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PATENT SPECIFICATION

NO DRAWINGS

925,723

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Date of filing Complete Specification: Sept. 4, 1961.

Application Date: Sept. 5, 1960. No. 30566/60.

Complete Specification Published: May 8, 1963.

Index at acceptance:—Class 2(3), C3A7V1(A4:E2:J1), C3A13C(6C:7:9:10F:10G:10H).

International Classification:—C07d.

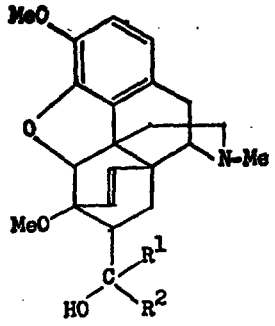
COMPLETE SPECIFICATION

Novel Thebaine 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 thebaine and to processes for their production.

Accordingly the present invention provides compounds of the general formula

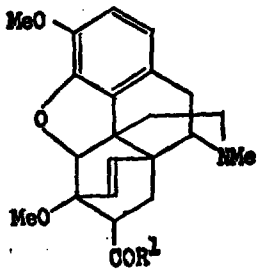


in which formula R^1 represents a hydrogen atom, an alkyl or alkenyl group containing up to 3 carbon atoms, or an aryl group, and R^2 represents an alicyclic group containing 5, 6 or 7 carbon atoms, or an alkyl or alkenyl group containing up to 8 carbon atoms which group may be substituted on carbon atoms 1 to 5 by an alicyclic, aryl, alkoxy, or aryloxy group or by a heterocyclic group containing oxygen.

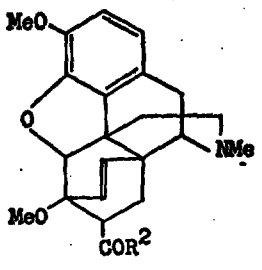
The invention also relates to salts of the above bases with pharmaceutically acceptable acids.

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 an aldehyde or ketone of general formula



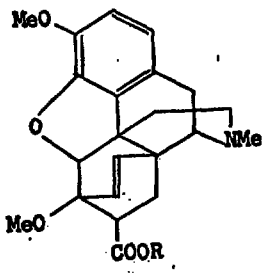
in which R^1 has the meaning given above is treated with a Grignard reagent R^2MgX or an organo lithium compound R^2Li in which R^2 has the meaning given above and X is a halogen atom, or wherein a ketone of general formula



in which R^2 has the meaning given above is treated with a compound R^1MgX or R^1Li in which R^1 has the meaning given above (excluding hydrogen) or is reduced for example with sodium borohydride, lithium aluminium hydride, aluminium isopropoxide or sodium amalgam, or, in the special case where

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$R^1 = R^2$ wherein an ester of general formula



in which R is an alkyl or aryl group is treated with a Grignard reagent R^1MgX where R^1 has the meaning given above.

Although the preferred organometallic compound used in the process of the invention is a Grignard reagent organo lithium compounds can be used instead.

Further, those familiar with the art will readily appreciate that during the production of those compounds of the invention in which R^1 and R^2 are different, a new asymmetric centre is generated, and that two diastereoisomers will result, generally, since other centres of dissymmetry are present, in unequal amounts.

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

EXAMPLE 1

6,14 - endo*Etheno* - *7* -(*1* - *hydroxy-1* - *ethyl*)*tetrahydrothebaine.*

(a) 10 parts of 6,14 - *endo*etheno - 7 - acetyltetrahydrothebaine were boiled with 20 parts of aluminium isopropoxide in 60 parts of isopropanol with slow distillation of the solvent through a fractionating column until the distillate no longer gave a precipitate with 2,4-dinitrophenylhydrazine in dilute hydrochloric acid. The mixture was then further rapidly evaporated to small bulk and poured in a thin stream into a vigorously stirred ice-cold solution of Rochelle salt containing crushed ice. The precipitated base was collected and washed well with water. When dry it had m.p. of 80°C., raised to 82°C. by recrystallisation from aqueous methanol.

(b) 10 parts of 6,14 - *endo*etheno - 7 - acetyltetrahydrothebaine were heated on the steam bath for 1 part of sodium borohydride in 50 parts of methanol for 30 minutes. The solution was concentrated, poured into water and the mixture extracted with ether. Evaporation of the dry ether extract afforded a colourless very viscous gum from which a small amount of the compound m.p. 82°C. described in (a) was obtained by crystallisation from ether at −70°C. The rest of the material remained uncrystallisable and was identified as a diastereoisomer by conversion into the O - acetyl derivative with acetic anhydride and pyridine, this derivative being obtained as white plates m.p. 170°C.

EXAMPLE 2

6,14 - endo*Etheno* - *7* -(*1* - *hydroxy-1* - *propyl*)*tetrahydrothebaine*

10 parts of 6,14 - *endo*etheno - 7 - formyltetrahydrothebaine in 150 parts of ether was added to a boiling stirred solution of ethylmagnesium bromide prepared from 1.70 parts of magnesium and 7.8 parts of ethyl bromide in 50 parts of ether. The mixture was then stirred and heated under reflux for one hour. The mixture was shaken with saturated ammonium chloride solution and the ether layer was separated, dried and evaporated leaving a highly viscous gum. This gum when treated with ethanolic hydrogen bromide afforded a crystalline hydrobromide, melting point 90°C. The base also gave a crystalline O - acetyl derivative m.p. 84°C. The second isomer was obtained as an uncharacterisable gum from the mother liquors of the preparation of the hydrobromide.

EXAMPLE 3

6,14 - endo*Etheno* - *7* -(*1* - *hydroxy-1* - *butyl*)*tetrahydrothebaine.*

This was prepared as described in Example 2 from 10 parts of 6,14 - *endo*etheno - 7-formyltetrahydrothebaine, 1.70 parts of magnesium and 5.60 parts of 1 - chloropropane. The α - isomer was a gum giving a bitartrate trihydrate m.p. 95°C. and an O - acetyl derivative m.p. 70°C. The β - isomer was non-crystalline.

EXAMPLE 4

6,14 - endo*Etheno* - *7* -(*1* - *hydroxy-1* - *nonyl*) - *tetrahydrothebaine.*

This was prepared as in Example 2 from 10 parts of 6,14 - *endo*etheno - 7 - formyltetrahydrothebaine, 1.70 parts of magnesium and 13.7 parts of 1 - bromo - *n* - octane. The α - isomer had m.p. 78°C.; the β-isomer was a gum.

EXAMPLE 5

6,14 - endo*Etheno* - *7* - (*cyclohexylhydroxymethyl*) - *tetrahydrothebaine.*

This base was prepared as in Example 2 from 10 parts of 6,14 - *endo*etheno - 7-formyltetrahydrothebaine, 1.70 parts of magnesium and 8.4 parts of 1 - chlorocyclohexane. The α - isomer had m.p. 98°C. and gave an O - ocetyl derivative m.p. 176 to 178°C. The β - isomer did not crystallise.

EXAMPLE 6

6,14 - endo*Etheno* - *7* - (*1* - *hydroxy* - *2-phenyl* - *1* - *ethyl*) - *tetrahydrothebaine* was prepared as in Example 2 from 10 parts of 6,14 - *endo*etheno - 7 - formyltetrahydrothebaine, 1.67 parts of magnesium and 12.1 parts of benzyl bromide. The α - isomer had m.p. 95°C. and gave a bitartrate dihydrate m.p. 125°C.; the β - isomer did not crystallise.

EXAMPLE 7

6,14 - endo*Etheno* - *7* - (*1* - *hydroxy-3* - *phenyl* - *1* - *propyl*) - *tetrahydrothebaine* was prepared as in Example 2 from 10 parts

of 6,14 - *endo*etheno - 7 - formyltetrahydrothebaine, 1.70 parts of magnesium and 13.8 parts of phenylethyl bromide. The α - isomer had m.p. 80°C. and gave a bitartrate dihydrate m.p. 140°C.; the β - isomer did not crystallise.

EXAMPLE 8

6,14 - endo*Etheno* - *7* - (*1* - *hydroxy-4* - *ethoxy* - *butyl*)*tetrahydrothebaine* was prepared as described in Example 2 from 10 parts of 6,14 - *endo*etheno - 7 - formyltetrahydrothebaine, 1.7 parts of magnesium and 8.7 parts of 1 - chloro - 3 - ethoxypropane. The α and β - isomers were oils but the α - isomer gave a bitartrate trihydrate m.p. 100°C.

EXAMPLE 9

6,14 - endo*Etheno* - *7* - (*1* - *hydroxy-4* - *tetrahydrofuryl* - *1* - *butyl*) - *tetrahydrothebaine* was prepared as described in Example 2 from 10 parts of 6,14 - *endo*etheno - 7-formyltetrahydrothebaine, 1.70 parts of magnesium and 13.7 parts of 1 - bromo - 3 - tetrahydrofurylpropane. The α - isomer had m.p. 114°C. and the β - isomer was non-crystalline.

EXAMPLE 10

6,14 - endo*Etheno* - *7* - (*2* - *hydroxy-2* - *propyl*) - *tetrahydrothebaine.*

(a) 10 parts 6,14 - *endo*etheno - 7 - acetyltetrahydrothebaine was extracted from a Soxhlet extractor into a boiling stirred solution of methylmagnesium iodide, prepared from 1.67 parts of magnesium and 9.9 parts of methyl iodide in 40 parts of ether and the mixture was stirred and heated under reflux for a further one hour. The mixture was then shaken with saturated ammonium chloride solution and the ether layer was separated, dried and evaporated, leaving the crystalline base m.p. 159°C. raised to 161°C. on recrystallisation from aqueous methanol.

(b) 10 parts of 6,14 - *endo*etheno - 7-ethoxycarbonyltetrahydrothebaine in ether was extracted from a Soxhlet extractor into a boiling stirred solution of methylmagnesium iodide, prepared from 2.30 parts of magnesium, 13.6 parts of methyl iodide and 80 parts of ether, and the mixture was stirred and heated under reflux for a further three hours. The mixture was then shaken with saturated ammonium chloride solution and the ether layer was separated, dried and evaporated leaving the crystalline base, m.p. 161°C. on recrystallisation from aqueous methanol, m.p. undepressed on mixing with material as in (a).

EXAMPLE 11

6,14 - endo*Etheno* - *7* - (*2* - *hydroxy-2* - *butyl*)*tetrahydrothebaine* was prepared by the method described in Example 10 (a) from 10 parts of 6,14 - *endo*etheno - 7-acetyltetrahydrothebaine, 1.67 parts of magnesium and 10.9 parts of iodoethane. Evaporation of the ether afforded a viscous gum that crystallised in part on trituration with methanol. The α - isomer so obtained had m.p. 132°C. and gave a hydrochloride m.p. 245°C. The β - isomer, recovered from the methanol solution failed to crystallise.

EXAMPLE 12

6,14 - endo*Etheno* - *7* - (*2* - *hydroxy-2* - *pentyl*) - *tetrahydrothebaine* was prepared by the method described in Example 10 (a) from 10 parts of 6,14 - *endo*etheno - 7-acetyltetrahydrothebaine, 1.67 parts of magnesium and 11.7 parts of 1 - iodopropane. The residue from the evaporation of the ether afforded the α - isomer on trituration with methanol; this had m.p. 176°C. and gave a hydrochloride m.p. 217°C. The β-isomer crystallised when the methanolic mother liquors were diluted with twice their volume of water and the liquid decanted after five minutes from a quantity of gummy material. It had m.p. 81° and gave a hydrochloride m.p. 240°C.

EXAMPLE 13

6,14 - endo*Etheno* - *7* - (*2* - *hydroxy-3* - *methyl* - *2* - *butyl*) - *tetrahydrothebaine.* This was prepared as described in Example 10 (a) from 10 parts of 6,14 - *endo*etheno-7 - acetyltetrahydrothebaine, 1.67 parts of magnesium and 11.7 parts of 2 - iodopropane. Trituration with methanol of the residue from evaporation of the ether afforded the α-isomer as crystals m.p. 92°C., giving a hydrochloride m.p. 248°C. The β - isomer recovered from the methanolic liquor was not crystalline.

EXAMPLE 14

6,14 - endo*Etheno* - *7* - (*2* - *hydroxy-2* - *hexyl*) - *tetrahydrothebaine.* This was prepared as described in Example 10 (a) from 10 parts of 6,14 - *endo*etheno - 7 - acetyltetrahydrothebaine, 1.67 parts of magnesium and 9.5 parts of 1 - bromobutane. The α-isomer had m.p. 150°C. and the β - isomer (from the mother liquors) m.p. 89°C.

EXAMPLE 15

6,14 - endo*Etheno* - *7* - (*2* - *hydroxy-4* - *methyl* - *2* - *pentyl*) - *tetrahydrothebaine.* This was prepared as in Example 10 (a) from 10 parts of 6,14 - *endo*etheno - 7 - acetyltetrahydrothebaine, 1.67 parts of magnesium and 9.5 parts of 1 - bromo - 2 - methylpropane (isobutyl bromide). The α - isomer had m.p. 152°C. and the β - isomer 82°C., the hydrochlorides had m.p.s. 188°C. and 250°C. respectively.

EXAMPLE 16

6,14 - endo*Etheno* - *7* - (*2* - *hydroxy-3,3* - *dimethyl* - *2* - *butyl*) - *tetrahydrothebaine.* This was obtained as described in Example 10 (a) from 10 parts of 6,14 - *endo*etheno - 7 - acetyl - tetrahydrothebaine, 1.67 parts of magnesium and 12.7 parts of 2 - iodo-2 - methylpropane (*tert.*butyl iodide). The α-isomer had m.p. 110°C. the β-isomer failed to crystallise.

EXAMPLE 17

6,14 - endo*Etheno* - *7* - (*2* - *hydroxy-2* - *heptyl*) - *tetrahydrothebaine*. 10 parts of 6,14 - *endo*etheno - 7 - acetyltetrahydrothebaine was extracted from a Soxhlet extractor into a boiling stirred solution of *n*-amylmagnesium iodide, prepared from 1.67 parts of magnesium and 10.7 parts of *n*-amylbromide. The mixture was stirred and heated under reflux for a further period of one hour, after which it was cooled and shaken with dilute acetic acid until the aqueous layer remained permanently acid, in order to separate basic material from any excess of amyl bromide. The acid layer was made alkaline with ammonia and the base extracted with ether. The ether layer was separated, dried and evaporated, leaving a viscous gum that on trituration with methanol afforded the α - isomer m.p. 103°C., hydrochloride m.p. 250°C. The β - isomer, obtained from the methanol solution failed to crystallise.

EXAMPLE 18

6,14 - endo*Etheno* - *7* - (*2* - *hydroxy-5* - *methyl* - *2* - *hexyl*) - *tetrahydrothebaine*. This was obtained by the method of Example 17 from 10 parts of 6,14 - *endo*etheno - 7-acetyltetrahydrothebaine, 1.67 parts of magnesium and 10.7 parts of 1 - bromo - 3-methylbutane (isoamyl bromide). The α-isomer had m.p. 126°C., its hydrochloride m.p. 258°C., the β - isomer m.p. 80°C. and its hydrochloride 190°C.

EXAMPLE 19

6,14 - endo*Etheno* - *7* - (*2* - *hydroxy-3,3* - *dimethyl* - *2* - *pentyl*) - *tetrahydrothebaine*. This was obtained by the method described in Example 17 from 10 parts of 6,14 - endoetheno - 7 - ~~acetyltetrahydrothebaine~~, 1.67 parts of magnesium and 13.5 parts of 2 - iodo - 2 - methylbutane. The isomers were non-crystalline and separation was not effected.

EXAMPLE 20

6,14 - endo*Etheno* - *7* - (*2* - *hydroxy-2* - *octyl*) - *tetrahydrothebaine*. This was prepared as described in Example 17 from 10 parts of 6,14 - *endo*etheno - 7 - acetyltetrahydrothebaine, 1.67 parts of magnesium and 11.5 parts of 1 - bromohexane. The α-isomer had m.p. 65°C. and gave a hydrochloride m.p. 270°C.; the β-isomer was not crystalline.

EXAMPLE 21

6,14 - endo*Etheno* - *7* - (*2* - *hydroxy-2* - *nonyl*) - *tetrahydrothebaine*. This was prepared as in Example 17 from 10 parts of 6,14 - *endo*etheno - 7 - acetyltetrahydrothebaine, 1.67 parts of magnesium and 12.2 parts of 1 - bromoheptane. Both α and β-isomers were non-crystalline but the α-isomer afforded a crystalline hydrochloride m.p. 245°C.

EXAMPLE 22

6,14 - endo*Etheno* - *7* - (*2* - *hydroxy-2* - *decyl*) - *tetrahydrothebaine*. This was prepared as described in Example 17 from 10 parts of 6,14 - *endo*etheno - 7 - acetyltetrahydrothebaine, 1.67 parts of magnesium and 13.5 parts of 1 - bromo - octane. The α-isomer had m.p. 79°C. and gave a hydrochloride m.p. 262°C.; the β-isomer did not crystallise.

EXAMPLE 23

6,14 - endo*Etheno* - *7* - (*1* - *hydroxy-1* - *cyclopentyl* - *1* - *ethyl*) - *tetrahydrothebaine*. This was prepared as described in Example 17 from 10 parts of 6,14 - *endo*etheno - 7 - acetyltetrahydrothebaine, 1.67 parts of magnesium and 10.5 parts of 1-bromocyclopentane. The α - isomer had m.p. 86°C. and gave a hydrochloride m.p. 240°C. The β - isomer did not crystallise.

EXAMPLE 24

6,14 - endo*Etheno* - *7* - (*1* - *hydroxy-1* - *cyclohexyl* - *1* - *ethyl*) - *tetrahydrothebaine*. This was prepared as described in Example 17 from 10 parts of 6,14 - *endo*etheno - 7-acetyltetrahydrothebaine, 1.67 parts of magnesium and 9.7 parts of 1 - chlorocyclohexane. The α - isomer had m.p. 201°C. hydrochloride 208°C. and the β - isomer m.p. 172°C., hydrochloride 183°C.

EXAMPLE 25

6,14 - endo*Etheno* - *7* - (*2* - *hydroxy-1* - *phenyl* - *2* - *propyl*) - *tetrahydrothebaine*. This base was obtained as described in Example 17 from 10 parts of 6,14 - *endo*etheno - 7 - acetyltetrahydrothebaine, 1.68 parts of magnesium and 12 parts of benzyl bromide. The α - isomer had m.p. 187°C.; the β - isomer failed to crystallise.

EXAMPLE 26

6,14 - endo*Etheno* - *7* - (*2* - *hydroxy-1* - p - *methoxyphenyl* - *2* - *propyl*) - *tetrahydrothebaine*. This was prepared as described in Example 17 from 10 parts of 6,14-*endo*etheno - 7 - acetyltetrahydrothebaine, 1.67 parts of magnesium and 12 parts of *p*-methoxybenzylchloride. The α - isomer had m.p. 117°C., hydrochloride m.p. 240°C.; the β - isomer had m.p. 99°C., (hydrochloride was not crystalline).

EXAMPLE 27

6,14 - endo*Etheno* - *7* - (*3* - *hydroxy-1* - *phenyl* - *3* - *butyl*) - *tetrahydrothebaine*. This was prepared as described in Example 17 from 10 parts of 6,14 - *endo*etheno - 7-acetyltetrahydrothebaine, 1.67 parts of magnesium and 12.8 parts of 2 - phenylethyl bromide. The α - isomer had m.p. 145°C., hydrochloride m.p. 236°C.; the β - isomer had m.p. 92°C., hydrochloride m.p. 180°C.

EXAMPLE 28

6,14 - endo*Etheno* - *7* - (*4* - *hydroxy-1* - *phenyl* - *4* - *pentyl*) - *tetrahydrothebaine*. This was prepared as described in Example 17 from 10 parts of 6,14 - *endo*etheno - 7-

acetyltetrahydrothebaine, 1.67 parts of magnesium and 13.7 parts of 1 - bromo - 3-phenylpropane. The α - isomer had m.p. 117°C., hydrochloride 248°C.; the β - isomer had m.p. 94°C., hydrochloride 235°C.

EXAMPLE 29

6,14 - endo*Etheno* - *7* - (*4* - *hydroxy-4* - *pent* - *1* - *enyl*) - *tetrahydrothebaine*. This was prepared as described in Example 17 from 10 parts of 6,14 - ~~*endotheno*~~ - 7 - acetyltetrahydrothebaine, 1.67 parts of magnesium and 8.5 parts of allyl bromide. The α - isomer had m.p. 160°C., hydrochloride m.p. 260°C. and the β - isomer m.p. 126°C., (hydrochloride was not crystalline).

EXAMPLE 30

6,14 - endo*Etheno* - *7* - (*3* - *hydroxy-1* - *phenyl* - *3* - *but* - *1* - *enyl*) - *tetrahydrothebaine*. This base was prepared as described in Example 17 from 10 parts of 6,14 - *endo*etheno - 7 - acetyltetrahydrothebaine, 1.67 parts of magnesium and 12.7 parts of β-styryl bromide. The α - isomer had m.p. 92°C., hydrochloride 248°C., the minor β-isomer failed to crystallise.

EXAMPLE 31

6,14 - endo*Etheno* - *7* - (*1* - *ethoxy-4* - *hydroxy* - *4* - *pentyl*) - *tetrahydrothebaine*. This was prepared as described in Example 17 from 10 parts of 6,14 - *endo*etheno - 7-acetyltetrahydrothebaine, 1.67 parts of magnesium and 8.5 parts of 1 - chloro - 3-ethoxypropane. The α - isomer had m.p. 107°C., hydrochloride 248°C. The minor β-isomer failed to crystallise.

EXAMPLE 32

6,14 - endo*Etheno* - *7* - (*5* - *hydroxy-1* - *phenoxy* - *hexyl*) - *tetrahydrothebaine*. This was prepared as described in Example 17 from 10 parts of 6,14 - *endo*etheno - 7 - acetyltetrahydrothebaine, 1.67 parts of magnesium and 16.0 parts of 1 - bromo - 4 - phenoxybutane. The α - isomer had m.p. 221°C., hydrochloride m.p. 260°C., the β - isomer had m.p. 116°C., hydrohloride m.p. 240°C.

EXAMPLE 33

6,14 - endo*Etheno* - *7* - (*2* - *hydroxy-1* - *tetrahydrofuryl* - *2* - *propyl*) - *tetrahydrothebaine*. This was prepared as described in Example 17 from 10 parts of 6,14 - *endo*etheno - 7 - acetyltetrahydrothebaine, 1.67 parts of magnesium and 11.5 parts of tetrahydrofurfuryl bromide. The α - isomer was crystallised with great difficulty; it had m.p. 140°C.; β - isomer failed to crystallise.

EXAMPLE 34

6,14 - endo*Etheno* - *7* - (*4* - *hydroxy-1* - *tetrahydrofuryl* - *4* - *pentyl*) - *tetrahydrothebaine*. This was prepared as described in Example 17 from 10 parts of 6,14 - *endo*etheno - 7 - acetyltetrahydrothebaine 1.67 parts of magnesium and 13.4 parts of 1-bromo - 3 - tetrahydrofurylpropane. The α-isomer had m.p. 128°C., hydrochloride m.p. 185°C.; the β - isomer failed to crystallise.

EXAMPLE 35

6,14 - endo*Etheno* - *7* - (*1* - *hydroxy-1* - *phenyl* - *1* - *ethyl*) - *tetrahydrothebaine*. (a) This was prepared by the method of Example 17 from 10 parts of 6,14 - *endo*etheno - 7 - acetyltetrahydrothebaine, 1.67 parts of magnesium and 11.0 parts of bromobenzene. The α - isomer had m.p. 254°C., hydrochloride m.p. 194°C.; the minor β-isomer had m.p. 208°C., hydrochloride m.p. 230°C.

(b) The bases were also prepared according to Example 10 (a) from 10 parts of 6,14-*endo*ethene - 7 - benzoyltetrahydrothebaine, 1.44 parts of magnesium and 9.9 parts of methyl iodide. In this reaction the major product was the β - isomer, the α - isomer being the minor product.

EXAMPLE 36

6,14 - endo*Etheno* - *7* - (*3* - *hydroxy-3* - *pentyl*) - *tetrahydrothebaine*. This was prepared essentially as described in Example 10 (b) from 10 parts of 6,14 - *endo*etheno-7 - ethoxycarbonyltetrahydrothebaine, 2.30 parts of magnesium and 10.5 parts of ethyl bromide. Removal of the ether left a viscous gum that crystallised in part on trituration with methanol. The crystalline material was collected and recrystallised from methanol when the base was obtained as white prisms m.p. 152°C., bitartrate 130°C.

EXAMPLE 37

6,14 - endo*Etheno* - *7* - (*4* - *hydroxy-4* - *heptyl*) - *tetrahydrothebaine*. This was prepared essentially as in Example 10 (b) from 10 parts of 6,14 - *endo*etheno - 7 - ethoxycarbonyltetrahydrothebaine, 2.30 parts of magnesium and 16.3 parts of 1 - iodopropane. Trituration with methanol of the residue after evaporation of the ether afforded the base m.p. 209°C. On recrystallisation from aqueous 2 - ethoxyethanol; the bitartrate had m.p. 186°C.

EXAMPLE 38

6,14 - endo*Etheno* - *7* - (*1* - *hydroxy-1* - *phenyl* - *1* - *butyl*) - *tetrahydrothebaine*. This was prepared as described in Example 17 from 10 parts of 6,14 - *endo*etheno - 7-benzoyltetrahydrothebaine, 1.44 parts of magnesium and 10.2 parts of 1 - iodopropane. The product had m.p. 177°C., hydrochloride m.p. 210°C. The second isomer was not detected.

EXAMPLE 39

6,14 - endo*Etheno* - *7* - (*cyclohexylphenyl-hydroxymethyl*) - *tetrahydrothebaine*. This was

prepared as described in Example 17 from 10 parts of 6,14 - *endo*etheno - 7 - benzoyltetrahydrothebaine, 1.44 parts of magnesium and 7.15 parts of chlorocyclohexane. The base had m.p. 232°C. and the hydrochloride m.p. 239°C.

EXAMPLE 40

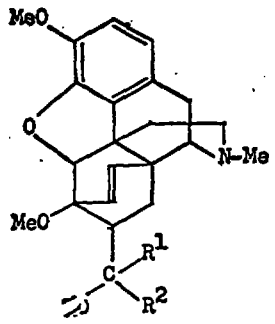
6,14 - endo*Etheno* - *7* - *(1* - *hydroxy-1,2* - *diphenyl* - *1* - *ethyl)* - *tetrahydrothebaine.* This was prepared as described in Example 17 from 10 parts of 6,14 - *endo*etheno - 7 - benzoyltetrahydrothebaine, 1.44 parts of magnesium and 10.3 parts of benzyl bromide. The base had m.p. 210°C. and the hydrochloride m.p. 220°C.

EXAMPLE 41

6,14 - endo*Etheno* - *7* - *(1* - *phenyl-1* - *hydroxy* - *1* - *but* - *3* - *enyl)* - *tetrahydrothebaine.* This was prepared as described in Example 17 from 10 parts of 6,14-*endo*etheno - 7 - benzoyltetrahydrothebaine, 1.44 parts of magnesium and 7.3 parts of allyl bromide. The base had m.p. 198°C., hydrochloride m.p. 210°C.

WHAT WE CLAIM IS:—

1. Compounds of the general formula



in which formula R^1 represents a hydrogen atom, an alkyl or alkenyl group containing up to 3 carbon atoms, or an aryl group, and R^2 represents an alicyclic group containing 5, 6 or 7 carbon atoms, or 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, aryl, alkoxy or aryloxy group or by a heterocyclic group containing oxygen.

2. Salts of the compounds claimed in claim 1 with pharmaceutically acceptable acids.

3. 6,14 - *endo*Etheno - 7 - (2 - hydroxy-2 - pentyl) - tetrahydrothebaine.

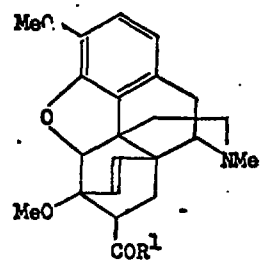
4. 6,14 - *endo*Etheno - 7 - (2 - hydroxy-2 - heptyl) - tetrahydrothebaine.

5. 6,14 - *endo*Etheno - 7 (2 - hydroxy-1 - phenyl - 2 - propyl) - tetrahydrothebaine.

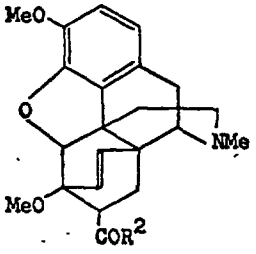
6. 6,14 - *endo*Etheno - 7 (3 - hydroxy-1 - phenyl - 3 - butyl) - tetrahydrothebaine.

7. 6,14 - *endo*Etheno - 7 - (4 - hydroxy-1 - tetrahydrofuryl - 4 - pentyl) - tetrahydrothebaine.

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



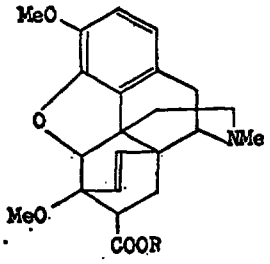
in which formula R^1 has the meaning defined in claim 1 with a Grignard reagent or organolithium compound of the formula R^2MgX or R^2Li in which R^2 has the meaning defined in claim 1 and X represents a halogen atom or reducing a compound of the general formula



in which formula R^2 has the meaning defined in claim 1 or reacting a compound of this second formula with a Grignard reagent or organolithium compound of the formula R^1MgX or R^1Li in which R^1 has the meaning defined in claim 1 (excluding hydrogen) and X is a halogen atom.

9. A process as claimed in claim 8 wherein the reduction is carried out with sodium borohydride, lithium aluminium hydride, aluminium isopropoxide or sodium amalgam.

10. A modification of the process claimed in claim 8 for the preparation of compounds as claimed in claim 1 in which R^1 has the same meaning as R^2 wherein a compound of the general formula



in which R is an alkyl group or an aryl group is reacted with a Grignard reagent or organo

prepared as described in Example 17 from 10 parts of 6,14 - *endo*etheno - 7 - benzoyltetrahydrothebaine, 1.44 parts of magnesium and 7.15 parts of chlorocyclohexane. The base had m.p. 232°C. and the hydrochloride m.p. 239°C.

EXAMPLE 40

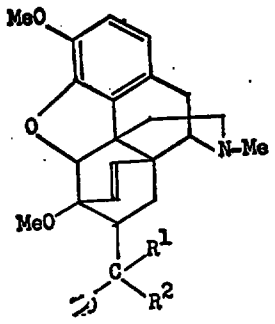
6,14 - endo*Etheno* - *7* - (*1* - *hydroxy-1,2* - *diphenyl* - *1* - *ethyl*) - *tetrahydrothebaine*. This was prepared as described in Example 17 from 10 parts of 6,14 - *endo*etheno - 7 - benzoyltetrahydrothebaine, 1.44 parts of magnesium and 10.3 parts of benzyl bromide. The base had m.p. 210°C. and the hydrochloride m.p. 220°C.

EXAMPLE 41

6,14 - endo*Etheno* - *7* - (*1* - *phenyl-1* - *hydroxy* - *1* - *but* - *3* - *enyl*) - *tetrahydrothebaine*. This was prepared as described in Example 17 from 10 parts of 6,14-*endo*etheno - 7 - benzoyltetrahydrothebaine, 1.44 parts of magnesium and 7.3 parts of allyl bromide. The base had m.p. 198°C., hydrochloride m.p. 210°C.

WHAT WE CLAIM IS:—

1. Compounds of the general formula



in which formula R^1 represents a hydrogen atom, an alkyl or alkenyl group containing up to 3 carbon atoms, or an aryl group, and R^2 represents an alicyclic group containing 5, 6 or 7 carbon atoms, or 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, aryl, alkoxy or aryloxy group or by a heterocyclic group containing oxygen.

2. Salts of the compounds claimed in claim 1 with pharmaceutically acceptable acids.

3. 6,14 - *endo*Etheno - 7 - (2 - hydroxy-2 - pentyl) - tetrahydrothebaine.

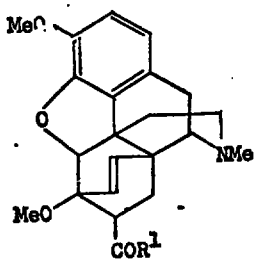
4. 6,14 - *endo*Etheno - 7 - (2 - hydroxy-2 - heptyl) - tetrahydrothebaine.

5. 6,14 - *endo*Etheno - 7 (2 - hydroxy-1 - phenyl - 2 - propyl) - tetrahydrothebaine.

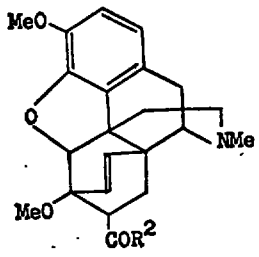
6. 6,14 - *endo*Etheno - 7 (3 - hydroxy-1 - phenyl - 3 - butyl) - tetrahydrothebaine.

7. 6,14 - *endo*Etheno - 7 - (4 - hydroxy-1 - tetrahydrofuryl - 4 - pentyl) - tetrahydrothebaine.

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



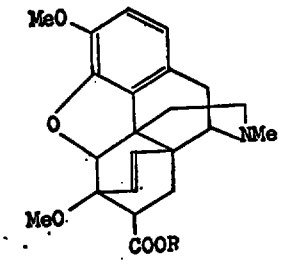
in which formula R^1 has the meaning defined in claim 1 with a Grignard reagent or organolithium compound of the formula R^2MgX or R^2Li in which R^2 has the meaning defined in claim 1 and X represents a halogen atom or reducing a compound of the general formula



in which formula R^2 has the meaning defined in claim 1 or reacting a compound of this second formula with a Grignard reagent or organolithium compound of the formula R^1MgX or R^1Li in which R^1 has the meaning defined in claim 1 (excluding hydrogen) and X is a halogen atom.

9. A process as claimed in claim 8 wherein the reduction is carried out with sodium borohydride, lithium aluminium hydride, aluminium isopropoxide or sodium amalgam.

10. A modification of the process claimed in claim 8 for the preparation of compounds as claimed in claim 1 in which R^1 has the same meaning as R^2 wherein a compound of the general formula



in which R is an alkyl group or an aryl group is reacted with a Grignard reagent or organo

lithium compound of the formula R^1MgX or R^1Li in which R^1 and X have the meanings defined in claim 8.

11. A process for the production of the compounds claimed in claim 1 substantially as described.

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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.

ERRATA

SPECIFICATION NO. 925,723

Page 4, line 39, *for* "actyltetrahydrothebaire" *read* "acetyltetrahydrothebaine"

Page 5, line 10, *for* "*endo*theno" *read* "*endoe*theno"

THE PATENT OFFICE,
19th June 1963

DS 74851/1(14)/R.109 200 6/63 PL

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