), propargyl bromide (1.5 parts) and anhydrous sodium carbonate (5 parts): it was obtained as colourless prisms m.p. 158° C, hydrochloride m.p. 293° C.

EXAMPLE 20.

N - Isobutyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - butyl) - tetra - hydronorthebaine.

The base was prepared as in Example 3 (a) from 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - butyl) - tetrahydronorthebaine (5 parts), isobutyl bromide (1.5 parts) and anhydrous sodium carbonate (5 parts): it was an uncrystallisable gum, from which a crystalline hydrochloride m.p. 268° C was obtained.

EXAMPLE 21.

N - 2 - Methylallyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 butyl) tetra - hydronorthebaine.

This base was prepared as in Example 3 (a) from 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - butyl) - tetrahydronorthebaine (5 parts) 2 - methylally bromide (1.5 parts), and anhydrous sodium carbonate (5 parts), and was obtained as prisms m.p. 124° C, crystalline hydrochloride m.p. 277° C.

EXAMPLE 22.

N - 3 - methylallyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - butyl) - tetra - hydronorthebaine.

This base was prepared by the method of Example 3 (a) from 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - butyl) - tetrahydro - northebaine (5 parts), crotyl chloride (1.3 parts) and anhydrous sodium carbonate (5 parts), and was obtained as a viscous uncrystallisable gum, giving a bitartrate m.p. 242° C.

EXAMPLE 23.

N - 3, 3 - Dimethylallyl - 6, 14 - *endo* - etheno - 7α - (2 - hydroxy - 2 - butyl) - tetrahydronorthebaine.

This base was prepared by the general method of Example 3 (a) from 6, 14 - *endo* - etheno - 7α - (2 - hydroxy - 2 - butyl) - tetrahydronorthebaine (5 parts), 3, 3 - di - methylallyl bromide (1.5 parts) and anhydrous sodium carbonate (5 parts) but using acetone as solvent. In this way it was obtained as an uncrystallisable gum giving a hydrochloride m.p. 210° C.

EXAMPLE 24.

6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - pentyl) - tetrahydronorthebaine.

This base was prepared as in Example 1 from 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - pentyl) - tetrahydrothebaine and cyanogen bromide, followed by hydrolysis at 170° C. The intermediate N - cyano - compound had m.p. 200° C and the secondary base had m.p. 173° C, hydrochloride m.p. 260° C.

EXAMPLE 25.

6, 14 - *endo*etheno - 7β - (2 - hydroxy - 2 - pentyl) - tetrahydronorthebaine.

This base was prepared as in Example 1 from 6, 14 - *endo*etheno - 7β - (2 - hydroxy - 2 - pentyl) - tetrahydrothebaine and cyanogen bromide, followed by hydrolysis at 170° C. The intermediate N - cyano - compound had m.p. 208° C and the secondary base had m.p. 102° C.

EXAMPLE 26.

N - Allyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - pentyl) - tetra - hydronorthebaine.

This base was prepared as in Example 3 (a) from 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - pentyl) - tetrahydronorthebaine (5 parts), allyl bromide (1.5 parts) and anhydrous sodium carbonate (5 parts). The base was dimorphic, being obtained from benzene as needles m.p. 80° C and from ethanol or methanol as needles m.p. 118° C; the hydrochloride had m.p. 163° C.

EXAMPLE 27.

N - Allyl - 6, 14 - *endo*etheno - 7β - (2 - hydroxy - 2 - pentyl) - tetra - hydronorthebaine.

This base was prepared as in Example 3 (a) from 6, 14 - *endo*etheno - 7β - (2 - hydroxy - 2 - pentyl) - tetrahydronorthebaine (5 parts), allyl bromide (1.5 parts) and anhydrous sodium carbonate (5 parts); it was non-crystalline but gave a crystalline hydrochloride m.p. 277° C. It was also prepared as in Example 3 (b) from N - allyl - 6, 14 - *endo*etheno - 7 - acetyltetrahydronorthebaine (13 parts), magnesium (3.8 parts) and *n*-propyl iodide (23 parts); in this case the α-isomer was obtained from the mother liquors of crystallisation of the β hydrochloride.

EXAMPLE 28.

N - *n* - Propyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - pentyl) - tetra - hydronorthebaine.

The base was prepared as in Example 3 (a) from 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - pentyl) - tetrahydronorthebaine (5 parts), *n*-propyl iodide (2 parts) and anhydrous sodium carbonate (5 parts); the base was obtained as an uncrystallisable gum giving a crystalline bitartrate m.p. 254° C.

EXAMPLE 29.

N - *n* - Propyl - 6, 14 - *endo*etheno - 7β - (2 - hydroxy - 2 - pentyl) - tetra - hydronorthebaine.

This base was prepared as in Example 3 (a) from 6, 14 - *endo*etheno - 7β - (2 - hydroxy - 2 - pentyl) - tetrahydronorthebaine (5 parts), *n*-propyl iodide (2 parts) and anhydrous sodium carbonate (5 parts) as an uncrystallisable gum giving a crystalline hydrochloride m.p. 315° C.

EXAMPLE 30.

N - Isobutyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - pentyl) - tetra - hydronorthebaine.

This base was prepared as in Example 3 (a) from 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - pentyl) - tetrahydronorthebaine (5 parts), isobutyl bromide (1.5 parts) and anhydrous sodium carbonate (5 parts) as prisms m.p. 174° C.

EXAMPLE 31.

N - Isobutyl - 6, 14 - *endo*etheno - 7β - (2 - hydroxy - 2 - pentyl) - tetra - hydronorthebaine.

This base was prepared as in Example 3 (a) from 6, 14 - *endo*etheno - 7β - (2 - hydroxy - 2 - pentyl) - tetrahydronorthebaine, isobutyl bromide and anhydrous sodium carbonate as an uncrystallisable gum giving a crystalline hydrochloride m.p. 300° C.

EXAMPLE 32.

N - Propargyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - pentyl) - tetra - hydronorthebaine.

This base was prepared as in Example 3 (a) from 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - pentyl) - tetrahydronorthebaine, propargyl bromide and anhydrous sodium carbonate as prisms m.p. 162° C.

EXAMPLE 33.

N - Propargyl - 6, 14 - *endo*etheno - 7β - (2 - hydroxy - 2 - pentyl) - tetra - hydronorthebaine.

This base was prepared as in Example 3 (a) from 6, 14 - *endo*etheno - 7β - (2 - hydroxy - 2 - pentyl) - tetrahydronorthebaine, propargyl bromide and sodium carbonate as an uncrystallisable gum, hydrochloride m.p. 260° C.

EXAMPLE 34.

N - 2 - Methylallyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - pentyl) - tetra - hydronorthebaine.

This base was prepared as in Example 3 (a) from 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - pentyl) - tetrahydronorthebaine, 2-methylallyl bromide and sodium carbonate as an uncrystallisable gum, hydrochloride, m.p. 277° C.

EXAMPLE 35.

N - 3, 3 - Dimethylallyl - 6, 14 - *endo* - etheno - 7α (2 - hydroxy - 2 - pentyl) - tetrahydronorthebaine

This base was prepared as in Example 3 (a) from 6, 14 - endoetheno - 7α - (2 - hydroxy - 2 - pentyl) - tetrahydronorthebaine, 3, 3 - dimethylallyl bromide and sodium car-

bonate, but using acetone as a solvent; it was obtained as colourless needles m.p. 106° C, hydrochloride m.p. 160° C.

EXAMPLE 36.

N - Cyclopropylmethyl - 6, 14 - *endo* - etheno - 7α - (2 - hydroxy - 2 - pentyl) - tetrahydronorthebaine

This base was prepared as in Example 5 from 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - pentyl) - tetrahydronorthebaine and the acid chloride of cyclopropylcarboxylic acid, followed by reduction with lithium aluminium hydride. The intermediate amide had m.p. 185° C and the tertiary base had m.p. 130° C.

EXAMPLE 37.

6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - pentyl) - tetrahydronororipavine.

This base was prepared as in Example 1 and 2 (a) from 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - pentyl) - tetrahydrothebaine, cyanogen bromide and chloroform, followed by hydrolysis at 210° C. So obtained it had m.p. 260° C, hydrochloride m.p. 305° C. It was also prepared as in example 2 (b) from 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - pentyl) - tetrahydronorthebaine by demethylation at 210° C.

EXAMPLE 38.

N - Allyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - pentyl) - tetra - hydronororipavine

This base was prepared as in Example 4 (a) from 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - pentyl) - tetrahydro - nororipavine, allyl bromide and anhydrous sodium carbonate; it had m.p. 126° C, hydrochloride m.p. 254° C.

EXAMPLE 39.

N - 3, 3 - Dimethylallyl - 6, 14 - *endo* - etheno - 7α - (2 - hydroxy - 2 - pentyl) - tetrahydronororipavine.

This base was prepared as in Example 4 (a) from 6, 14 - endoetheno - 7α - (2 - hydroxy - 2 - pentyl) - tetrahydro - nororipavine, 3, 3 - dimethylallyl bromide and anhydrous sodium carbonate, using acetone as solvent; it was obtained as prisms m.p. 190° C.

EXAMPLE 40.

N - Cyclopropylmethyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - pentyl) -tetra-hydronororipavine.

This base was prepared as in Example 5 from 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - pentyl) - tetrahydronororipavine, and cyclopropylcarbonyl chloride followed by reduction with lithium aluminium hydride. The intermediate amide had m.p. 270° C and the tertiary base had m.p. 180° C hydrochloride m.p. 262° C.

EXAMPLE 41.

6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - hexyl) - tetrahydronorthebaine.

This base was prepared as in Example 1 from 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - hexyl) - tetrahydrothebaine, cyanogen bromide and chloroform, followed by hydrolysis at 170° C. So obtained it formed prisms m.p. 110° C.

EXAMPLE 42.

N - Allyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - hexyl) - tetra - hydronorthebaine.

This base was prepared as in Example 3 (a) from 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - hexyl) - tetrahydronorthebaine, allyl bromide and sodium carbonate, it had m.p. 102° C.

EXAMPLE 43.

N - Propargyl - 6, 14 - *endo*etheno - 7α - (2 hydroxy - 2 - hexyl) - tetrahydro - northebaine.

This base was prepared as in Example 3 (a) from 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - hexyl) - tetrahydronorthebaine, propargyl bromide and sodium carbonate; it had m.p. 152° C.

EXAMPLE 44.

6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - hexyl) - tetrahydronororipavine.

This base was prepared from 6, 14 - *endo* - etheno - 7α - (2 - hydroxy - 2 - hexyl) - tetrahydrothebaine by treatment with cyanogen bromide and subsequent hydrolysis at 210° C as in Examples 1 and 2 (a). So obtained it had m.p. 210° C.

EXAMPLE 45.

N - Allyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - hexyl) - tetrahydro - nororipavine.

This was prepared as in Example 4 (a) from 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - hexyl) - tetrahydronororipavine, allyl bromide and sodium carbonate and was obtained as prisms m.p. 122° C, hydrochloride m.p. 263° C.

EXAMPLE 46.

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

This was prepared as in Example 1 from 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 4 - methyl - 2 - pentyl) - tetrahydrothebaine and cyanogen bromide, followed by hydrolysis at 170° C. The intermediate N-cyano compound had m.p. 170° C and the secondary base had m.p. 131° C.

EXAMPLE 47.

N - Allyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 4 - methyl - 2 - pentyl) - tetrahydronorthebaine.

This base was prepared as in Example 3 (a) from 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 4 - methyl - 2 - pentyl) - tetra - hydrothebaine, allyl bromide and anhydrous sodium carbonate, it had m.p. 102° C.

EXAMPLE 48.

6, 14 - *endo*etheno - 7β - (2 - hydroxy - 4 - methyl - 2 - pentyl) - tetrahydro - northebaine.

This base was prepared as in Example 3 (a) from 6, 14 *endo*etheno - 7β - (2 - hydroxy - 4 - methyl - 2 - pentyl) - tetrahydrothebaine. The intermediate N-cyano-compound had m.p. 210° C and the secondary base had m.p. 110° C.

EXAMPLE 49.

N - 3, 3 - Dimethylallyl - 6, 14 - *endo* - etheno - 7β - (2 - hydroxy - 4 - methyl - 2 - pentyl) - tetrahydro - northebaine.

This base was prepared as in Example 3 (a) from 6, 14 - *endo*etheno - 7β - (2 - hydroxy - 4 - methyl - 2 - pentyl) - tetra - hydrothebaine, 3, 3, - dimethylallyl bromide and sodium carbonate using acetone as solvent, it was obtained as prisms m.p. 115° C, hydrochloride m.p. 230° C.

EXAMPLE 50.

6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - heptyl) - tetrahydronorthebaine.

This base was prepared as in Example 1 from 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - heptyl) - tetrahydrothebaine, cyanogen bromide and chloroform, followed by hydrolysis at 170° C; so obtained it had m.p. 135° C, the intermediate N-cyano compound having m.p. 129° C.

EXAMPLE 51.

N - 2 - Methylallyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - heptyl) - tetra-hydronorthebaine.

This was prepared as in Example 3 (a) from 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - heptyl) - tetrahydrothebaine, 2 - methyl - allyl bromide and sodium carbonate, and obtained in this way it had m.p. 100° C.

EXAMPLE 52.

N - 3, 3 - Dimethylallyl - 6, 14 - *endo* - etheno - 7α - (2 - hydroxy - 2 - heptyl) - tetrahydronorthebaine.

This was prepared as in Example 3 (a) from 6, 14 - endoetheno - 7α - (2 - hydroxy - 2 - heptyl) - tetrahydrothebaine, 3, 3 - di - methylallyl bromide and sodium carbonate, using acetone as solvent and was obtained as an uncrystallisable gum from which a crystalline hydrochloride m.p. 230° C was obtained.

EXAMPLE 53.

N - 1 - Methylcyclopropylmethyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - heptyl) - tetrahydronorthebaine.

This base was prepared as in Example 5 from 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - heptyl) - tetrahydrothebaine and 1 - methylcyclopropyl - carbonyl chloride, followed by reduction with lithium aluminium hydride. The intermediate amide was non-crystalline and the tertiary base had m.p. 118° C.

EXAMPLE 54.

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

This was prepared by the method of Example 1 from 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 5 - methyl - 2 - hexyl) - tetra - hydrothebaine and cyanogen bromide followed by hydrolysis at 170° C. The intermediate N - cyano - compound had m.p. 164° C and the secondary base m.p. 134° C.

EXAMPLE 55.

N - Allyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 5 - methyl - 2 - hexyl) - tetrahydronorthebaine.

This was prepared by the method of Example 3 (a) from 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 5 - methyl - 2 - hexyl) - tetrahydronorthebaine, allyl bromide and sodium carbonate and was obtained as colourless prisms, m.p. 118° C.

EXAMPLE 56.

N - Propargyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 5 - methyl - 2 - hexyl) - tetrahydronorthebaine.

This was prepared by the method of Example 3 (a) from 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 5 - methyl - 2 - hexyl) - tetrahydronorthebaine, propargyl bromide and sodium carbonate and was obtained as prisms, m.p. 128° C, hydrochloride m.p. 340° C.

EXAMPLE 57.

N - *n* - Propyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 5 - methyl - 2 - hexyl) - tetrahydronorthebaine.

This was prepared by the method of Example 3 (a) from 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 5 - methyl - 2 - hexyl) - tetrahydronorthebaine, *n*-propyl iodide and sodium carbonate and was obtained as prisms m.p. 90° C, hydrochloride m.p. 220° C.

EXAMPLE 58.

N - Isobutyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 5 - methyl - 2 - hexyl) - tetrahydronorthebaine.

This was prepared by the method of Example 3 (a) from 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 5 - methyl - 2 - hexyl) - tetrahydronorthebaine, isobutyl bromide and sodium carbonate and was obtained as prisms m.p. 72° C, hydrochloride m.p. 301° C.

EXAMPLE 59.

N - 2 - Methylallyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 5 - methyl - 2 - hexyl) - tetrahydronorthebaine.

This was prepared by the method of Example 3 (a) from 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 5 - methyl - 2 - hexyl) - tetrahydronorthebaine, 2 - methylallyl bromide and sodium carbonate, it formed prisms m.p. 105° C.

EXAMPLE 60.

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

This was prepared by the method of Example 2 (b) from 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 5 - methyl - 2 - hexyl) - tetra - hydronorthebaine, potassium hydroxide and diethylene glycol at 210° C, so obtained the phenolic base had m.p. 262° C.

EXAMPLE 61.

N - 3, 3 - Dimethylallyl - 6, 14 - *endo* - etheno - 7α - (2 - hydroxy - 5 - methyl - 2 - hexyl) - tetrahydro - nororipavine.

This was prepared by the method of Example 3 (a) from 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 5 - methyl - 2 - hexyl) - tetrahydronororipavine, 3, 3 - dimethylallyl bromide and sodium carbonate using acetone as solvent and was obtained as colourless prisms m.p. 218° C.

The 3-acetyl ester was obtained by heating the phenolic base under reflux with acetic anhydride and anhydrous sodium acetate for 2 hours; isolated in the usual way this base was obtained as colourless prisms m.p. 152° C.

EXAMPLE 62.

N - Cyclopropylmethyl - 6, 14 - *endo* - etheno - 7α - (2 -hydroxy - 5 - methyl - 2 - hexyl) - tetrahydronororipavine.

This was prepared by the method of Example 5 from 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 5 - methyl - 2 - hexyl) - tetra - hydronororipavine and cyclopropylcarbonyl chloride followed by reduction with lithium aluminium hydride. Obtained in this way the base had m.p. 176° C.

EXAMPLE 63.

6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - decyl) - tetrahydronorthebaine.

This was prepared by the method of Example 1 from 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - decyl) - tetrahydrothebaine and cyanogen bromide followed by hydrolysis at 170° C. The intermediate N-cyano compound had m.p. 108° C and the secondary base could not be crystallised.

EXAMPLE 64.

N - 3, 3 - Dimethylallyl - 6, 14 - *endo* - etheno - 7α - (2 - hydroxy - 2 - decyl) - tetrahydronorthebaine.

This was prepared by the method of Example 3 (a) from 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - decyl) - tetrahydro - northebaine, 3, 3 - dimethylallyl bromide and sodium carbonate using acetone as solvent; obtained in this way the base formed prisms m.p. 96° C.

EXAMPLE 65.

6, 14 - *endo*etheno - 7α - (1 - hydroxy - 1 - cyclopentyl - 1 - ethyl) - tetra - hydronorthebaine.

This was prepared by the method of Example 1 from 6, 14 - *endo*etheno - 7α - (1 - hydroxy - 1 - cyclopentyl - 1 - ethyl) - tetra - hydrothebaine and cyanogen bromide followed by hydrolysis at 170° C; obtained in this way the intermediate N-cyano-compound had m.p. 210° C, and the secondary base had m.p. 110° C.

EXAMPLE 66.

N - 3, 3 - Dimethylallyl - 6, 14 - *endo* - etheno - 7α - (1 - hydroxy - 1 - cyclo - pentyl - 1 - ethyl) - tetrahydro - northebaine.

This was prepared by the method of Example 3 (a) from 6, 14 - *endo*etheno - 7α - (1 - hydroxyl - cyclopentyl - 1 - ethyl) - tetrahydronorthebaine, 3, 3 - dimethylallyl bromide and sodium carbonate using acetone as solvent, and in this way was obtained as prisms m.p. 112° C.

EXAMPLE 67.

6, 14 - *endo*etheno - 7α - (1 - hydroxy - 1 - cyclohexyl - 1 - ethyl) - tetra - hydronorthebaine.

This was prepared by the method of Example 1 from 6, 14 - *endo*etheno - 7α - (1 - hydroxy - 1 - cyclohexyl - 1 - ethyl) - tetra - hydrothebaine, and cyanogen bromide, followed by hydrolysis at 170° C. The intermediate N-cyano-compound had m.p. 213° C and the secondary base had m.p. 203° C.

EXAMPLE 68.

N - Allyl - 6, 14 - *endo*etheno - 7α - (1 - hydroxy - 1 - cyclohexyl - 1 - ethyl) - tetrahydronorthebaine.

This base was prepared by the method of Example 3 (a) from 6, 14 - *endo*etheno - 7α - (1 - hydroxy - 1 - cyclohexyl - 1 ethyl) - tetrahydronorthebaine, allyl bromide and sodium carbonate, and was obtained as colourless prisms m.p. 204° C.

EXAMPLE 69.

N - *n* - Propyl - 6, 14 - *endo*etheno - 7α - (1 - hydroxy - 1 - cyclohexyl - 1 - ethyl) - tetrahydronorthebaine.

When prepared as in Example 3 (a) from 6, 14 - *endo*etheno - 7α - (1 - hydroxy - 1 - cyclohexyl - 1 - ethyl) - tetrahydro - northebaine, *n*-propyl iodide and sodium carbonate this base was obtained as prisms m.p. 180° C.

EXAMPLE 70.

N - 2 - Methylallyl - 6, 14 - *endo*etheno - 7α - (1 - hydroxy - 1 - cyclohexyl - 1 - ethyl) - tetrahydronorthebaine.

When prepared as in Example 3 (a) from 6, 14 - *endo*etheno - 7α - (1 - hydroxy - 1 - cyclohexyl - 1 - ethyl) - tetrahydro - northebaine, 2 methylallyl bromide and sodium carbonate this base was obtained as crystals m.p. 203° C.

EXAMPLE 71.

N - 3, 3 - Dimethylallyl - 6, 14 - *endo* - etheno - 7α - (1 - hydroxy - 1 - cyclo - hexyl - 1 - ethyl) -tetrahydronorthe - baine.

When prepared as in Example 3 (a) from 6, 14 - *endo*etheno - 7α - (1 - hydroxy - 1 - cyclohexyl - 1 - ethyl) - tetrahydro - northebaine, 3, 3 - dimethylallyl bromide and sodium carbonate, using acetone as solvent, this base was obtained as prisms m.p. 190° C.

EXAMPLE 72.

N - Propargyl - 6, 14 - *endo*etheno - 7α - (1 - hydroxy - 1 - cyclohexyl - 1 - ethyl) - tetrahydronorthebaine.

When prepared as in Example 3 (a) from 6, 14 - *endo*etheno - 7α - (1 - hydroxy - 1 - cyclohexyl - 1 - ethyl) - tetrahydro - northebaine, propargyl bromide and sodium carbonate, this was obtained as prisms m.p. 172° C.

EXAMPLE 73.

N - Cyclopropylmethyl - 6, 14 - *endo* - etheno - 7α - (1 - hydroxy - 1 - cyclo - hexyl - 1 - ethyl) - tetrahydronorthe - baine.

The base was prepared as in Example 5 from 6, 14 - *endo*etheno - 7α - (1 - hydroxy - 1 - cyclohexyl - 1 - ethyl) - tetrahydro - northebaine and cyclopropylcarbonyl chloride, followed by reduction with lithium aluminium hydride, and was obtained as prisms m.p. 228° C; the intermediate amide had m.p. 220° C.

EXAMPLE 74.

N - 1 - Methylcyclopropylmethyl - 6, 14 - *endo*etheno - 7α - (1 - hydroxy - 1 - cyclohexyl - 1 - ethyl) - tetrahydro - northebaine.

This base was prepared by the general method of Example 5 from 6, 14 - *endo* - etheno - 7α (1 - hydroxy - 1 - cyclohexyl - 1 - ethyl) - tetrahydronorthebaine and 1 - methylcyclopropylcarbonyl chloride, followed by reduction with lithium aluminium hydride. So obtained it formed prisms m.p. 98° C; the intermediate amide had m.p. 258° C.

EXAMPLE 75.

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

This base was prepared as in Examples 1 and 2 (a) from 6, 14 - *endo*etheno - 7α - (1 - hydroxy - 1 - cyclohexyl - 1 - ethyl) - tetra - hydrothebaine by treatment with cyanogen bromide and hydrolysis at 210° C and also as in the method of Example 2 (b) by the demethylation of 6, 14 - *endo*etheno - 7α - (1 - hydroxy - 1 - cyclohexyl - 1 - ethyl) - tetrahydronorthebaine with potassium hydroxide and diethylene glycol at 210° C. It was obtained as prisms, m.p. 310° C from ethanol.

EXAMPLE 76.

N - Allyl - 6, 14 - *endo*etheno - 7α - (1 - hydroxy - 1 - cyclohexyl - 1 - ethyl) - tetrahydronororipavine.

When prepared by the method of Example 3 (a) from 6, 14 - *endo*etheno - 7α - (1 - hydroxy - 1 - cyclohexyl - 1 - ethyl) - tetra - hydronororipavine, allyl bromide and sodium carbonate, this base could not be crystallised but gave a crystalline hydrochloride m.p. 251° C.

EXAMPLE 77.

N - Propargyl - 6, 14 - *endo*etheno - 7α - (1 - hydroxy 1 - cyclohexyl - 1 - ethyl) - tetrahydronororipavine.

When prepared by the method of Example 3 (a) from 6, 14 - *endo*etheno - 7α - (1 - hydroxy - 1 - cyclohexyl - 1 - ethyl) - tetra - hydronororipavine, propargyl bromide and sodium carbonate this base could not be crystallised but gave a crystalline hydrochloride m.p. 202° C.

EXAMPLE 78.

N - *n* - Propyl - 6, 14 - *endo*etheno - 7α - (1 - hydroxy - 1 - cyclohexyl - 1 - ethyl) - tetrahydronororipavine.

This base was prepared by the general method of Example 3 (a) from 6, 14 - *endo* - etheno - 7α - (1 - hydroxy - 1 - cyclohexyl - 1 - ethyl) - tetrahydronororipavine, *n*-propyl iodide and sodium carbonate; it could not be crystallised but gave a crystalline hydrochloride m.p. 275° C.

EXAMPLE 79.

N - Cyclopropylmethyl - 6, 14 - *endo* - etheno - 7α - (1 - hydroxy - 1 - cyclo - hexyl - 1 - ethyl) - tetrahydronorori - pavine.

This base was prepared by the general method of Example 5 from 6, 14 - *endo* - etheno - 7α - (1 - hydroxy - 1 - cyclohexyl - 1 - ethyl) - tetrahydronororipavine and cyclopropylcarbonyl chloride, followed by reduction with lithium aluminium hydride. The intermediate amide had m.p. 268° C and the tetiary base was dimorphic; recovered from methanol it was obtained as needles m.p. 134° C which slowly changed to fine prisms m.p. 198° C. The hydrochloride had m.p. 180° C.

EXAMPLE 80.

6, 14 - *endo*etheno - 7α - (1 - cyclohexyl - 3 - hydroxy - 3 - butyl) - tetrahydro - northebaine.

6, 14 - *endo*etheno - 7α - (1 - cyclohexyl - 3 - hydroxy - 3 - butyl) - tetrahydro - thebaine was prepared by the general method given in British patent Specification No. 925723 from 6, 14 - *endo*etheno - 7 - acetyltetrahydrothebaine and cyclohexylethylmagnesium bromide. The base was demethylated at the nitrogen atom by reaction with cyanogen bromide and hydrolysis of the N-cyano-compound with potassium hydroxide and diethylene glycol at 170° C as described in Example 1. The base so obtained had m.p. 117° C.

EXAMPLE 81.

N - Allyl - 6, 14 - *endo*etheno - 7α - (1 - cyclohexyl - 3 - hydroxy - 3 - butyl) - tetrahydronorthebaine.

This was prepared by the method of Example 3 (a) from 6, 14 - *endo*etheno - 7α - (1 - cyclohexyl - 3 - hydroxy - 3 - butyl) - tetrahydronorthebaine, allyl bromide and sodium carbonate; it could not be crystallised but gave a crystalline hydrochloride m.p. 289° C.

EXAMPLE 82.

N - Allyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 1 - phenyl - 2 - propyl) - tetrahydronorthebaine.

This base was prepared by the general method of Example 3 (b) from N - Allyl - 6, 14 - *endo*etheno - 7 - acetyltetrahydro - northebaine (100 parts), magnesium (1.68 parts) and benzyl bromide (12 parts). The α-isomer was obtained through the hydrochloride (m.p. 225° C) as an uncrystallisable gum.

EXAMPLE 83.

6, 14 - *endo*etheno - 7α - (3 - hydroxy - 1 - phenyl - 3 - butyl) - tetrahydronorthebaine.

This base was prepared by the general method of Example 1 from 6, 14 - *endo* - etheno - 7α - (3 - hydroxy - 1 - phenyl - 3 - butyl) - tetrahydrothebaine and cyanogen bromide, followed by hydrolysis at 170° C. The intermediate N-cyano-compound had m.p. 98° C and the secondary base m.p. 138° C.

EXAMPLE 84.

N - Cyclopropylmethyl - 6, 14 - *endo* - etheno - 7α - (3 - hydroxy - 1 - phenyl - 3 - butyl) - tetrahydro - northebaine.

This base was prepared by the general method of Example 5 from 6, 14 - *endo* - etheno - 7α - (3 - hydroxy - 1 - phenyl - 3 - butyl) - tetrahydronorthebaine and cyclopropylcarbonyl chloride, followed by reduction with lithium aluminium hydride. The intermediate amide had m.p. 160° C and the tertiary base m.p. 189° C, hydrochloride m.p. 243° C.

EXAMPLE 85.

N - Allyl - 6, 14 - *endo*etheno - 7 - (4 - hydroxy - 4 - pent - 1 - enyl) - tetrahydronorthebaine.

This base was prepared as in Example 3 (b) from N - allyl - 6, 14 - *endo*etheno - 7 - acetyl - tetrahydronorthebaine (10 parts), magnesium (1.67 parts) and allyl bromide (8.5 parts). The α-isomer, isolated through its hydrochloride, m.p. 275° C, was an uncrystallisable gum; the β-isomer and its salts could not be crystallised.

EXAMPLE 86.

N - Allyl - 6, 14 - *endo*etheno - 7 - (6 - hydroxy - 6 - hept - 1 - enyl) - tetrahydronorthebaine.

This base was prepared as in Example 3 (b) from N - allyl - 6, 14 - *endo*etheno - 7 - acetyl - tetrahydronorthebaine (10 parts), magnesium (1.67 parts) and 1 - bromopent - 4 - ene (9.4 parts). The two isomers were both non-crystalline, but the α-isomer gave a crystalline bitartrate m.p. 239° C.

EXAMPLE 87.

N - Allyl - 6, 14 - *endo*etheno - 7 - (1 - ethoxy - 4 - hydroxy - 4 - pentyl) - tetrahydronorthebaine.

This base was prepared as in Example 3 (b) from N - allyl - 6, 14 - *endo*etheno - 7 - acetyltetrahydronorthebaine (10 parts), magnesium (1.67 parts) and 1 - chloro - 3 - ethoxy - propane (8.5 parts). The α-isomer had m.p. 113° C, hydrochloride m.p. 262° C, the β-isomer failed to crystallise.

EXAMPLE 88.

N - Allyl - 6, 14 - *endo*etheno - 7 - (5 - hydroxy - 1 - phenoxy - 5 - hexyl) - tetrahydronorthebaine.

This was prepared as in Example 3 (b) from N - allyl - 6, 14 - *endo*etheno - 7 - acetyltetrahydronorthebaine (10 parts), magnesium (1.67 parts) and 1 - bromo - 4 - penoxybutane (16.0 parts). The α-isomer had m.p. 136° C, hydrobromide m.p. 285° C; the β-isomer failed to crystallise.

EXAMPLE 89.

N - Allyl - 6, 14 - *endo*etheno - 7 - (4 - hydroxy - 1 - tetrahydrofuryl - 4 - pentyl) - tetrahydronorthebaine.

This base was prepared as in Example 3 (b) from N - allyl - 6, 14 - *endo*etheno - 7 - acetyltetrahydronorthebaine (10 parts), magnesium (1.67 parts) and 1 - bromo - 3 - tetrahydrofurylpropane (13.4 parts). The α-isomer had m.p. 72° C, hydrochloride m.p. 182° C, and the β-isomer failed to crystallise.

EXAMPLE 90.

6, 14 - *endo*etheno - 7α - (1 - hydroxy - 1 - *p* - tolyl - 1 - ethyl) - tetrahydro - northebaine.

This was prepared as in Example 1 from 6, 14 - endoetheno - 7α - (1 - hydroxy - 1 - *p* - tolyl - 1 - ethyl) - tetrahydrothebaine and cyanogen bromide, followed by hydrolysis with potassium hydroxide and diethylene glycol at 170° C. The intermediate N-cyano-compound had m.p. 210° C and the secondary base had m.p. 190° C.

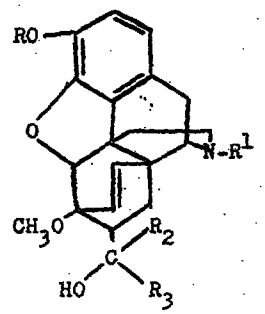
EXAMPLE 91.

N - Allyl - 6, 14 - *endo*etheno - 7α - (1 - hydroxy - 1 - *p* - tolyl - 1 - ethyl) - tetrahydronorthebaine.

This base was prepared as in Example 3 (a) from 6, 14 - *endo*etheno - 7α - (1 - hydroxy - 1 - *p* - tolyl - ethyl) - tetrahydro - northebaine (5 parts), allyl bromide (1.5 parts) and anhydrous sodium carbonate (5 parts); it was obtained as white prisms m.p. 201° C.

WHAT WE CLAIM IS:—

1. Compounds of the formula



in which formula R represents a hydrogen atom a methyl group, or an acyl group of composition $C_nH_{2n+1}CO-$ wherein n is an integer; R^1 represents a hydrogen atom or an alkyl group containing 2 to 8 carbon atoms, an alkenyl group containing 2 to 8 carbon atoms, a propargyl group, a cyclopropylmethyl group, a methyl cyclopropylmethyl group or a dimethyl cyclopropylmethyl group, R^2 represents a hydrogen atom, or alkyl group containing up to 3 carbon atoms or an aryl group, and R^3 represents a hydrogen atom, an alicyclic group containing 5, 6 or 7 carbon atoms or an alkyl or alkenyl group containing up to 8 carbon atoms which may be substituted on carbon atoms 1 to 4 by an alicyclic, aral, alkoxy or aryloxy group, or by a heterocyclic group containing oxygen, provided that when R represents a hydrogen atom or an acyl group or when R^1 represents a hydrogen atom, a cyclopropylmethyl, methyl cyclopropyl methyl or dimethyl cyclopropylmethyl group, R^3 does not contain the system —CH—aryl or —CH—C=C attached directly to the carbon atom bearing the alcoholic hydroxyl group, and salts of these bases with pharmaceutically acceptable acids.

2. 6, 14 - *endo*etheno - 7 - (2 - hydroxy - 2 - propyl) - tetrahydronorthebaine and salts thereof.

3. N - Allyl - 6, 14 - *endo*etheno - 7 - (2 - hydroxy - 2 - propyl) - tetrahydro - northebaine and salts thereof.

4. N - cyclopropylmethyl - 6, 14 - *endo* - etheno - 7 - (2 - hydroxy - 2 - propyl) - tetrahydronorthebaine and salts thereof.

5. N - *n* - Propyl - 6, 14 - *endo*etheno - 7 - (2 - hydroxy - 2 - propyl) - tetrahydro - northebaine and salts thereof.

6. N - Isobutyl - 6, 14 - *endo*etheno - 7 - (2 - hydroxy - 2 - propyl) - tetrahydro - northebaine and salts thereof.

7. N - 2 - Methylallyl - 6, 14 - *endo* - etheno - 7 - (2 - hydroxy - 2 - propyl) - ~~tetrahydronorthebain~~ and salts thereof.

8. N - 3, 3 - Dimethylallyl - 6, 14, *endo* - etheno - 7 - (2 - hydroxy - 2 - propyl) - tetrahydronorthebaine and salts thereof.

9. N - propargyl - 6, 14 - *endo*etheno - 7 - (2 - hydroxy - 2 - propyl) - tetrahydro - northebaine and salts thereof.

10. 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - butyl) - tetrahydronorthebaine and salts thereof.

11. N - allyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - butyl) - tetrahydro - northebaine and salts thereof.

12. N - *n* - propyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - butyl) - ~~tetrahydro - northebain~~ and salts thereof.

13. N - propargyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - butyl) - tetrahydronorthebaine and salts thereof.

14. N - isobutyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - butyl) - tetrahydro - northebaine and salts thereof.

15. N - 2 - methylallyl - 6, 14 - *endo* - etheno - 7α - (2 - hydroxy - 2 - butyl) - tetrahydronorthebaine and salts thereof.

16. N - 3 - methylallyl - 6, 14 - *endo* - etheno - 7α - (2 - hydroxy - 2 - butyl) - tetrahydronorthebaine and salts thereof.

17. N - 3, 3 - dimethylallyl - 6, 14 - *endo* - etheno - 7α - (2 - hydroxy - 2 - butyl) - tetrahydronorthebaine and salts thereof.

18. 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - pentyl) - tetrahydronorthebaine and salts thereof.

19. 6, 14 - *endo*etheno - 7β - (2 - hydroxy - 2 - pentyl) - tetrahydronorthebaine and salts thereof.

20. N - allyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - pentyl) - tetrahydro - northebaine and salts thereof.

21. N - allyl - 6, 14 - *endo*etheno - 7β - (2 - hydroxy - 2 - pentyl) - tetrahydro - northebaine and salts thereof.

22. N - *n* - propyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - pentyl) - tetrahydro - northebaine salts thereof.

23. N - *n* - propyl - 6, 14 - *endo*etheno - 7β - (2 - hydroxy - 2 - pentyl) - tetrahydro - northebaine and salts thereof.

EXAMPLE 90.

6, 14 - *endo*etheno - 7α - (1 - hydroxy - 1 - *p* - tolyl - 1 - ethyl) - tetrahydro - northebaine.

This was prepared as in Example 1 from 6, 14 - endoetheno - 7α - (1 - hydroxy - 1 - *p* - tolyl - 1 - ethyl) - tetrahydrothebaine and cyanogen bromide, followed by hydrolysis with potassium hydroxide and diethylene glycol at 170° C. The intermediate N-cyano-compound had m.p. 210° C and the secondary base had m.p. 190° C.

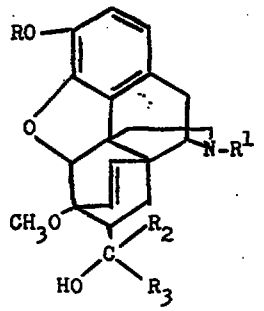
EXAMPLE 91.

N - Allyl - 6, 14 - *endo*etheno - 7α - (1 - hydroxy - 1 - *p* - tolyl - 1 - ethyl) - tetrahydronorthebaine.

This base was prepared as in Example 3 (a) from 6, 14 - *endo*etheno - 7α - (1 - hydroxy - 1 - *p* - tolyl - ethyl) - tetrahydro - northebaine (5 parts), allyl bromide (1.5 parts) and anhydrous sodium carbonate (5 parts); it was obtained as white prisms m.p. 201° C.

WHAT WE CLAIM IS:—

1. Compounds of the formula



in which formula R represents a hydrogen atom a methyl group, or an acyl group of composition $C_nH_{2n+1}CO-$ wherein n is an integer; R^1 represents a hydrogen atom or an alkyl group containing 2 to 8 carbon atoms, an alkenyl group containing 2 to 8 carbon atoms, a propargyl group, a cyclopropylmethyl group, a methyl cyclopropylmethyl group or a dimethyl cyclopropylmethyl group, R^2 represents a hydrogen atom, or alkyl group containing up to 3 carbon atoms or an aryl group, and R^3 represents a hydrogen atom, an alicyclic group containing 5, 6 or 7 carbon atoms or an alkyl or alkenyl group containing up to 8 carbon atoms which may be substituted on carbon atoms 1 to 4 by an alicyclic, aral, alkoxy or aryloxy group, or by a heterocyclic group containing oxygen, provided that when R represents a hydrogen atom or an acyl group or when R^1 represents a hydrogen atom, a cyclopropylmethyl, methyl cyclopropyl methyl or dimethyl cyclopropylmethyl group, R^3 does not contain the system —CH—aryl or —CH—C=C attached directly to the carbon atom bearing the alcoholic hydroxyl group, and salts of these bases with pharmaceutically acceptable acids.

2. 6, 14 - *endo*etheno - 7 - (2 - hydroxy - 2 - propyl) - tetrahydronorthebaine and salts thereof.

3. N - Allyl - 6, 14 - *endo*etheno - 7 - (2 - hydroxy - 2 - propyl) - tetrahydro - northebaine and salts thereof.

4. N - cyclopropylmethyl - 6, 14 - *endo* - etheno - 7 - (2 - hydroxy - 2 - propyl) - tetrahydronorthebaine and salts thereof.

5. N - *n* - Propyl - 6, 14 - *endo*etheno - 7 - (2 - hydroxy - 2 - propyl) - tetrahydro - northebaine and salts thereof.

6. N - Isobutyl - 6, 14 - *endo*etheno - 7 - (2 - hydroxy - 2 - propyl) - tetrahydro - northebaine and salts thereof.

7. N - 2 - Methylallyl - 6, 14 - *endo* - etheno - 7 - (2 - hydroxy - 2 - propyl) - ~~tetrahydronorthebain~~ and salts thereof.

8. N - 3, 3 - Dimethylallyl - 6, 14, *endo* - etheno - 7 - (2 - hydroxy - 2 - propyl) - tetrahydronorthebaine and salts thereof.

9. N - propargyl - 6, 14 - *endo*etheno - 7 - (2 - hydroxy - 2 - propyl) - tetrahydro - northebaine and salts thereof.

10. 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - butyl) - tetrahydronorthebaine and salts thereof.

11. N - allyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - butyl) - tetrahydro - northebaine and salts thereof.

12. N - *n* - propyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - butyl) - ~~tetrahydro - northebain~~ and salts thereof.

13. N - propargyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - butyl) - tetrahydronorthebaine and salts thereof.

14. N - isobutyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - butyl) - tetrahydro - northebaine and salts thereof.

15. N - 2 - methylallyl - 6, 14 - *endo* - etheno - 7α - (2 - hydroxy - 2 - butyl) - tetrahydronorthebaine and salts thereof.

16. N - 3 - methylallyl - 6, 14 - *endo* - etheno - 7α - (2 - hydroxy - 2 - butyl) - tetrahydronorthebaine and salts thereof.

17. N - 3, 3 - dimethylallyl - 6, 14 - *endo* - etheno - 7α - (2 - hydroxy - 2 - butyl) - tetrahydronorthebaine and salts thereof.

18. 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - pentyl) - tetrahydronorthebaine and salts thereof.

19. 6, 14 - *endo*etheno - 7β - (2 - hydroxy - 2 - pentyl) - tetrahydronorthebaine and salts thereof.

20. N - allyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - pentyl) - tetrahydro - northebaine and salts thereof.

21. N - allyl - 6, 14 - *endo*etheno - 7β - (2 - hydroxy - 2 - pentyl) - tetrahydro - northebaine and salts thereof.

22. N - *n* - propyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - pentyl) - tetrahydro - northebaine salts thereof.

23. N - *n* - propyl - 6, 14 - *endo*etheno - 7β - (2 - hydroxy - 2 - pentyl) - tetrahydro - northebaine and salts thereof.

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24. N - isobutyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - pentyl) - tetrahydro - northebaine and salts thereof.

25. N - isobutyl - 6, 14 - *endo*etheno - 7β - (2 - hydroxy - 2 - pentyl) - tetrahydro - northebaine and salts thereof.

26. N - propargyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - pentyl) - tetrahydro - northebaine and salts thereof.

27. N - propargyl - 6, 14 - *endo*etheno - 7β - (2 - hydroxy - 2 - pentyl) - tetrahydro - northebaine and salts thereof.

28. N - 2 - methylallyl - 6, 14 - *endo* - etheno - 7α - (2 - hydroxy - 2 - pentyl) - tetrahydronorthebaine and salts thereof.

29. N - 3, 3 - dimethylallyl - 6, 14 - *endo* - etheno - 7α - (2 - hydroxy - 2 - pentyl) - tetrahydronorthebaine and salts thereof.

30. N - cyclopropylmethyl - 6, 14 - *endo* - etheno - 7α - (2 - hydroxy - 2 - pentyl) - tetrahydronorthebaine and salts thereof.

31. 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - hexyl) - tetrahydronorthebaine and salts thereof.

32. N - allyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - hexyl) - tetrahydro - northebaine and salts thereof.

33. N - Propargyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - hexyl) - tetrahydro - northebaine and salts thereof.

34. 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 4 - methyl - 2 - pentyl) - tetrahydro - northebaine and salts thereof.

35. N - Allyl - 6, 14 - *endo*etheno 7α - (2 - hydroxy - 4 - methyl - 2 - pentyl) - tetrahydronorthebaine and salts thereof.

36. 6, 14 - *endo*etheno - 7β - (2 - hydroxy - 4 - methyl - 2 - pentyl) - tetrahydronorthe - baine and salts thereof.

37. N - 3, 3 - Dimethylallyl - 6, 14 - *endo*etheno - 7β - (2 - hydroxy - 4 - methyl - 2 - pentyl) - tetrahydronorthebaine and salts thereof.

38. 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - heptyl) - tetrahydronorthebain and salts thereof.

39. N - 2 - Methylallyl - 6, 14 - *endo* - etheno - 7α - (2 - hydroxy - 2 - heptyl) - tetrahydronorthebaine and salts thereof.

40. N - 3, 3 - Dimethylallyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - heptyl) - tetrahydronorthebaine and salts thereof.

41. N - 1 - Methylcyclopropylmethyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - heptyl) - tetrahydronorthebaine and salts thereof.

42. 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 5 - methyl - 2 - hexyl) - tetrahydronorthe - baine and salts thereof.

43. N - Allyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 5 - methyl - 2 - hexyl) - tetrahydronorthebaine and salts thereof.

44. N - Propargyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 5 - methyl - 2 - hexyl) - tetrahydronorthebaine and salts thereof.

45. N - *n* - Proyl - 6, - 14 - *endo*etheno - 7α - (2 - hydroxy - 5 - methyl - 2 - hexyl) - tetrahydronorthebaine and salts thereof.

46. N - Isobutyl - 6, - 14 - *endo*etheno - 7α - (2 - hydroxy - 5 - methyl - 2 - hexyl) - tetrahydronorthebaine and salts thereof.

47. N - 2 - Methylallyl - 6, 14 - *endo* - etheno - 7α - (2 - hydroxy - 5 - methyl - 2 - hexyl) - tetrahydronorthebaine and salts thereof.

48. 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - decyl) - tetrahydronorthebaine and salts thereof.

49. N - 3, 3 - Dimethylallyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - decyl) - tetrahydronorthebaine and salts thereof.

50. 6, 14 - *endo*etheno - 7α - (1 - hydroxy - 1 - cyclopentyl - 1 - ethyl) - tetrahydro - northebaine and salts thereof.

51. N - 3, 3 - Dimethylallyl - 6, 14 - *endo* - etheno - 7α - (1 - hydroxy - 1 - cyclopentyl - 1 - ethyl) - tetrahydronorthebaine and salts thereof.

52. 6, 14 - *endo*etheno - 7α - (1 - hydroxy - 1 - cyclohexyl - 1 - ethyl) - tetrahydronorthe - baine and salts thereof.

53. N - Allyl - 6, 14 - *endo*etheno - 7α - (1 - hydroxy - 1 - cyclohexyl - 1 - ethyl) - tetrahydronorthebaine and salts thereof.

54. N - *n* - Propyl - 6, 14 - *endo*etheno - 7α - (1 - hydroxy - 1 - cyclohexyl - 1 - ethyl) - tetrahydronorthebaine and salts thereof.

55. N - 2 - Methylallyl - 6, 14 - *endo* - etheno - 7α - (1 - hydroxy - 1 - cyclohexyl - 1 - ethyl) - tetrahydronorthebaine and salts thereof.

56. N - 3, 3 - Dimethylallyl - 6, 14 - *endo*etheno - 7α - (1 - hydroxy - 1 - cyclo - hexyl - 1 - ethyl) - tetrahydronorthebaine and salts thereof.

57. N - Propargyl - 6, 14 - *endo*etheno - 7α - (1 - hydroxy - 1 - cyclo - hexyl - 1 - ethyl) - tetrahydronorthebaine and salts thereof.

58. N - Cyclopropylmethyl - 6, 14 - *endo* - etheno - 7α - (1 - hydroxy - 1 - cyclohexyl - 1 - ethyl) - tetrahydronorthebaine and salts thereof.

59. N - 1 - Methylcyclopropylmethyl - 6, 14 - *endo*etheno - 7α - (1 - hydroxy - 1 - cyclohexyl - 1 - ethyl) - tetrahydronorthebaine and salts thereof.

60. 6, 14 - *endo*etheno - 7α - (1 - cyclo - hexyl - 3 - hydroxy - 3 - butyl) - tetrahydro - northebaine and salts thereof.

61. N - Allyl - 6, 14 - *endo*etheno - 7α - (1 - cyclohexyl - 3 - hydroxy - 3 - butyl) - tetrahydronorthebaine and salts thereof.

62. N - Allyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 1 - phenyl - 2 - propyl) - tetrahydronorthebaine and salts thereof.

63. 6, 14 - *endo*etheno - 7α - (3 - hydroxy - 1 - phenyl - 3 - butyl) - tetrahydronorthebaine and salts thereof.

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64. N - Cyclopropylmethyl - 6, 14 - *endo* - etheno - 7α - (3 - hydroxy - 1 - phenyl - 3 - butyl) - tetrahydronorthebaine and salts thereof.

65. N - Allyl - 6, 14 - *endo*etheno - 7 - (4 - hydroxy - 4 - pent - 1 - enyl) - tetra - hydronorthebaine and salts thereof.

66. N - Allyl - 6, 14 - *endo*etheno - 7 - (6 - hydroxy - 6 - hept - 1 - enyl) - tetra - hydronorthebaine and salts thereof.

67. N - Allyl - 6, 14 - *endo*etheno - 7 - (1 - ethoxy - 4 - hydroxy - 4 - pentyl) - tetrahydronorthebaine and salts thereof.

68. N - Allyl - 6, 14 - *endo*etheno - 7 - (5 - hydroxyl - 1 - phenoxy - 5 - hexyl) - tetrahydronorthebaine and salts thereof.

69. N - Allyl - 6, 14 - *endo*etheno - 7 - (4 - hydroxy - 1 - tetrahydrofuryl - 4 - pentyl) - tetrahydronorthebaine and salts thereof.

70. 6, 14 - *endo*etheno - 7α - (1 - hydroxy - 1 - *p* - tolyl - 1 - ethyl) - tetrahydronorthe - baine and salts thereof.

71. N - Allyl - 6, 14 - *endo*etheno - 7α - (1 - hydroxy - 1 - p - tolyl - 1 - ethyl) - tetrahydronorthebaine and salts thereof.

72. 6, 14 - *endo*etheno - 7 - (2 - hydroxy - 2 - propyl) - tetrahydronororipavine and salts thereof.

73. N - Allyl - 6, 14 - *endo*etheno - 7 - (2 - hydroxy - 2 - propyl) - tetrahydro - nororipavine and salts thereof.

74. N - Cyclopropylmethyl - 6, 14 - *endo* - etheno - 7 - (2 - hydroxy - 2 - propyl) - tetrahydronororipavine and salts thereof.

75. N - Propargyl - 6, 14 - *endo*etheno - 7 - (2 - hydroxy - 2 - propyl) - tetrahydro - nororipavine and salts thereof.

76. N - 3, 3 - Dimethylallyl - 6, 14 - *endo*etheno - 7 -(2 - hydroxy - 2 - propyl) - tetrahydronororipavine and salts thereof.

77. 6, 14 - *endo*etheno - 7 - hydroxy - methylnororipavine and salts thereof.

78. N - Allyl - 6, 14 - *endo*etheno - 7 - hydroxymethylnororipavine and salts thereof.

79. 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - pentyl) - tetrahydronororipavine and salts thereof.

80. N - Allyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - pentyl) - tetrahydronororipavine and salts thereof.

81. N - 3, 3 - Dimethylallyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - pentyl) - tetrahydronororipavine and salts thereof.

82. N - Cyclopropylmethyl - 6, 14 - *endo* - etheno - 7α - (2 - hydroxy - 2 - pentyl) - tetrahydronororipavine and salts thereof.

83. 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - hexyl) - tetrahydronororipavine and salts thereof.

84. N - Allyl - 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 2 - hexyl) - tetrahydronororipavine and salts thereof.

85. 6, 14 - *endo*etheno - 7α - (2 - hydroxy - 5 - methyl - 2 - hexyl) -tetrahydronororipavine and salts thereof.

86. N - 3, 3 - Dimethylallyl - 6, 14 - *endo* - etheno - 7α - (2 - hydroxy - 5 - methyl - 2 - hexyl) - tetrahydronororipavine and salts thereof.

87. N - Cyclopropylmethyl - 6, 14 - *endo* - etheno - 7α - (2 - hydroxy - 5 - methyl - 2 - hexyl) - tetrahydronororipavine and salts thereof.

88. 6, 14 - *endo*etheno - 7α - (1 - hydroxy - 1 - cyclohexyl - 1 - ethyl) - tetrahydronororipavine and salts thereof.

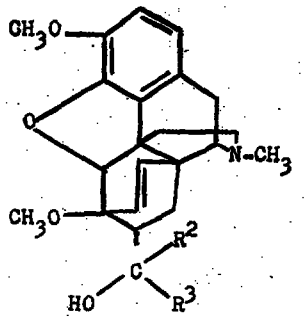
89. N - Allyl - 6, 14 - *endo*etheno - 7α - (1 - hydroxy - 1 - cyclohexyl - 1 - ethyl) - tetrahydronororipavine and salts thereof.

90. N - propargyl - 6, 14 - *endo*etheno - 7α - (1 - hydroxy - 1 - cyclohexyl - 1 - ethyl) - tetrahydronororipavine and salts thereof.

91. N - *n* - Propyl - 6, 14 - *endo*etheno - 7α - (1 - hydroxy - 1 - cyclohexyl - 1 - ethyl) - tetrahydronoripavine and salts thereof.

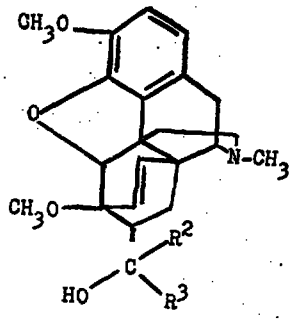
92. N - Cyclopropylmethyl - 6, 14 - *endo* - etheno - 7α - (1 - hydroxy - 1 - cyclohexyl - 1 - ethyl) - tetrahydronororipavine and salts thereof.

93. A process for the preparation of compounds claimed in claim 1 in which R is a methyl group and in which R^3 does not contain the system —CH—aryl or —CH—C=C linked directly to the carbon atom bearing the alcoholic hydroxyl group and R^1 and R^2 have the meanings given in claim 1 wherein a compound of the formula:



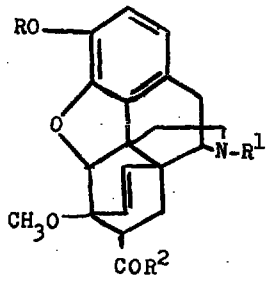
is treated with cyano bromide, the resulting N-cyano compound, is hydrolysed by heating in a solvent with an alkali metal hydroxide or alkoxide at temperatures up to 180° C, the resulting secondary amine is converted into a tertiary amine either by treatment with an alkyl, alkenyl, cycloalkyl or propargyl halide or by treatment with an acyl halide followed by reduction with lithium aluminium hydride.

94. A process for the preparation of compounds claimed in claim 1 in which R is a hydrogen atom and R^3 does not contain the system CH—aryl or CH—C=C attached directly to the carbon atom bearing the alcoholic hydroxyl group wherein a compound of the formula



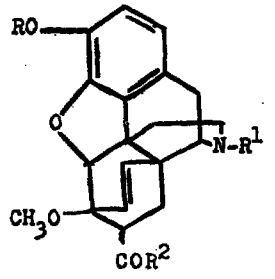
in which R^2 and R^3 have the meanings given in claim 1, is treated with cyanogen bromide, the resulting N-cyano compound is hydrolysed by heating in a solvent with an alkali metal hydroxide or alkoxide at temperatures above 180° C, the resulting secondary amine is converted into a tertiary amine either by treatment with an alkyl, alkenyl, cycloalkyl or propargyl halide or by treatment with an acyl halide followed by reduction with lithium aluminium hydride.

95. A process for the preparation of compounds claimed in claim 1 wherein compounds of the formula



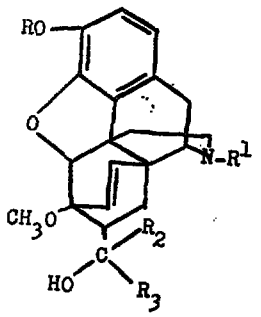
in which R is a methyl group, R^1 is one of n-propyl, isobutyl, allyl, methylallyl, dimethylallyl and propargyl and R^2 has the meaning given in claim 1, are treated with alkyl halides of formula R^3MgX wherein X represents a halogen atom and R^3 has the meaning given in claim 1.

96. A process for the preparation of compounds claimed in claim 1 wherein compounds of the formula



in which R^1 represents a methyl group and R and R^2 have the meanings given in claim 95 are treated with cyanogen bromide, the resulting N-cyano compound is hydrolysed by treatment with dilute mineral acid to give a substituted urea which is hydrolysed by sodium nitrite followed by ammonia giving a secondary amine which is alkylated by treatment with the appropriate alkyl halide R^1X wherein R^1 has the meaning given in claim 95 and X represents a halogen atom and the resulting ketone is reacted with a Grignard reagent of formula R^3MgX in which R^3 has the meaning given in claim 1 to give the tertiary alcohol.

97. A process for the preparation of compound of the formula



in which R represents an acyl group of formula $C_nH_{2n+1}CO-$, in which n is an integer and R^1, R^2 and R^3 have the meanings given in claim 1, wherein compounds of the above formula, in which R represents a hydrogen atom, are heated under reflux with an acid anhydride and an alkali metal salt of the corresponding acid.

98. A process for the preparation of compounds claimed in claim 1 wherein R represents an acyl group of the formula $C_nH_{2n+1}CO-$ in which n is an integer and R^1, R^2 and R^3 have the meanings given in claim 1, wherein a compound of the same formula in which R represents a hydrogen atom is heated with an aqueous solution of an alkali metal hydroxide and with a halide or the anhydride of an acid.

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

100. Compounds as claimed in claim 1 prepared by a process claimed in any of the preceding claims.

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