

PATENT SPECIFICATION

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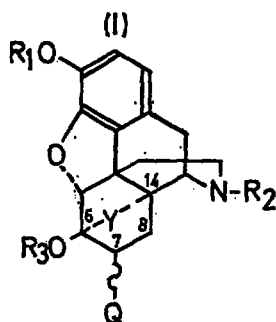
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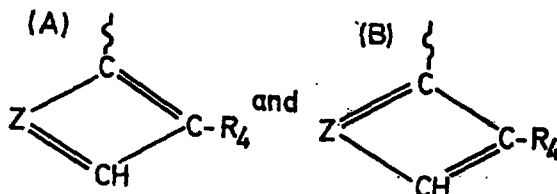
(54) 7-HETEROCYCLIC CODIDES AND MORPHIDES

(71) We, AMERICAN CYANAMID COMPANY, a corporation organised and existing under the laws of the State of Maine, United States of America, of Berdan Avenue, Township of Wayne, State of New Jersey, United States of America, 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:—

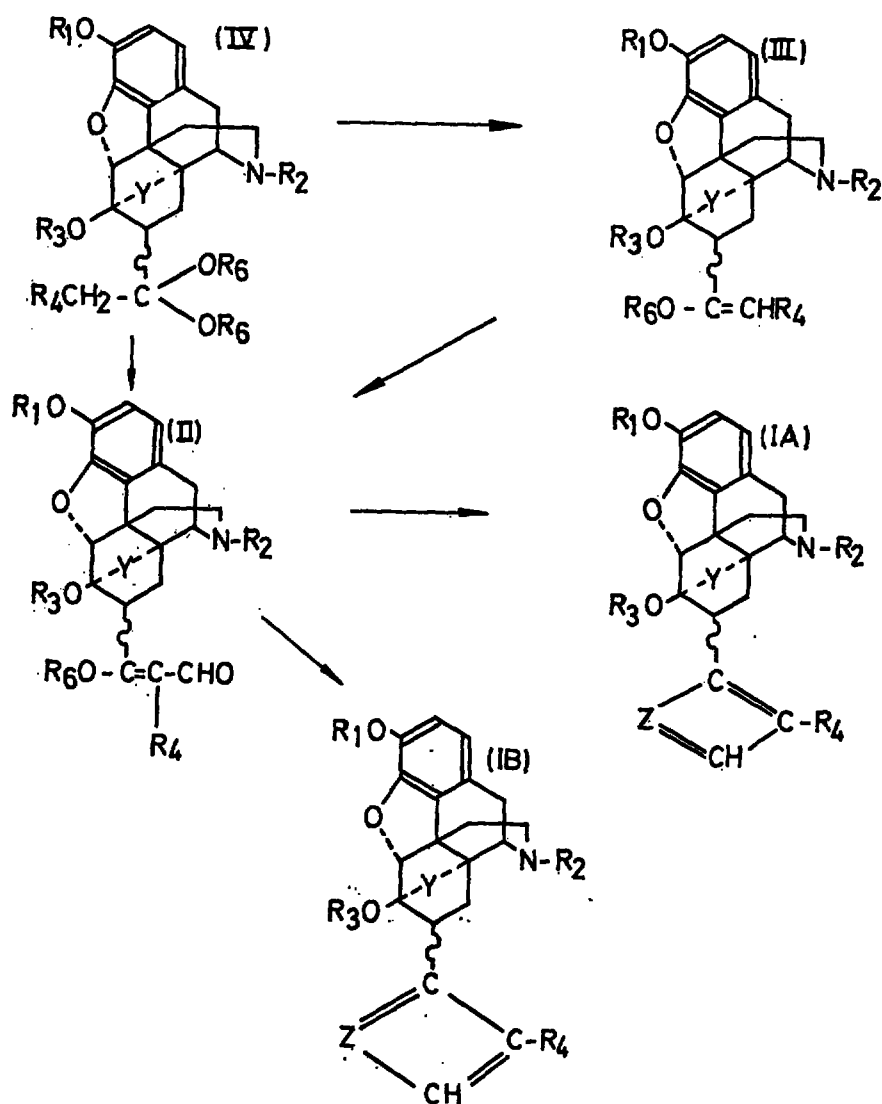
This invention relates to novel substituted 7-heterocyclic-7,8-dihydro-6-(hydroxy or methoxy)-6,14-endo(etheno or ethano)codides and morphides, to methods of preparing these compounds, and to pharmaceutical preparations containing them. The compounds of the present invention may be represented by the following general formula:



wherein R_1 is hydrogen, (C_1-C_4) alkyl or (C_2-C_5) alkanoyl; R_2 is hydrogen, cyano, propargyl, (C_1-C_4) alkyl, phenyl (C_1-C_4) alkyl, (C_2-C_6) alkenyl or (C_4-C_7) cycloalkylmethyl; R_3 is hydrogen or methyl; Y is etheno or ethano; and Q is a moiety selected from those of the formulae:



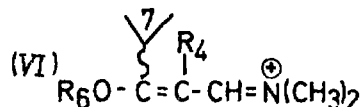
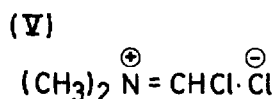
- wherein R_4 is hydrogen or (C_1-C_7) alkyl; and Z is $-N(R_5)-N=$, $-O-N=$ or $-N=C(NH_2)-N=$ wherein R_5 is hydrogen, (C_1-C_4) alkyl, phenyl, halophenyl, (C_1-C_4) alkylphenyl, (C_1-C_4) alkoxyphenyl, trifluoromethylphenyl, pyridyl, quinolyl, benzothiazolyl, dimethylpyrimidyl or dimethyl-*s*-triazinyl. Examples of alkyl, alkoxy and alkancyl groups, having from 1 to 4 carbon atoms in the alkyl moiety are methyl, ethyl, *isopropyl*, *n*-butyl, methoxy, ethoxy, *n*-propoxy, *n*-butoxy, formyl, acetyl, propionyl and *isobutyryl*. Typical alkyl groups of from 1 to 7 carbon atoms are, for example, methyl, ethyl, *n*-propyl, *n*-butyl, *isoamyl*, *sec*.-hexyl and *n*-heptyl. Exemplary alkenyl groups having up to 6 carbon atoms are allyl, methallyl and dimethallyl. Suitable cycloalkylmethyl groups having from 4 to 7 carbon atoms are cyclopropylmethyl, cyclobutylmethyl and cyclopentylmethyl. Phenyl (C_1-C_6) alkyl is exemplified by benzyl, α -phenylethyl and β -phenylethyl. Suitable halophenyl groups are, for example, *p*-fluorophenyl, *p*-chlorophenyl, *m*-chlorophenyl, *m*-bromophenyl, *o*-fluorophenyl, 2,5-dichlorophenyl, 2,4,6-trichlorophenyl, 3,5-dichlorophenyl, 2,6-dibromophenyl and pentafluorophenyl. Suitable (C_1-C_4) alkylphenyl groups are, for example, *p*-tolyl, *m*-tolyl, *o*-tolyl, *p*-ethylphenyl, *p*-isopropylphenyl and *m*-isobutylphenyl. Suitable (C_1-C_4) alkoxyphenyl groups are, for example, *m*-methoxyphenyl, *o*-methoxyphenyl, *m*-ethoxyphenyl and *p*-isopropoxyphenyl. Pyridyl, quinolyl and dimethylpyrimidyl are exemplified by 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-quinolyl, 3-quinolyl, 4-quinolyl, 4,6-dimethyl-2-pyrimidyl and 5,6-dimethyl-2-pyrimidyl. It should be noted that when Z is $-N=C(NH_2)-N=$ then structures (A) and (B) represent two resonance forms of the pyrimidine ring; that when Z is $-NH-N=$ then structures (A) and (B) represent tautomers of the pyrazole ring, these tautomers not ordinarily separable; and that when Z is $-N(R_5)-N=$ or $-O-N=$ then structures (A) and (B) represent pyrazole or oxazole ring isomers which can be separated from one another.
- The compounds of the present invention are generally obtainable as crystalline materials having characteristic melting points and absorption spectra. They are appreciably soluble in many organic solvents such as ethanol, chloroform, benzene and ethyl acetate. They are, however, generally insoluble in water.
- The organic bases of this invention form acid-addition salts with a variety of organic and inorganic salt-forming agents. Thus acid-addition salts, formed by admixture of the organic free base with an equivalent amount of an acid, suitably in a neutral solvent, are formed with such acids as sulfuric, phosphoric, hydrochloric, hydrobromic, citric, lactic, tartaric, acetic, gluconic and ascorbic. Also, included within the purview of the present invention are the alkali metal phenolates (e.g., sodium and potassium) of the organic free bases when R_1 in the above general formula is hydrogen. For purposes of this invention, the organic free bases are equivalent to their acid-addition salts and their alkali metal salts.
- The substituted 7-heterocyclic-7,8-dihydro-6-(hydroxy or methoxy)-6,14-*endo*-(etheno or ethano) codides and morphides (IA) and (IB) of the present invention may be readily prepared by treating an appropriately substituted 7-(2-formyl-1-alkoxyvinyl)-derivative (II) with a suitable heterocycle-forming reagent in accordance with the following reaction scheme:



wherein R₁, R₂, R₃, R₄, Z and Y are as previously defined and R₅ is (C₁—C₄) alkyl. By this procedure, a suitably substituted 7-[di(lower alkoxy)methyl] derivative (IV), prepared as described in Belgian Patent No. 714,349, is treated with a formylating agent followed by hydrolysis and the intermediates (II) are isolated directly. Alternatively, a suitably substituted 7-(1-alkoxy-1-alken-1-yl) derivative (III), prepared as described in Dutch Patent Application No. 68.05648, published October 28, 1968 may be converted to the intermediates (II) by formylation and hydrolysis. By this route, the 7-(1-alkoxy-1-alken-1-yl) derivatives (III) may be isolated and purified or may be prepared "in situ" and formylated without isolation or purification depending upon the circumstances.

The formylating reagent is prepared by treating a substituted formamide such as N,N-dimethylformamide, N,N-diethylformamide, N-formylpiperidine, N-formylmorpholine and N-methylformanilide, with phosgene, phosphoryl chloride or thionyl chloride in an inert solvent such as methylene chloride, ethylene chloride or chloroform. Alternatively, an excess of the substituted formamide may be used as the solvent. The formylation reaction (IV→II or III→II) is also most conveniently carried out in an inert solvent such as methylene chloride, ethylene chloride, chloroform, or an excess of the substituted formamide, employed to prepare the formylating reagent. The temperature range for the formylation reaction is from 0° C. to 35° C. although room temperature is preferred. The hydrolysis step may be carried out with dilute acid or dilute alkali but preferably with aqueous sodium acetate. When the formylation reaction is substantially complete (usually from several minutes to

several hours or more), the reaction mixture is stirred with aqueous sodium acetate or aqueous sodium hydroxide for from several minutes to several hours at room temperature and the product is isolated. The above described formylation reaction may be considered to be effected via a formylating reagent such as that shown by compound (V), the formylating reagent formed from N,N-dimethylformamide and phosgene. This formylating reagent then reacts with the ketal (IV) or enol-



-ether (III) to form an iminium intermediate (VI) (partial structure only shown) which is converted by hydrolysis to the intermediates (II).

The conversion of the 7-(2-formyl-1-alkoxyvinyl) derivatives (II) to the corresponding 7-heterocyclic-7,8-dihydro-6-(hydroxy or methoxy)-6,14-*endo*(etheno or ethano)codides and morphides (IA) and (IB) of the present invention may be readily accomplished by treating an appropriately substituted 7-(2-formyl-1-alkoxyvinyl) derivative (II) with a heterocycle-forming reagent selected from hydrazine, a substituted hydrazine of the formula R_5NHNH_2 , hydroxylamine or guanidine. By this scheme, selection of the heterocycle-forming reagent and the appropriate condensation conditions then determines the isomeric form of the product as (IA) or (IB). For example, when the heterocycle-forming reagent is hydrazine, the products (IA) and (IB), where Z is $-NH-N=$, represent tautomers of the pyrazole ring. As such, these tautomers are not ordinarily separable, and the tautomeric structure of an individual product in crystal form or in solution is determined by the individual properties of the specific compound. Physical methods such as infrared, nuclear magnetic resonance and ultraviolet spectra may be useful in determining tautomeric formulae as is X-ray crystallographic analysis, also.

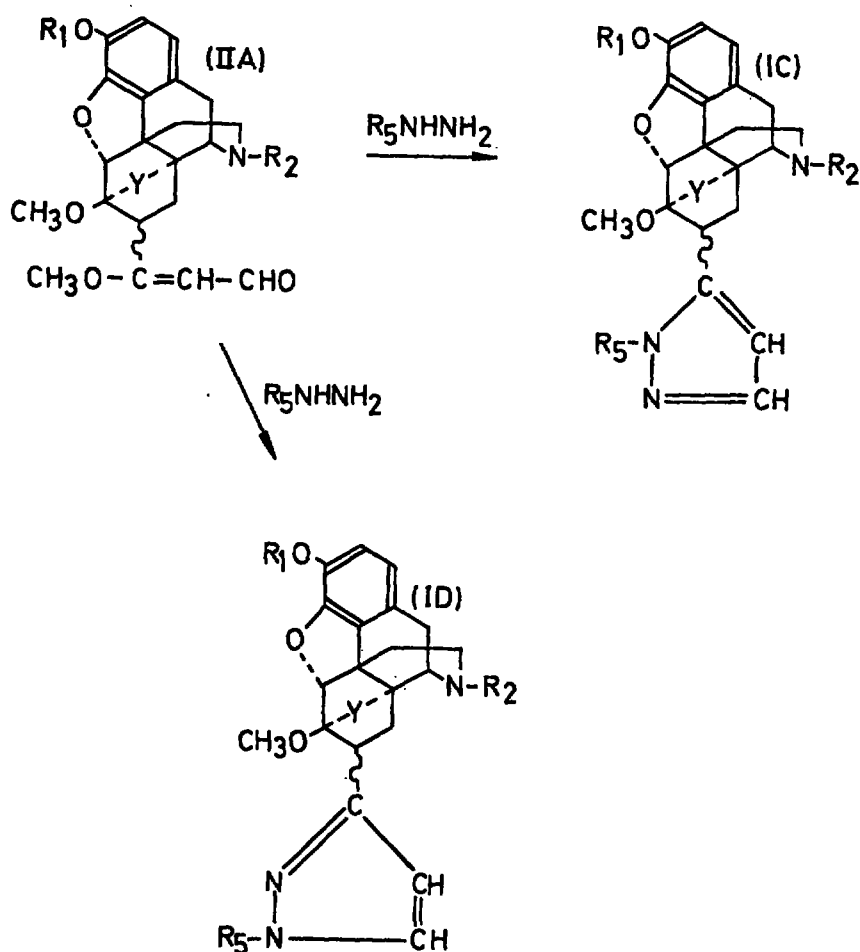
When the heterocycle-forming reagent is a substituted hydrazine (R_5NHNH_2) or hydroxylamine, the products (IA) and (IB), where Z is $-N(R_5)-N=$ or $-O-N=$, represent pyrazole or oxazole ring isomers capable of individual existence and separation from each other with distinct and different properties. The isomer formed in a given condensation reaction is governed by the specific condensation conditions (solvent, temperature, etc.), and the individual condensing reagent (substituted hydrazine or hydroxylamine). The products of these condensation reactions may be one isomer or the other (IA or IB) in a substantially pure state or a mixture of the two isomers. Methods of separation and purification well known to those skilled in the art such as extraction, fractional crystallization, chromatographic separation and purification, may then be used to isolate the individual isomers (IA and IB). Physical methods particularly including nuclear magnetic resonance and ultraviolet spectra are useful in establishing the isomeric structure of individual condensation products (IA or IB).

When the heterocycle-forming reagent is guanidine then structures (IA) and (IB), where Z is $-N=C(NH_2)-N=$, represent two resonance forms of the pyrimidine ring.

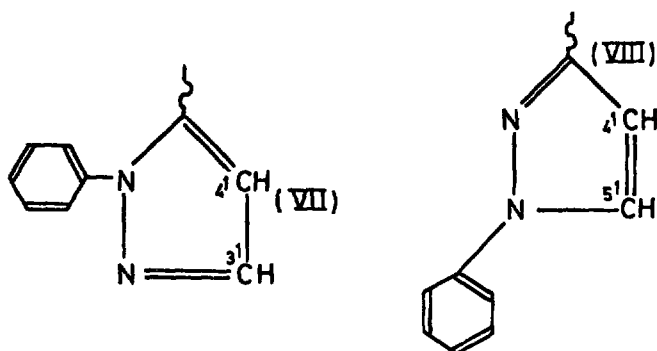
These condensation reactions are conveniently carried out in protic solvents such as acetic acid, dilute hydrochloric acid, ethanol and propanol. The temperature range employed is from 50° C. to 125° C. with the preferred range being from 80° C. to 125° C. The reaction is conveniently carried out by heating on the steam bath or at the refluxing temperature of the solvent, and is substantially complete within about one hour to several hours or more. The novel products of the present invention are isolated therefrom and purified by standard procedures.

A more specific embodiment of the novel process (II→IA or IB) of the present invention may be illustrated by the following reaction scheme:

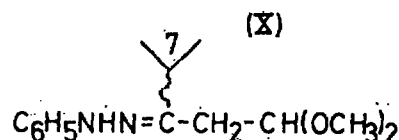
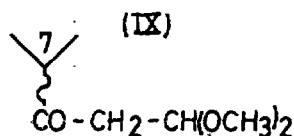
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wherein R_1 , R_2 , R_5 and Y are as previously defined. By this procedure, an appropriately substituted 7-(2-formyl-1-methoxyvinyl) derivative (IIA) is condensed with a hydrazine derivative R_5NHNH_2 . The condensation products are the isomers (IC) or (ID) which may be isolated in substantially pure form or obtained as mixtures and separated by well known methods. The nuclear magnetic resonance and ultraviolet spectra of these compounds provide definitive structural assignments for these pyrazole isomers. For example, a specific pair of isomers derived from condensation with phenylhydrazine is illustrated by (VII) and (VIII) (partial structures only shown) related to (IC) and (ID), respectively:



- The nuclear magnetic resonance and ultraviolet spectra of (VII) and (VIII) ($R_1=H$, R_2 =cyclopropylmethyl, Y =etheno) are characteristic for the pyrazole isomers. The pyrazole olefinic protons in the nuclear magnetic resonance spectrum of (VII) (C_{α} , —H and C_{β} , —H, doublets at $\delta 7.50$ and $\delta 6.13$, respectively, in d_6 —DMSO) have a coupling constant of 1.8 cps, whereas the coupling constant of the analogous protons in isomer (VIII) (C_{α} , —H and C_{β} , —H, doublets at $\delta 8.25$ and $\delta 6.17$, respectively, in d_6 —DMSO) is numerically larger (i.e. 2.5 cps), as expected. In addition, the N-phenyl protons of the 1-phenyl-5-pyrazolyl isomer (VII) appear as a sharp singlet at $\delta 7.54$, while those of the 1-phenyl-3-pyrazolyl compound (VIII) appear as a broad multiplet at $\delta 7.2$ — 8.0 indicating non-equivalence of the *o,m*- and *o',m'*-protons in this isomer. This suggests an unhindered, co-planar and conjugated conformation between the phenyl and pyrazole rings in (VIII). Further support is obtained from the ultraviolet spectrum of (VIII) which has a $\lambda_{\text{max}}^{\text{CH}_3\text{OH}}$ 259 $m\mu$ ($\epsilon 21,300$) consistent with the absorption expected for conjugated 1-phenyl-3-substituted pyrazoles. In the 1-phenyl-5-substituted isomer (VII) the bulky tetrahydrothebaine substituent adjacent to the pyrazole nitrogen bearing the phenyl substituent hinders this co-planar conformation, and both the nuclear magnetic resonance and ultraviolet (VII; $\lambda_{\text{max}}^{\text{CH}_3\text{OH}}$ 242 $m\mu$ ($\epsilon 13,300$), inflection because of end-absorption interference) spectra are consistent.
- The condensation solvents may also determine the predominant isomer (IC or ID). For example, when acetic acid is used for the condensation of (IIA) with substituted hydrazines, the 1-aryl (or other substituent)-5-pyrazolyl isomers (IC) are generally obtained substantially free of the other isomer (ID). A modified procedure which produces predominantly the other isomer, the 1-aryl (or other substituent)-3-pyrazolyl compounds (ID) is illustrated as follows. The 7-(2-formyl-1-methoxyvinyl) derivative (IIA) is treated with perchloric acid in methanol, and a keto-ketal (IX) (partial structure only shown) intermediate is presumably formed *in situ* and condensed, without isolation, with an appropriate arylhydrazine such as phenylhydrazine.



- The phenylhydrazone (X) (partial structure only shown) is then obtained as a crude intermediate, and is cyclized, without further purification, by heating with dilute hydrochloric acid in acetic acid.
- The substituted 7-heterocyclic-7,8-dihydro-6-(hydroxy or methoxy)-6,14-endo-(etheno or ethano)codides and morphides (IA and IB) of the present invention are active analgesics when measured by the "writhing syndrome" test for analgesic activity as described by Siegmund *et al.*, Pros. Soc. Exptl. Biol. Med., Vol. 95, p. 729 (1957), with modifications. This method is based upon the reduction of the number of writhes following the intraperitoneal injection of one mg./kg. of body weight of phenyl-*p*-quinone in male Swiss Albino mice weighing 15—25 grams per mouse. The syndrome is characterized by intermittent contractions of the abdomen, twisting and turning of the trunk, and extension of the hind legs beginning 3 to 5 minutes after injection of the phenyl-*p*-quinone. The test compound is administered orally to groups of two mice each 30 minutes before injection of the phenyl-*p*-quinone. The total number of writhes exhibited by each group of mice is recorded for a 3 minute period commencing 15 minutes after injection of the phenyl-*p*-quinone. A compound is considered active if it reduces the total number of writhes in two test mice from a control value of approximately 30 pair to a value of 18 or less per pair. If desired, the results of this test procedure for 10 pairs of mice at each of several dose levels may be used to determine a median effective dose (ED_{50}), defined as the dose required to reduce the number of writhes from about 30 per pair to 18 or less per pair in 50% of the pairs. In a representative operation, and merely by way of illustration, the following compounds of the present invention are active analgesics when tested in this procedure at the indicated oral dose as set forth in Table I below:



TABLE I

Compound	Oral Dose mg./kg. of body weight
7 α -(5-pyrazolyl)-6, 7, 8, 14-tetrahydro-6, 14-endoethenothebaine	100
7 α -(1-phenyl-5-pyrazolyl)-6, 7, 8, 14-tetrahydro-6, 14-endoethenothebaine	200
7 α -[1-(<i>p</i> -fluorophenyl)-5-pyrazolyl]-6, 7, 8, 14-tetrahydro-6, 14-endoethenothebaine	200
7 α -[1-(4, 6-dimethyl-2- <i>s</i> -triazinyl)-5-pyrazolyl]-6, 7, 8, 14-tetrahydro-6, 14-endoethenothebaine	200
7 α -[1-(4, 6-dimethyl-2-pyrimidinyl)-5-pyrazolyl]-6, 7, 8, 14-tetrahydro-6, 14-endoethenothebaine	200
7 α -[1-(2-pyridyl)-5-pyrazolyl]-6, 7, 8, 14-tetrahydro-6, 14-endoethenothebaine	200
7 α -[1-(2-quinolyl)-5-pyrazolyl]-6, 7, 8, 14-tetrahydro-6, 14-endoethenothebaine	100
7 α -[1-(2-benzothiazolyl)-5-pyrazolyl]-6, 7, 8, 14-tetrahydro-6, 14-endoethenothebaine	200
7 α -(2-amino-4-pyrimidinyl)-6, 7, 8, 14-tetrahydro-6, 14-endoethenothebaine	200
N-cyclopropylmethyl-7 α -(5-pyrazolyl)-6, 7, 8, 14-tetrahydro-6, 14-endoethenothebaine hydrochloride	25
N-cyclopropylmethyl-7 α -(5-isoxazolyl)-6, 7, 8, 14-tetrahydro-6, 14-endoethenothebaine	25
N-cyclopropylmethyl-7 α -(1-phenyl-5-pyrazolyl)-6, 7, 8, 14-tetrahydro-6, 14-endoethenonoripavine citrate	0.01 (ED ₅₀)
N-cyclopropylmethyl-7 α -(1- <i>m</i> -chlorophenyl-5-pyrazolyl)-6, 7, 8, 14-tetrahydro-6, 14-endoethenonoripavine hydrochloride	0.004 (ED ₅₀)

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5 10 15	A supplementary procedure is the rat tail-flick method described by F. E. D'Amour and D. L. Smith, J. Pharmacol. Exptl. Therap., Vol. 72, p. 74 (1941), with modifications. The compounds (generally as hydrochloride salts in 0.9% saline) are administered subcutaneously to groups of 5 rats each. Graded doses are given to several groups of rats. These rats are then individually subjected to a graded intensity heat stimulus from a spot light lamp and a condensing lens focused on the blackened tip of the rat tail. The characteristic response to this presumably painful heat stimulus is to flick the tail out of the concentrated beam of the heat source. The response time (in seconds) is measured for control and treated groups, and the criterion of analgesia is an approximate 100% increase in response time over controls. Established clinically active analgesics such as meperidine, codeine, morphine, are active in the above test. If desired, a median effective dose (ED₅₀) for 100% increase in response time over controls may be determined from the results obtained from several graded dose levels. When tested by this procedure using a "high intensity" heat stimulus calibrated to produce an average 4—6 second response time in untreated animals (controls), certain compounds of the present invention show this type of analgesic activity as indicated by the appropriate median effective doses as set forth in Table II below:	5 10 15
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TABLE II

Compound	ED ₅₀ mg./kg. of body weight
7 α -(5-isoxazolyl)-6, 7, 8, 14-tetrahydro-6, 14-endoethenothebaine	ca. 10
7 α -(1-phenyl-5-pyrazolyl)-6, 7, 8, 14-tetrahydro-6, 14-endoethenothebaine	ca. 3
7 α -[1-(<i>p</i> -fluorophenyl)-5-pyrazolyl]-6, 7, 8, 14-tetrahydro-6, 14-endoethenothebaine	ca. 5
7 α -[1-(4, 6-dimethyl-2-s-triazinyl)-5-pyrazolyl]-6, 7, 8, 14-tetrahydro-6, 14-endoethenothebaine	ca. 25
7 α -[1-(2-pyridyl)-5-pyrazolyl]-6, 7, 8, 14-tetrahydro-6, 14-endoethenothebaine	ca. 10
N-cyclopropylmethyl-7 α -(1-phenyl-5-pyrazolyl)-6, 7, 8, 14-tetrahydro-6, 14-endoethenonoripavine citrate	0.14
N-cyclopropylmethyl-7 α -(1- <i>m</i> -chlorophenyl-5-pyrazolyl)-6, 7, 8, 14-tetrahydro-6, 14-endoethenonoripavine hydrochloride	0.32

Additionally, supplementary routine tests known to those skilled in the art may be carried out to assess the importance of side effects frequently associated with the morphine-like analgesics. These include such actions as onset and duration of action, development of tolerance, respiratory depression, addiction liability, relative effects by oral and parenteral administration, and inhibitory effects on the gastrointestinal system.

Other compounds of this invention may show analgesic antagonist activity when tested against a selected dose of morphine or other morphine-like agents. This antagonist activity may be considered useful as a specific antidote for an overdose of a morphine-like agent, or for its non-narcotic analgesic action. Experience has shown that such narcotic antagonists are also capable of relieving pain despite the fact that they are generally inactive in the rat tail-flick procedure (see above), and have little or no addiction hazard; see L. S. Harris and A. K. Pierson, J. Pharmacol. Exptl. Therap., Vol. 143, p. 141 (1964). Analgesics which produce satisfactory pain-relief without serious side effects, particularly with regard to the tolerance, habituation and drug dependence of the opiates have been sought for many years. When

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tested by a procedure similar to that described by Harris and Pierson (above), N-cyclopropylmethyl - 7 α - (5 - pyrazolyl) - 6,7,8,14 - tetrahydro - 6,14 - *endo*-ethenonorthebaine, N - cyclopropylmethyl - 7 α - (5 - isoxazolyl) - 6,7,8,14 - tetrahydro - 6,14 - *endo*-ethenonorthebaine, and N - cyclopropylmethyl - 7 α - (1 - phenyl-5 - pyrazolyl) - 6,7,8,14 - tetrahydro - 6,14 - *endo*-ethenonoripavine show analgesic antagonist actions when tested against morphine.

In addition, supplementary test procedures such as measuring the elevation of the pain threshold of rat paws inflamed with brewer's yeast may be carried out to confirm the analgesic action of the compounds of the present invention. In certain cases, these compounds also show anti-inflammatory activity.

When mixed with suitable carriers or diluents the compounds of this invention can be prepared as pills, capsules, tablets, powders, solutions, suspensions and the like for unit dosage and to simplify administration. As analgesics, they will relieve pain by direct action on the nerve centers or by diminishing the conductivity of the sensory nerve fibers. The compounds of the present invention may be administered in combination with salicylates such as aspirin.

The compounds of the present invention may exist in several isomeric forms such as stereoisomers. It is to be understood that the present invention includes within its scope all such isomeric forms. For example, the codides used as starting materials have several asymmetric carbon atoms, and spimers at the C-7 asymmetric center are possible. Formation of stereoisomers, or epimers, at C-7 is therefore possible in the products of this invention. The nuclear magnetic resonance spectra of these 7 α - and 7 β - heterocyclic - 7,8 - dihydro - 6 - (hydroxy or methoxy) - 6,14 - *endo*(etheno or ethano) codides and morphides are particularly helpful in characterizing the mixtures of epimers or the substantially pure stereoisomers as obtained from the reaction mixtures or from subsequent purifications and separations. These isomers may then be separated by methods (such as fractional crystallization and partition-chromatography) well known to those skilled in the art.

In accordance with accepted convention, an α -substituent at the 7-position is behind the plane of the paper whereas a β -substituent at the 7-position is in front of the plane of the paper. This usually represented by a - - - bond for an α -substituent, a — bond for a β -substituent, and a ~~~ bond where both are indicated.

The invention is illustrated by the Examples which follow.

EXAMPLE 1

Preparation of 7 α -(5-isoxazolyl)-6,7,8,14-tetrahydro-6,14-*endo*-ethenonorthebaine
7 α - (2 - Formyl - 1 - methoxyvinyl) - 6,7,8,14 - tetrahydro - 6,14 - *endo*-ethenonorthebaine (500 mg.), hydroxylamine hydrochloride (500 mg.), and acetic acid (10 ml.) are heated on the steam bath for 1 hour. The reaction mixture is diluted with water and the solution is neutralized with sodium bicarbonate. The mixture is extracted with methylene chloride and the extract is washed with water and dried. The residue obtained by evaporation is crystallized from methanol to give 7 α -(5-isoxazolyl)-6,7,8,14 - tetrahydro - 6,14 - *endo*-ethenonorthebaine (430 mg., 90%), m.p. 172—174° C.

EXAMPLE 2

Preparation of 7 α -(5-pyrazolyl)-6,7,8,14-tetrahydro-6,14-*endo*-ethenonorthebaine
7 α - (2 - Formyl - 1 - methoxyvinyl) - 6,7,8,14 - tetrahydro - 6,14 - *endo*-ethenonorthebaine (3 g.), acetic acid (60 ml.), and hydrazine hydrate (3 ml.) are heated on the steam bath for 30 minutes and the crude product is isolated as in Example 1. Crystallization from aqueous methanol gives 7 α -(5-pyrazolyl)-6,7,8,14-tetrahydro-6,14-*endo*-ethenonorthebaine (2.8 g., 97%), m.p. 120—122° C. with effervescence.

EXAMPLE 3

Preparation of 7 α - (1 - methyl - 5 - pyrazolyl) - 6,7,8,14 - tetrahydro - 6,14-*endo*-ethenonorthebaine
7 α - (2 - Formyl - 1 - methoxyvinyl) - 6,7,8,14 - tetrahydro - 6,14 - *endo*-ethenonorthebaine (500 mg.), methylhydrazine sulfate (250 mg.), and acetic acid (10 ml.) are heated on the steam bath for 30 minutes. The crude product, isolated as in Example 1, is crystallized from aqueous methanol to give 7 α -(1-methyl-5-pyrazolyl)-6,7,8,14-tetrahydro-6,14-*endo*-ethenonorthebaine (300 mg., 60%), m.p. 203—205° C.

EXAMPLE 4

Preparation of 7 α - (1 - phenyl - 5 - pyrazolyl) - 6,7,8,14 - tetrahydro - 6,14 - *endoethenothebaine*

5 7 α - (2 - Formyl - 1 - methoxyvinyl) - 6,7,8,14 - tetrahydro - 6,14 - *endoethenothebaine* (500 mg.), phenylhydrazine hydrochloride (250 mg.) and acetic acid (10 ml.) are heated on the steam bath for 30 minutes. The mixture is diluted with water and then neutralized with aqueous sodium bicarbonate. The material which separated is collected, dried *via* methylene chloride solution followed by evaporation, and crystallized from aqueous methanol to give 7 α - (1 - phenyl - 5 - pyrazolyl) - 6,7,8,14 - tetrahydro - 6,14 - *endoethenothebaine* (355 mg., 60%), m.p. 175—177° C. 10

EXAMPLE 5

Preparation of 7 α - [1-(*p*-fluorophenyl)-5-pyrazolyl] - 6,7,8,14 - tetrahydro - 6,14 - *endoethenothebaine*

15 7 α - (2 - Formyl - 1 - methoxyvinyl) - 6,7,8,14 - tetrahydro - 6,14 - *endoethenothebaine* (500 mg.), *p*-fluorophenylhydrazine (195 mg.), and acetic acid (10 ml.) are heated on the steam bath for 1 hour. The crude product is isolated in the same manner as in Example 1 and crystallization from methanol gives 7 α - [1-(*p*-fluorophenyl) - 5 - pyrazolyl] - 6,7,8,14 - tetrahydro - 6,14 - *endoethenothebaine* (410 mg., 70%), m.p. 211—213° C. 20

EXAMPLE 6

Preparation of 7 α - [1 - (4,6 - dimethyl - 2 - *s* - triazinyl) - 5 - pyrazolyl] - 6,7,8,14 - tetrahydro - 6,14 - *endoethenothebaine*

25 7 α - (2 - Formyl - 1 - methoxyvinyl) - 6,7,8,14 - tetrahydro - 6,14 - *endoethenothebaine* (725 mg.), 2-hydrazino-4,6-dimethyl-*s*-triazine (240 mg.), and acetic acid (15 ml.) are heated on the steam bath for 1 hour. The crude product is isolated in the same manner as in Example 1 and crystallization from ethyl acetate-*n*-hexane gives 7 α - [1 - (4,6 - dimethyl - 2 - *s* - triazinyl) - 5 - pyrazolyl] - 6,7,8,14 - tetrahydro - 6,14 - *endoethenothebaine* (500 mg., 57%) m.p. 182—185° C. (inserted at 140° C.). 30

EXAMPLE 7

Preparation of 7 α - [1-(4,6-dimethyl-2-pyrimidinyl)-5-pyrazolyl] - 6,7,8,14 - tetrahydro - 6,14 - *endoethenothebaine*

35 7 α - (2 - Formyl - 1 - methoxyvinyl) - 6,7,8,14 - tetrahydro - 6,14 - *endoethenothebaine* (1 g.), 2-hydrazino-4,6-dimethylpyrimidine (500 mg.), and acetic acid (20 ml.) are heated under reflux for 1—1/2 hours. The crude product, isolated in the same manner as in Example 1, is heated with water (50 ml.) on the steam bath to remove the excess of 2-hydrazino-4,6-dimethylpyrimidine which is water-soluble. The solid is collected and a solution in methylene chloride is dried and passed through a short column of Magnesol[®]. Evaporation of the eluate followed by crystallization of the residue from acetone-*n*-hexane gives 7 α - [1-(4,6-dimethyl-2-pyrimidinyl)-5-pyrazolyl] - 6,7,8,14 - tetrahydro - 6,14 - *endoethenothebaine* (670 mg., 55%), m.p. 194—198° C. 40

EXAMPLE 8

Preparation of 7 α - [1-(2-pyridyl)-5-pyrazolyl] - 6,7,8,14 - tetrahydro - 6,14 - *endoethenothebaine*

45 7 α - (2 - Formyl - 1 - methoxyvinyl) - 6,7,8,14 - tetrahydro - 6,14 - *endoethenothebaine* (500 mg.), 2 - hydrazinopyridine (250 mg.), and acetic acid (10 ml.) are heated under reflux for 1—1/2 hours. The crude product is obtained as in Example 7 and crystallization from acetone-*n*-hexane gives 7 α - [1-(2-pyridyl)-5-pyrazolyl] - 6,7,8,14 - *endoethenothebaine* (360 mg., 70%) m.p. 156—158° C. 50

EXAMPLE 9

Preparation of 7 α - [1-(2-quinolyl)-5-pyrazolyl] - 6,7,8,14 - tetrahydro - 6,14 - *endoethenothebaine*

55 7 α - (2 - Formyl - 1 - methoxyvinyl) - 6,7,8,14 - tetrahydro - 6,14 - *endoethenothebaine* (500 mg.), 2-hydrazinoquinoline (188 mg.), and acetic acid (10 ml.) are heated under reflux for 1 hour. The crude product is obtained as in Example 1 and crystallization from methanol gives 7 α - [1-(2-quinolyl)-5-pyrazolyl] - 6,7,8,14 - tetrahydro - 6,14 - *endoethenothebaine* (440 mg.), m.p. 116—120° C. 55

EXAMPLE 10

Preparation of 7 α -[1-(2-benzothiazolyl)-5-pyrazolyl]-6,7,8,14-tetrahydro-6,14-*endoethenonthebaine*

5 7 α - (2 - Formyl - 1 - methoxyvinyl) - 6,7,8,14 - tetrahydro - 6,14 - *endoethenonthebaine* (1 g.), 2-hydrazinobenzothiazole (400 mg.), and acetic acid (20 ml.) are heated under reflux for 1 hour. The crude product is obtained as in Example 1 and crystallization from methylene chloride-methanol gives 7 α -[1-(2-benzothiazolyl)-5-pyrazolyl]-6,7,8,14-tetrahydro-6,14-*endoethenonthebaine* (1.1 g.), m.p. 209—211° C.

EXAMPLE 11

10 Preparation of 7 α -(2-amino-4-pyrimidinyl)-6,7,8,14-tetrahydro-6,14-*endoethenonthebaine*

15 7 α - (2 - Formyl - 1 - methoxyvinyl) - 6,7,8,14 - tetrahydro - 6,14 - *endoethenonthebaine* (1 g.), guanidine carbonate (500 mg.), and ethanol (100 ml.) are heated under reflux for 48 hours. The cooled mixture is filtered and solvent is evaporated. The residue is collected with the aid of water and crystallization from aqueous methanol gives 7 α -(2-amino-4-pyrimidinyl)-6,7,8,14-tetrahydro-6,14-*endoethenonthebaine* (700 mg.; 70%), m.p. 175—178° C.

EXAMPLE 12

20 Preparation of N-cyclopropylmethyl-7 α -(5-pyrazolyl)-6,7,8,14-tetrahydro-6,14-*endoethenonthebaine* hydrochloride

25 N - Cyclopropylmethyl - 7 α - (2 - formyl - 1 - methoxyvinyl) - 6,7,8,14-tetrahydro - 6,14 - *endoethenonthebaine* hydrochloride (2 g.), hydrazine hydrate (2 ml.) and acetic acid (40 ml.) are heated on the steam bath for 30 min. The mixture is diluted with water and neutralized with powdered sodium carbonate. The mixture is extracted with methylene chloride and the extract is washed with water and dried. Evaporation of solvent gives a gum which is dissolved in dilute hydrochloric acid (5%) and the solution is washed with ether. The aqueous phase is neutralized with powdered sodium bicarbonate and the material which separates is collected and dried. Crystallization from methylene chloride-methanol-acetone gives N-cyclopropylmethyl-7 α -(5-pyrazolyl)-6,7,8,14-tetrahydro-6,14-*endoethenonthebaine* hydrochloride (400 mg.), m.p. 303—305° C. dec. The mother liquor is evaporated and the residue is treated with dilute hydrochloric acid and then with dilute hydrochloric acid and then with sodium bicarbonate as before. The material which separates is collected, washed with acetone, and dried to give a further amount (450 mg.) of product, m.p. 302—305° C., and a total yield of 45%.

EXAMPLE 13

40 Preparation of N-cyclopropylmethyl-7 α -(5-isoxazolyl)-6,7,8,14-tetrahydro-6,14-*endoethenonthebaine*

45 N - Cyclopropylmethyl - 7 α - (2 - formyl - 1 - methoxyvinyl) - 6,7,8,14 - tetrahydro - 6,14 - *endoethenonthebaine* hydrochloride (1 g.), hydroxylamine hydrochloride (1 g.), and acetic acid (20 ml.) are heated on the steam bath for 1 hr. After the addition of water, the mixture is neutralized with powdered sodium bicarbonate and extracted with methylene chloride. The extract is washed with water and dried. Evaporation of solvent gives a gum, a solution of which in methylene chloride is passed through a short column of Magnesol. The eluate is evaporated and the residue crystallized from methanol to give N-cyclopropylmethyl-7 α -(5-isoxazolyl)-6,7,8,14-tetrahydro-6,14-*endoethenonthebaine* (500 mg., 56%), m.p. 144—146° C.

EXAMPLE 14

50 Preparation of N-cyclopropylmethyl-7 α -(5-pyrazolyl)-6,7,8,14-tetrahydro-6,14-*endoethenonoripavine*

55 N - Cyclopropylmethyl - 7 α - (2 - formyl - 1 - methoxyvinyl) - 6,7,8,14 - tetrahydro - 6,14 - *endoethenonoripavine* (1 g.), hydrazine hydrate (1 ml.), and acetic acid (20 ml.) are heated on the steam bath for 30 min. The mixture is diluted with water and is then basified with ammonium hydroxide. The material which separates is collected, dried, and crystallized from acetone - *n* - hexane to give N-cyclopropylmethyl - 7 α - (5 - pyrazolyl) - 6 - 7,8,14 - tetrahydro - 6,14 - *endoethenonoripavine* (380 mg., 40%), m.p. 198—200° C.

EXAMPLE 15

60 Preparation of N-cyclopropylmethyl-7 α -(5-isoxazolyl)-6,7,8,14-tetrahydro-6,14-*endoethenonoripavine*

N - Cyclopropylmethyl - 7 α - (2 - formyl - 1 - methoxyvinyl) - 6,7,8,14 - tetrahydro - 6,14 - *endoethenonoripavine* (1 g.), hydroxylamine hydrochloride (1 g.), and

acetic acid (20 ml.) are heated on the steam bath for 1 hr. The mixture is diluted with water and is then neutralized with aqueous sodium carbonate. The precipitated product is extracted into methylene chloride, and the extract is washed with water and dried. Evaporation of solvent gives a gum, a solution of which in methylene chloride is passed through a short column of Magnesol. The eluate is evaporated and the residue collected with the aid of ether. Crystallization from acetone-*n*-hexane gives N - cyclopropylmethyl - 7 α - (5 - isoxazolyl) - 6,7,8,14 - tetrahydro - 6,14 - *endo*-ethenonoripavine (280 mg.), mp. 182—184° C. An additional amount (50 mg.), m.p. 185—186° C., was obtained from the mother liquor to give a total yield of 35%.

EXAMPLE 16

Preparation of N-cyclopropylmethyl-7 α -(1-phenyl-5-pyrazolyl)-6,7,8,14-tetrahydro-6,14-*endo*ethenonorthebaine hydrochloride

N - Cyclopropylmethyl - 7 α - (2 - formyl - 1 - methoxyvinyl) - 6,7,8,14 - tetrahydro - 6,14 - *endo*ethenonorthebaine (5 g.), phenyl hydrazine hydrochloride (2.5 g.), and acetic acid (100 ml.) are heated on the steam bath for 30 min. The mixture is diluted with water and is then basified with ammonium hydroxide. The material which separates is collected and dried *via* methylene chloride solution. The residue obtained by evaporation of solvent is dissolved in methylene chloride and the solution is passed through a short column of Magnesol. The eluate is evaporated to give a gum. A portion of this gum (500 mg.) is dissolved in methanol, and dilute hydrochloric acid (5%) is added in excess. The solution is extracted with methylene chloride and the extract is dried and evaporated. The residue is collected with the aid of acetone and crystallized from methanol-acetone to give N-cyclopropylmethyl-7 α -(1-phenyl-5-pyrazolyl) - 6,7,8,14 - tetrahydro - 6,14 - *endo*ethenonorthebaine hydrochloride (250 mg.), m.p. 272—274° C. dec. The remainder of the above gum is treated in a similar fashion to give further amounts (1.147 g. and 1.243 g.), m.p. 274° C. dec. and m.p. 277° C. dec., respectively, and a total yield of 39%.

EXAMPLE 17

Preparation of N-cyclopropylmethyl-7 α -(1-phenyl-5-pyrazolyl)-6,7,8,14-tetrahydro-6,14-*endo*ethenonoripavine

N - Cyclopropylmethyl - 7 α - (2 - formyl - 1 - methoxyvinyl) - 6,7,8,14 - tetrahydro - 6,14 - *endo*ethenonoripavine (5 g.), phenylhydrazine hydrochloride (2.5 g.), and acetic acid (100 ml.) are heated on the steam bath for 30 min. The mixture is diluted with water and is then made basic with ammonium hydroxide. The material which separates is collected and dried *via* methylene chloride solution followed by evaporation of solvent to give a glass. A solution of this glass in methylene chloride is passed through a short column of Magnesol. Evaporation of the eluate gives a gum which crystallizes on the addition of ether, and is collected with the aid of ether to give N - cyclopropylmethyl - 7 α - (1 - phenyl - 5 - pyrazolyl) - 6,7,8,14 - tetrahydro - 6,14 - *endo*ethenonoripavine (2.8 g., 43%), m.p. 184—186° C. The compound has $\lambda_{\text{max}}^{\text{CH}_3\text{OH}}$ 242 (inflection point; ϵ 13,300) and 289 m μ (ϵ 9000).

A hot solution of citric acid (1.5 g.) in ethanol (5 ml.) is added to a hot solution of pyrazole (1.5 g.) in ethanol (15 ml.). N - Cyclopropylmethyl - 7 α - (1 - phenyl - 5 - pyrazolyl) - 6,7,8,14 - tetrahydro - 6,14 - *endo*ethenonoripavine citrate (1.416 g.), m.p. 216° C. dec., separates on standing for several hours. The mother liquor is warmed and ether is added, when a further amount (450 mg.) of product, m.p. 217° C. dec., separates to give a total yield of 98%. The compound has $\lambda_{\text{max}}^{\text{KBr}}$ 2.93, 3.85 (broad), 5.74, 5.82 (shoulder), and 6.25 μ ; nuclear magnetic resonance (d_s —DMSO) 87.50 and 6.13 (pyrazole C₂, —H and C₁₁H, doublets, J_{3,11}=1.8 cps), 5.83 and 5.72 (C₈—H and C₁₇—H; doublets, J_{1,17}=9 cps), 4.48 (C₆—H), 3.08 (C₆-methoxyl), and 2.70 (—CH₂— of citrate; 2 protons or one mole of citric acid per mole of thebaine derivative).

EXAMPLE 18

Preparation of 7 α -(5-isoxazolyl)-6,7,8,14-tetrahydro-6,14-*endo*ethenooripavine

Following the general procedure of Example 1, 7 α -(2-formyl-1-methoxyvinyl)-6,7,8,14-tetrahydro-6,14-*endo*ethenooripavine is treated with hydroxylamine hydrochloride in acetic acid to give 7 α -(5-isoxazolyl)-6,7,8,14-tetrahydro-6,14-*endo*ethenooripavine.

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EXAMPLE 19

6,7,8,14-tetrahydro-6,14-*endo*ethenoripavine is treated with hydrazine hydrate in Preparation of 7 α -(5-pyrazolyl)-6,7,8,14-tetrahydro-6,14-*endo*ethenoripavine
Following the general procedure of Example 2, 7 α -(2-formyl-1-methoxyvinyl)-acetic acid to give 7 α -(5-pyrazolyl)-6,7,8,14-tetrahydro-6,14-*endo*ethenoripavine.

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EXAMPLE 20

Preparation of 3-acetyl-N-cyclopropylmethyl-7 α -(5-isoxazolyl)-6,7,8,14-tetrahydro-6,14-*endo*ethenonoripavine

Acetylation of N - cyclopropylmethyl - 7 α - (5 - isoxazolyl) - 6,7,8,14 - tetrahydro-6,14-*endo*ethenonoripavine using acetic anhydride in pyridine gives 3-acetyl-N-cyclopropylmethyl-7 α -(5-isoxazolyl)-6,7,8,14-tetrahydro-6,14-*endo*ethenonoripavine.

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EXAMPLE 21

Preparation of 7 α -(5-isoxazolyl)-6,7,8,14-tetrahydro-6,14-*endo*ethenonorthebaine

Following the general procedure of Example 1, 7 α -(2-formyl-1-methoxyvinyl)-6,7,8,14-tetrahydro-6,14-*endo*ethenonorthebaine is treated with hydroxylamine hydrochloride in acetic acid to give 7 α -(5-isoxazolyl)-6,7,8,14-tetrahydro-6,14-*endo*ethenonorthebaine.

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EXAMPLE 22

Preparation of N-allyl-7 α -(5-isoxazolyl)-6,7,8,14-tetrahydro-6,14-*endo*ethenonorthebaine

7 α - (5 - Isoxazolyl) - 6,7,8,14 - tetrahydro - 6,14 - *endo*ethenonorthebaine is treated with allyl bromide in an inert solvent to give N-allyl-7 α -(5-isoxazolyl)-6,7,8,14-tetrahydro-6,14-*endo*ethenonorthebaine.

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EXAMPLE 23

Preparation of 7 α -(5-isoxazolyl)-N-propyl-6,7,8,14-tetrahydro-6,14-*endo*ethenonorthebaine

7 α -(5-Isoxazolyl)-6,7,8,14-tetrahydro-6,14-*endo*ethenonorthebaine is treated with propyl bromide in an inert solvent to give 7 α -(5-isoxazolyl)-N-propyl-6,7,8,14-tetrahydro-6,14-*endo*ethenonorthebaine.

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EXAMPLE 24

Preparation of 7 α -(5-isoxazolyl)-N-phenethyl-6,7,8,14-tetrahydro-6,14-*endo*ethenonorthebaine

7 α -(5-Isoxazolyl)-6,7,8,14-tetrahydro-6,14-*endo*ethenonorthebaine is treated with phenethyl chloride in an inert solvent to give 7 α - (5 - isoxazolyl) - N - phenethyl-6,7,8,14 - tetrahydro - 6,14 - *endo*ethenonorthebaine.

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EXAMPLE 25

Preparation of 7 α -(5-isoxazolyl)-N-(3-methyl-2-buten-1-yl)-6,7,8,14-tetrahydro-6,14-*endo*ethenonorthebaine

7 α -(5-Isoxazolyl)-6,7,8,14-tetrahydro-6,14-*endo*ethenonorthebaine is treated with 3 - methyl - 2 - buten - 1 - yl bromide in an inert solvent to give 7 α - (5 - isoxazolyl)-N-(3-methyl-2-buten-1-yl)-6,7,8,14-tetrahydro-6,14-*endo*ethenonorthebaine.

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EXAMPLE 26

Preparation of 7 α -(5-isoxazolyl)-N-propargyl-6,7,8,14-tetrahydro-6,14-*endo*ethenonorthebaine

7 α -(5-Isoxazolyl)-6,7,8,14-tetrahydro-6,14-*endo*ethenonorthebaine is treated with propargyl bromide in an inert solvent to give 7 α -(5-isoxazolyl)-N-propargyl-6,7,8,14-tetrahydro-6,14-*endo*ethenonorthebaine.

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EXAMPLE 27

Preparation of 7 α -(4-ethyl-5-pyrazolyl)-6,7,8,14-tetrahydro-6,14-*endo*ethenonorthebaine

Following the general procedure of Example 2, 7 α -(2-formyl-1-methoxy-1-butenyl)-6,7,8,14-tetrahydro-6,14-*endo*ethenonorthebaine is treated with hydrazine hydrate in acetic acid to give 7 α -(4-ethyl-5-pyrazolyl)-6,7,8,14-tetrahydro-6,14-*endo*ethenonorthebaine.

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EXAMPLE 28

Preparation of 7 α -(5-isoxazolyl)-6,7,8,14-tetrahydro-6,14-endoethanothebaine

Following the general procedure of Example 1, 7 α -(2-formyl-1-methoxyvinyl)-6,7,8,14-tetrahydro-6,14-endoethanothebaine is treated with hydroxylamine hydrochloride in acetic acid to give 7 α -(5-isoxazolyl)-6,7,8,14-tetrahydro-6,14-endoethanothebaine.

EXAMPLE 29

Preparation of 7 β -(5-pyrazolyl)-6,7,8,14-tetrahydro-6,14-endoethenothebaine

Following the general procedure of Example 2, 7 β -(2-formyl-1-methoxyvinyl)-6,7,8,14-tetrahydro-6,14-endoethenothebaine is treated with hydrazine hydrate in acetic acid to give 7 β -(5-pyrazolyl)-6,7,8,14-tetrahydro-6,14-endoethenothebaine.

EXAMPLE 30

Preparation of 7 α -(5-isoxazolyl)-7,8-dihydro-6-hydroxy-6,14-endoethenocodide

Following the general procedure of Example 1, 7 α -(2-formyl-1-methoxyvinyl)-7,8-dihydro-6-hydroxy-6,14-endoethenocodide is treated with hydroxylamine hydrochloride in acetic acid to give 7 α -(5-isoxazolyl)-7,8-dihydro-6-hydroxy-6,14-endoethenocodide.

EXAMPLE 31

Preparation of N-cyano-7 α -(5-isoxazolyl)-6,7,8,14-tetrahydro-6,14-endoethenonorthebaine

Following the general procedure of Example 1, N-cyano-7 α -(2-formyl-1-methoxyvinyl)-6,7,8,14-tetrahydro-6,14-endoethenonorthebaine is treated with hydroxylamine hydrochloride in acetic acid to give N-cyano-7 α -(5-isoxazolyl)-6,7,8,14-tetrahydro-6,14-endoethenonorthebaine.

EXAMPLE 32

Preparation of N-cyclopropylmethyl-7 α -[1-(*m*-chlorophenyl)-5-pyrazolyl]-6,7,8,14-tetrahydro-6,14-endoethenonoripavine

Following the general procedure of Example 17 N-cyclopropylmethyl-7 α -(2-formyl-1-methoxyvinyl)-6,7,8,14-tetrahydro-6,14-endoethenonoripavine is treated with *m*-chlorophenyl hydrazine hydrochloride in acetic acid to give N-cyclopropylmethyl-7 α -[1-(*m*-chlorophenyl)-5-pyrazolyl]-6,7,8,14-tetrahydro-6,14-endoethenonoripavine. The hydrochloride crystallizes from ethanol and has m.p. 281—282° C. dec. The compound has nuclear magnetic resonance (CDCl₃/d₆-DMSO) δ 7.48 and 6.08 (pyrazole C₃/—H and C₄/—H, doublets, J_{3/4} = 1.7 cps.).

EXAMPLE 33

Preparation of N-cyclopropylmethyl-7 α -[1-(2-pyridyl)-5-pyrazolyl]-6,7,8,14-tetrahydro-6,14-endoethenonoripavine

Following the general procedure of Example 17, N-cyclopropylmethyl-7 α -(2-formyl-1-methoxyvinyl)-6,7,8,14-tetrahydro-6,14-endoethenonoripavine is treated with 2-hydrazinopyridine in acetic acid to give N-cyclopropylmethyl-7 α -[1-(2-pyridyl)-5-pyrazolyl]-6,7,8,14-tetrahydro-6,14-endoethenonoripavine. The compound is crystallized from acetone-*n*-hexane and has m.p. 136—138° C.

EXAMPLE 34

Preparation of N-cyclopropylmethyl-7 α -[1-(*p*-fluorophenyl)-5-pyrazolyl]-6,7,8,14-tetrahydro-6,14-endoethenonoripavine

N-Cyclopropylmethyl-7 α -(2-formyl-1-methoxyvinyl)-6,7,8,14-tetrahydro-6,14-endoethenonoripavine (1.4 g.), *p*-fluorophenylhydrazine hydrochloride (700 mg.), and acetic acid (40 ml.) are heated on the steam bath for 1 hr. The cooled mixture is diluted with water and neutralized with dilute ammonium hydroxide. The material which separates is collected and dried. A solution of this material in methylene chloride is passed through a short column of Magnesol and evaporation of the eluate followed by crystallization of the residue from acetone-*n*-hexane gives N-cyclopropylmethyl-7 α -[1-(*p*-fluorophenyl)-5-pyrazolyl]-6,7,8,14-tetrahydro-6,14-endoethenonoripavine (1.038 g.), m.p. 151—153° C.

EXAMPLE 35

Preparation of N-cyclopropylmethyl-7 α -(1-phenyl-3-pyrazolyl)-6,7,8,14-tetrahydro-6,14-endoethenonoripavine

N-Cyclopropylmethyl-7 α -(2-formyl-1-methoxyvinyl)-6,7,8,14-tetrahydro-6,14-endoethenonoripavine (1 g.), methanol (25 ml.), and perchloric acid (0.4 ml.) are heated under reflux for 1—1/2 hours. Phenylhydrazine (1 ml.) is then

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added and the mixture is heated under reflux for 1 hour. The solution is then added dropwise with stirring, to an excess of aqueous sodium bicarbonate and the material which separates is collected and dried (72.8 mg.) $\lambda_{\text{max}}^{\text{KBr}}$ 6.28, 8.99 and 9.09 μ .

5 The above material (540 mg.) without further purification, is heated on the steam bath with acetic acid (5 ml.) and dilute hydrochloric acid (5 ml.; 5%) for 1 hr. This solution is added dropwise, with stirring, to dilute ammonium hydroxide (20% v/v) and the material which separates is collected and dried. A solution of this material in methylene chloride is passed through a short column of Magnesol and the eluate is evaporated to give a gum. Citric acid (540 mg.) is added to a solution of this gum in ethanol (5 ml.) and the mixture is heated on the steam bath until solution takes place. This solution is poured into ether with stirring and the material which separates is collected and crystallized from ethyl acetate to give N-cyclopropylmethyl-7 α -(1-phenyl-3-pyrazolyl)-6,7,8,14-tetrahydro-6,14-endoethenonoripavine citrate (140 mg.), m.p. indefinite from 90—140° C. This compound has nuclear magnetic resonance (d₆-DMSO) δ 8.25 and 6.17 (pyrazole C₅/—H and C₄/—H; doublets, J_{4/5} = 2.5 cps), 5.63 (C₁/—H and C₈/—H; singlet), 4.87 (C₃/—H), 3.37 (C₆-methoxyl), 2.70 (—CH₂— of citrate; 2 protons or one mole of citric acid per mole of thebaine derivative; peaks at δ 4.47 (C₅/—H) and 3.06 (C₆-methoxyl indicate the presence of ca. 15% of the 7 α -(1-phenyl-5-pyrazolyl) isomer.

20 The mother liquor from this citrate is evaporated, and the residue is dissolved in a little methanol. This solution is added dropwise, with stirring, to dilute ammonium hydroxide (20% v/v) and the material which separates is collected and dried. This material (ca. 220 mg.) is subjected to partition chromatography on "Celite" (registered Trade Mark) 545 using the solvent system heptane:ethylacetate:-methanol:water (95:5:17:4). The eluate is monitored at 230 m μ . The main peak (Cut 6) is evaporated, and the residue is dissolved in acetone. n-Hexane is then added to turbidity and the solvent allowed to evaporate at room temperature. The residue (100 mg.), m.p. 143—145° C., is collected. This pure isomer has $\lambda_{\text{max}}^{\text{CH}_3\text{OH}}$ 259 m μ (ϵ 21,300) and nuclear magnetic resonance δ 7.72 and 6.17 (pyrazole C₅/—H and C₄/—H, doublets, J_{4/5} = 2.3 cps), 7.45 (N-phenyl; multiplet), 4.75 (C₃/—H), and 3.42 (C₆-methoxy), 2.33 (doublet, J = 5.5 cps, N—CH₂—<|).

EXAMPLE 36

Preparation of N-cyclopropylmethyl-7 α -[1-(2,5-dichlorophenyl)-5-pyrazolyl]-6,7,8,14-tetrahydro-6,14-endoethenonoripavine

35 A hot solution of 2,5-dichlorophenylhydrazine (500 mg.) in dilute hydrochloric acid (20 ml.; 5%) is added dropwise with stirring to a hot solution of N-cyclopropylmethyl-7 α -(2-formyl-1-methoxyvinyl)-6,7,8,14-tetrahydro-6,14-endoethenonoripavine (1 g.) in dilute hydrochloric acid (10 ml.; 5%). After the addition is completed, the reaction mixture is stirred for 20 min., and extracted with methylene chloride (and a little methanol is used to dissolve material adhering to the flask). The extract is shaken with dilute ammonium hydroxide (20% v/v), then with water, and dried. The dried methylene chloride solution is passed through a short column of Magnesol and the column finally washed with ether. The eluate is evaporated and, after crystallization of the residue from acetone-n-hexane, N-cyclopropylmethyl-7 α -[1-(2,5-dichlorophenyl)-5-pyrazolyl]-6,7,8,14-tetrahydro-6,14-endoethenonoripavine (700 mg.), m.p. 161—163°C. (with effervescence) is obtained. The compound has nuclear magnetic resonance (CDCl₃) δ 7.57 and 6.10 (pyrazole C₅/—H and C₄/—H, doublets, J_{3/4}, J_{4/5} = 1.8 cps), 4.25 (C₃/—H), 3.27 (C₆-methoxyl).

EXAMPLE 37

Preparation of N-cyclopropylmethyl-7 α -(1-benzyl-5-pyrazolyl)-6,7,8,14-tetrahydro-6,14-endoethenonoripavine

50 Following the general procedure of Example 17, N-cyclopropylmethyl-7 α -(2-formyl-1-methoxyvinyl)-6,7,8,14-tetrahydro-6,14-endoethenonoripavine is treated with benzylhydrazine hydrochloride in acetic acid to give N-cyclopropylmethyl-7 α -(1-benzyl-5-pyrazolyl)-6,7,8,14-tetrahydro-6,14-endoethenonoripavine. The compound is crystallized from ethanol and has m.p. 195—197° C.

EXAMPLE 38

Preparation of N-cyclopropylmethyl-7 α -(1-pentafluorophenyl-5-pyrazolyl)-6,7,8,14-tetrahydro-6,14-endoethenonoripavine

Following the general procedure of Example 17, N-cyclopropylmethyl-7 α -(2-formyl-1-methoxyvinyl)-6,7,8,14-tetrahydro-6,14-endoethenonoripavine is treated with pentafluorophenylhydrazine hydrochloride in acetic acid to give N-cyclopropylmethyl-7 α -(1-pentafluorophenyl)-5-pyrazolyl-6,7,8,14-tetrahydro-6,14-endoethenonoripavine. The compound is crystallized from *n*-hexane and has m.p. 211—213° C.

EXAMPLE 39

Preparation of N-cyclopropylmethyl-7 α -[1-(*p*-chlorophenyl)-3-pyrazolyl]-6,7,8,14-tetrahydro-6,14-endoethenonoripavine

A hot solution of *p*-chlorophenylhydrazine hydrochloride (500 mg.) in dilute hydrochloric acid (20 ml.; 5%) is added dropwise, with stirring, to a hot solution of N-cyclopropylmethyl-7 α -(2-formyl-1-methoxyvinyl)-6,7,8,14-tetrahydro-6,14-endoethenonoripavine (1 g.) in dilute hydrochloric acid (10 ml.; 5%). The mixture is stirred for 20 min. after the addition is complete and is then extracted with methylene chloride. The extract is washed with dilute ammonium hydroxide (20% v/v), water, and then dried. The solution is passed through a short column of Magnesol and the eluate is evaporated to give N-cyclopropylmethyl-7 α -[1-(*p*-chlorophenyl)-3-pyrazolyl]-6,7,8,14-tetrahydro-6,14-endoethenonoripavine as a gum (790 mg.) having $\lambda_{\text{max}}^{\text{CH}_3\text{OH}}$ 264 m μ .

EXAMPLE 40

Preparation of N-cyclopropylmethyl-7 α -[1-(*m*-chlorophenyl)-3-pyrazolyl]-6,7,8,14-tetrahydro-6,14-endoethenonoripavine

Following the general procedure of Example 39, N-cyclopropylmethyl-7 α -(2-formyl-1-methoxyvinyl)-6,7,8,14-tetrahydro-6,14-endoethenonoripavine is treated with *m*-chlorophenylhydrazine in dilute hydrochloric acid to give N-cyclopropylmethyl-7 α -[1-(*m*-chlorophenyl)-3-pyrazolyl]-6,7,8,14-tetrahydro-6,14-endoethenonoripavine hydrochloride after separation and purification from the 7 α -[1-(*m*-chlorophenyl)-5-pyrazolyl] isomer by partition chromatography. The compound has $\lambda_{\text{max}}^{\text{CH}_3\text{OH}}$ 264 m μ ; nuclear magnetic resonance (δ —DMSO) 8.40 and 6.20 (pyrazole C₅—H and C₄—H; doublets, $J_{4,5}$, τ = 2—2.5 cps), 5.86 (C₁₇—H and C₁₈—H; singlet), 5.02 (C₈—H), 3.38 (C₆-methoxyl).

EXAMPLE 41

Preparation of N-cyclopropylmethyl-7 α -[1-(*o*-chlorophenyl)-5-pyrazolyl]-6,7,8,14-tetrahydro-6,14-endoethenonoripavine

Following the general procedure of Example 17, N-cyclopropylmethyl-7 α -(2-formyl-1-methoxyvinyl)-6,7,8,14-tetrahydro-6,14-endoethenonoripavine is treated with *o*-chlorophenyl hydrazine hydrochloride in acetic acid to give N-cyclopropylmethyl-7 α -[1-(*o*-chlorophenyl)-5-pyrazolyl]-6,7,8,14-tetrahydro-6,14-endoethenonoripavine.

EXAMPLE 42

Preparation of N-cyclopropylmethyl-7 α -[1-(*p*-chlorophenyl)-5-pyrazolyl]-6,7,8,14-tetrahydro-6,14-endoethenonoripavine

Following the general procedure of Example 17, N-cyclopropylmethyl-7 α -(2-formyl-1-methoxyvinyl)-6,7,8,14-tetrahydro-6,14-endoethenonoripavine is treated with *p*-chlorophenyl hydrazine hydrochloride in acetic acid to give N-cyclopropylmethyl-7 α -[1-(*p*-chlorophenyl)-5-pyrazolyl]-6,7,8,14-tetrahydro-6,14-endoethenonoripavine.

EXAMPLE 43

Preparation of N-cyclopropylmethyl-7 α -[1-(*m*-fluorophenyl)-5-pyrazolyl]-6,7,8,14-tetrahydro-6,14-endoethenonoripavine

Following the general procedure of Example 17, N-cyclopropylmethyl-7 α -(2-formyl-1-methoxyvinyl)-6,7,8,14-tetrahydro-6,14-endoethenonoripavine is treated with *m*-fluorophenyl hydrazine hydrochloride in acetic acid to give N-cyclopropylmethyl-7 α -[1-(*m*-fluorophenyl)-5-pyrazolyl]-6,7,8,14-tetrahydro-6,14-endoethenonoripavine.

EXAMPLE 44

Preparation of N-cyclopropylmethyl-7 α -[1-(*m*-methoxyphenyl)-5-pyrazolyl]-6,7,8,14-tetrahydro-6,14-endoethenonoripavine

5 Following the general procedure of Example 17, N-cyclopropylmethyl-7 α -(2-formyl-1-methoxyvinyl) - 6,7,8,14 - tetrahydro - 6,14 - endoethenonoripavine is treated with *m*-methoxyphenyl hydrazine hydrochloride in acetic acid to give N-cyclopropylmethyl - 7 α - [1 - (*m* - methoxyphenyl) - 5 - pyrazolyl] - 6,7,8,14-tetrahydro - 6,14 - endoethenonoripavine. 5

EXAMPLE 45

10 Preparation of N-cyclopropylmethyl-7 α -[1-(*m*-bromophenyl)-5-pyrazolyl]-6,7,8,14-tetrahydro-6,14-endoethenonoripavine 10

15 Following the general procedure of Example 17, N-cyclopropylmethyl-7 α -(2-formyl - 1 - methoxyvinyl) - 6,7,8,14 - tetrahydro - 6,14 - endoethenonoripavine is treated with *m*-bromophenyl hydrazine hydrochloride in acetic acid to give N-cyclopropylmethyl - 7 α - [1 - (*m* - bromophenyl) - 5 - pyrazolyl] - 6,7,8,14-tetrahydro - 6,14 - endoethenonoripavine. 15

EXAMPLE 46

20 Preparation of N-cyclopropylmethyl-7 α -[1-(α,α,α -trifluoro-*m*-tolyl)-pyrazolyl]-6,7,8,14-tetrahydro-6,14-endoethenonoripavine 20

Following the general procedure of Example 4, N-cyclopropylmethyl-7 α -(2-formyl - 1 - methoxyvinyl) - 6,7,8,14 - tetrahydro - 6,14 - endoethenonoripavine is treated with α,α,α -trifluoro-*m*-tolylhydrazine hydrochloride in acetic acid to give N - cyclopropylmethyl - 7 α - [1 - (α,α,α - trifluoro - *m* - tolyl) - 5 - pyrazolyl]-6,7,8,14 - tetrahydro - 6,14 - endoethenonoripavine.

EXAMPLE 47

25 Preparation of N-cyclopropylmethyl-7 α -[1-(*m*-tolyl)-5-pyrazolyl]-6,7,8,14-tetrahydro-6,14-endoethenonoripavine 25

30 Following the general procedure of Example 4, N-cyclopropylmethyl-7 α -(2-formyl - 1 - methoxyvinyl) - 6,7,8,14 - tetrahydro - 6,14 - endoethenonoripavine is treated with *m*-tolylhydrazine hydrochloride in acetic acid to give N - cyclopropylmethyl-7 α -[1-(*m*-tolyl)-5-pyrazolyl]-6,7,8,14-endoethenonoripavine. 30

EXAMPLE 48

35 Preparation of N-cyclopropylmethyl-7 α -(1-methyl-5-pyrazolyl)-6,7,8,14-tetrahydro-6,14-endoethenonoripavine 35

Following the general procedure of Example 4, N-cyclopropylmethyl-7 α -(2 - formyl - 1 - methoxyvinyl) - 6,7,8,14 - tetrahydro - 6,14 - endoethenonoripavine is treated with methylhydrazine hydrochloride in acetic acid to give N-cyclopropylmethyl - 7 α - (1 - methyl - 5 - pyrazolyl) - 6,7,8,14 - tetrahydro - 6,14 - endoethenonoripavine. 40

EXAMPLE 49

40 Preparation of N-allyl-7 α -(1-phenyl-5-pyrazolyl)-6,7,8,14-tetrahydro-6,14-endoethenonoripavine 40

45 Following the general procedure of Example 17, N-allyl-7 α -(2-formyl-1-methoxyvinyl) - 6,7,8,14 - tetrahydro - 6,14 - endoethenonoripavine is treated with phenylhydrazine hydrochloride in acetic acid to give N-allyl-7 α -(1-phenyl-5-pyrazolyl)-6,7,8,14-tetrahydro-6,14-endoethenonoripavine. 45

EXAMPLE 50

50 Preparation of N-allyl-7 α -[1-(*m*-chlorophenyl)-5-pyrazolyl]-6,7,8,14-tetrahydro-6,14-endoethenonoripavine 50

Following the general procedure of Example 17, N-allyl-7 α -(2-formyl-1-methoxyvinyl)-6,7,8,14 - tetrahydro - 6,14 - endoethenonoripavine is treated with *m* - chlorophenylhydrazine hydrochloride in acetic acid to give N-allyl-7 α -[1-(*m*-chlorophenyl)-5-pyrazolyl]-6,7,8,14-tetrahydro-6,14-endoethenonoripavine.

EXAMPLE 51

55 Preparation of N-(3-methyl-2-buten-1-yl)-7 α -(1-phenyl-5-pyrazolyl)-6,7,8,14-tetrahydro-6,14-endoethenonoripavine 55

Following the general procedure of Example 17, N-(3-methyl-2-buten-1-yl)-7 α -(2-formyl-1-methoxyvinyl) - 6,7,8,14 - tetrahydro - 6,14 - endoethenonoripavine is treated with phenylhydrazine hydrochloride in acetic acid to give N-(3-methyl-2-

buten - 1 - yl) - 7 α - (1 - phenyl - 5 - pyrazolyl) - 6,7,8,14 - tetrahydro - 6,14 - endoethenonoripavine.

EXAMPLE 52

Preparation of N-(3-methyl-2-buten-1-yl)-7 α -[1-(*m*-chlorophenyl)-5-pyrazolyl]-6,7,8,14-tetrahydro-6,14-endoethenonoripavine

Following the general procedure of Example 17, N-(3-methyl-2-buten-1-yl)-7 α -(2-formyl - 1 - methoxyvinyl) - 6,7,8,14 - tetrahydro - 6,14 - endoethenonoripavine is treated with *m*-chlorophenylhydrazine hydrochloride in acetic acid to give N-(3-methyl - 2 - buten - 1 - yl) - 7 α - [1 - (*m* - chlorophenyl) - 5 - pyrazolyl]-6,7,8,14-tetrahydro-6,14-endoethenonoripavine.

EXAMPLE 53

Preparation of N-cyclobutylmethyl-7 α -(1-phenyl-5-pyrazolyl)-6,7,8,14-tetrahydro-6,14-endoethenonoripavine

Following the general procedure of Example 17, N-cyclobutylmethyl-7 α -(2-formyl - 1 - methoxyvinyl) - 6,7,8,14 - tetrahydro - 6,14 - endoethenonoripavine is treated with phenylhydrazine hydrochloride in acetic acid to give N-cyclobutylmethyl-7 α -(1-phenyl-5-pyrazolyl)-6,7,8,14-tetrahydro-6,14-endoethenonoripavine.

EXAMPLE 54

Preparation of N-cyclobutylmethyl-7 α -[1-(*m*-chlorophenyl)-5-pyrazolyl]-6,7,8,14-tetrahydro-6,14-endoethenonoripavine

Following the general procedure of Example 4, N-cyclobutylmethyl-7 α -(2-formyl-1-methoxyvinyl)-6,7,8,14-tetrahydro-6,14-endoethenonoripavine is treated with *m*-chlorophenylhydrazine hydrochloride in acetic acid to give N-cyclobutylmethyl - 7 α - [1 - (*m* - chlorophenyl) - 5 - pyrazolyl] - 6,7,8,14 - tetrahydro - 6,14 - endoethenonoripavine.

EXAMPLE 55

Preparation of 7 α -(2-formyl-1-methoxyvinyl)-6,7,8,14-tetrahydro-6,14-endoethenothebaine

A solution of phosgene (20 g.) in methylene chloride (200 ml.) is added rapidly dropwise with stirring to a mixture of dimethyl formamide (200 ml.; dried over molecular sieves) and methylene chloride (600 ml.). The mixture is stirred for a further 15 minutes after the addition is complete. A solution of 7 α -(1,1-dimethoxyethyl) - 6,7,8,14 - tetrahydro - 6,14 - endoethenothebaine (19.4 g.) in methylene chloride (200 ml.) and pyridine (10 ml.) is then added in a slow stream and the mixture is stirred for 45 minutes. Aqueous sodium acetate (1200 ml.; 5%) is then added and the mixture is stirred vigorously for 30 minutes. If necessary, the mixture is adjusted to pH 8 by the addition of aqueous sodium bicarbonate and the layers are separated. The aqueous layer is washed with methylene chloride and is then made strongly alkaline with sodium hydroxide solution (10%). The mixture is extracted with ether and the extract is washed with water and dried. Evaporation of solvent followed by crystallization of the residue from acetone-*n*-hexane gives 7 α -(2-formyl-1-methoxyvinyl)-6,7,8,14-tetrahydro-6,14-endoethenothebaine (15.37 g.), m.p. 152—153° C. A further amount (1.42 g.) m.p. 150—152° C., is obtained from the mother liquor to give a total yield of 87%.

EXAMPLE 56

Preparation of N-cyclopropylmethyl-7 α -(2-formyl-1-methoxyvinyl)-6,7,8,14-tetrahydro-6,14-endoethenonorthobaine hydrochloride

A solution of phosgene (1 g.) in methylene chloride (10 ml.) is added rapidly dropwise with stirring to a mixture of dimethylformamide (10 ml.; dried over molecular sieves) and methylene chloride (30 ml.). The mixture is stirred for a further 15 minutes after the addition is complete. A solution of N-cyclopropylmethyl-7 α -(1,1-dimethoxyethyl) - 6,7,8,14 - tetrahydro - 6,14 - endoethenonorthobaine (1 g.) in methylene chloride (10 ml.) and pyridine (0.5 ml.) is then added in a slow stream, and the mixture is stirred at room temperature for 45 minutes. Aqueous sodium hydroxide (60 ml.; 5%) is then added, and the mixture is stirred vigorously for 30 minutes. The layers are separated and the organic phase is washed with water and dried. The oil obtained by evaporation of solvent is dissolved in dilute hydrochloric acid (5%), and the solution is washed with ether and extracted with methylene chloride. The extract is dried and evaporated. Acetone is added to cause crystallization and the material is collected with the aid of ether to give N-cyclopropylmethyl-7 α - (2 - formyl - 1 - methoxyvinyl) - 6,7,8,14 - tetrahydro - 6,14 - endoethenonorthobaine hydrochloride (835 mg.), m.p. 213—215° C.

EXAMPLE 57

Preparation of 7 α -(2-formyl-1-methoxyvinyl)-6,7,8,14-tetrahydro-6,14-*endoethenonoripavine*

5 Following the general procedure of Example 56, 7 α -(1,1-dimethoxyethyl)-6,7,8,14-tetrahydro-6,14-*endoethenonoripavine* is treated with phosgene-dimethylformamide followed by hydrolysis to give 7 α -(2-formyl-1-methoxyvinyl)-6,7,8,14-tetrahydro-6,14-*endoethenonoripavine*. 5

EXAMPLE 58

10 Preparation of N-cyclopropylmethyl-7 α -(2-formyl-1-methoxyvinyl)-6,7,8,14-tetrahydro-6,14-*endoethenonoripavine* 10

15 A solution of phosgene (8.5 f.) in methylene chloride (255 ml.) is added dropwise, with slow stirring, to a mixture of dimethylformamide (85 ml.; dried over molecular sieves) and methylene chloride (255 ml.). Fifteen minutes after the addition was complete, a solution of N-cyclopropylmethyl-7 α -(1,1-dimethoxyethyl)-6,7,8,14-tetrahydro-6,14-*endoethenonoripavine* (8.5 g.) in methylene chloride (85 ml.) and pyridine (4.5 ml.) is added in a slow stream, and the mixture is stirred at room temperature for 45 min. Aqueous sodium hydroxide (510 ml.; 5%) is then added and the mixture is stirred vigorously for 30 min. The layers are separated and the methylene chloride extract is washed with water and dried. Evaporation of solvent gives a gum which solidifies on the addition of water. This material is collected and dried *via* methylene chloride solution followed by evaporation of solvent to give N-cyclopropylmethyl-7 α -(2-formyl-1-methoxyvinyl)-6,7,8,14-tetrahydro-6,14-*endoethenonoripavine* as a glass (8 g.; quantitative yield). 20

EXAMPLE 59

25 Preparation of 7 α -(2-formyl-1-methoxyvinyl)-6,7,8,14-tetrahydro-6,14-*endoethenonorthobaine* 25

30 Following the general procedure of Example 56, 7 α -(1,1-dimethoxyethyl)-6,7,8,14-tetrahydro-6,14-*endoethenonorthobaine* is treated with phosgene-dimethylformamide followed by hydrolysis to give 7 α -(2-formyl-1-methoxyvinyl)-6,7,8,14-tetrahydro-6,14-*endoethenonorthobaine*. 30

EXAMPLE 60

35 Preparation of 7 α -(2-formyl-1-methoxy-1-butenyl)-6,7,8,14-tetrahydro-6,14-*endoethenothebaine*

Following the general procedure of Example 55, 7 α -(1,1-dimethoxybutyl)-6,7,8,14-tetrahydro-6,14-*endoethenothebaine* is treated with phosgene-dimethylformamide followed by hydrolysis to give 7 α -(2-formyl-1-methoxy-1-butenyl)-6,7,8,14-tetrahydro-6,14-*endoethenothebaine*. 35

EXAMPLE 61

40 Preparation of 7 α -(2-formyl-1-methoxyvinyl)-6,7,8,14-tetrahydro-6,14-*endoethanothebaine* 40

Following the general procedure of Example 55, 7 α -(1,1-dimethoxyethyl)-6,7,8,14-tetrahydro-6,14-*endoethanothebaine* is treated with phosgene-dimethylformamide followed by hydrolysis to give 7 α -(2-formyl-1-methoxyvinyl)-6,7,8,14-tetrahydro-6,14-*endoethanothebaine*.

EXAMPLE 62

45 Preparation of 7 β -(2-formyl-1-methoxyvinyl)-6,7,8,14-tetrahydro-6,14-*endoethenothebaine* 45

50 Following the general procedure of Example 55, 7 β -(1,1-dimethoxyethyl)-6,7,8,14-tetrahydro-6,14-*endoethenothebaine* is treated with phosgene-dimethylformamide followed by hydrolysis to give 7 β -(2-formyl-1-methoxyvinyl)-6,7,8,14-tetrahydro-6,14-*endoethenothebaine*. 50

EXAMPLE 63

Preparation of 7 α -(2-formyl-1-methoxyvinyl)-7,8-dihydro-6-hydroxy-6,14-*endoethenocodide*

55 Following the general procedure of Example 55, 7 α -(1,1-dimethoxyethyl)-7,8-dihydro-6-hydroxy-6,14-*endoethenocodide* is treated with phosgene-dimethylformamide followed by hydrolysis to give 7 α -(2-formyl-1-methoxyvinyl)-7,8-dihydro-6-hydroxy-6,14-*endoethenocodide*. 55

EXAMPLE 64

Preparation of N-cyano-7 α -(2-formyl-1-methoxyvinyl)-6,7,8,14-tetrahydro-6,14-*endoethenonorthebaine*

Following the general procedure of Example 55, N-cyano-7 α -(1,1-dimethoxyethyl) - 6,7,8,14 - tetrahydro - 6,14 - *endoethenonorthebaine* is treated with phosgene-dimethylformamide followed by hydrolysis to give N-cyano-7 α -(2-formyl-1-methoxyvinyl)-6,7,8,14-tetrahydro-6,14-*endoethenonorthebaine*.

EXAMPLE 65

Preparation of N-allyl-7 α -(2-formyl-1-methoxyvinyl)-6,7,8,14-tetrahydro-6,14-*endoethenonororipavine*

Following the general procedure of Example 56, N-allyl-7 α -(1,1-dimethoxyethyl) - 6,7,8,14 - tetrahydro - 6,14 - *endoethenonororipavine* is treated with phosgene-dimethylformamide followed by hydrolysis to give N-allyl-7 α -(2-formyl-1-methoxyvinyl)-6,7,8,14-tetrahydro-6,14-*endoethenonororipavine*.

EXAMPLE 66

Preparation of 7 α -(2-formyl-1-methoxyvinyl)-N-(3-methyl-2-buten-1-yl)-6,7,8,14-tetrahydro-6,14-*endoethenonororipavine*

Following the general procedure of Example 56, 7 α -(1,1-dimethoxyethyl)-N-(3-methyl - 2 - buten - 1 - yl) - 6,7,8,14 - tetrahydro - 6,14 - *endoethenonororipavine* is treated with phosgene-dimethylformamide followed by hydrolysis to give 7 α -(2-formyl - 1 - methoxyvinyl) - N - (3 - methyl - 2 - buten - 1 - yl) - 6,7,8,14-tetrahydro - 6,14 - *endoethenonororipavine*.

EXAMPLE 67

Preparation of N-cyclobutylmethyl-7 α -(2-formyl-1-methoxyvinyl)-6,7,8,14-tetrahydro-6,14-*endoethenonororipavine*

Following the general procedure of Example 56, N-cyclobutylmethyl-7 α -(1,1-dimethoxyethyl) - 6,7,8,14 - tetrahydro - 6,14 - *endoethenonororipavine* is treated with phosgene-dimethylformamide followed by hydrolysis to give N-cyclobutylmethyl-7 α - (2 - formyl - 1 - methoxyvinyl) - 6,7,8,14 - tetrahydro - 6,14 - *endoethenonororipavine*.

EXAMPLE 68

Pharmaceutical Preparation containing N-cyclopropylmethyl-7 α -(1-phenyl-5-pyrazolyl)-6,7,8,14-tetrahydro-6,14-*endoethenonororipavine*

The compound N-Cyclopropylmethyl-7 α -(1-phenyl-5-pyrazolyl)-6,7,8,14-tetrahydro-6,14-*endoethenonororipavine* is incorporated into a standard pharmaceutical tablet according to the following formulation.

Ingredient	Per Tablet mg.	For 10,000 Tablets, g.
N-cyclopropylmethyl-7 α -(1-phenyl-5-pyrazolyl)-6,7,8,14-tetrahydro-6,14- <i>endoethenonororipavine</i>	2.5	25
Lactose	225	2250
Corn Starch (for mix)	50	500
Corn Starch (for paste)	25	250
Magnesium stearate	5	50
	307.5	3075

The active ingredient, 2-amino-5-nitrothiazole, lactose and corn starch for mix are blended together. The corn starch for paste is suspended in water at a ratio of 100 g. of corn starch per 800 ml. of water and heated with stirring to form a paste. The resulting paste is then used to granulate the blended powder. Additional water is used if necessary. The wet granules are passed through a No. 8 screen and dried at 120° F. The dry granules are passed through a No. 16 screen and lubricated with the magnesium stearate. The granulation is then compressed into tablets (tablet wt. 355 mg.) in a suitable tableting machine. Each tablet contains 50 mg. of active ingredient.

EXAMPLE 69

Pharmaceutical Preparation containing N-cyclopropylmethyl-7 α -[1-(*m*-chlorophenyl)-5-pyrazolyl]-6,7,8,14-tetrahydro-6,14-endoethenonoripavine

5 The active ingredient N-cyclopropylmethyl-7 α -[1-(*m*-chlorophenyl)-5-pyrazolyl]-6,7,8,14-tetrahydro-6,14-endoethenonoripavine may be dispensed in hard shell capsules. A formulation found useful for preparing such capsules is as follows: 5

	Ingredient	Per Capsule mg.	For 1000 Capsules, g.	
10	N-cyclopropylmethyl-7 α -[1-(<i>m</i> -chlorophenyl)-5-pyrazolyl]-6,7,8,14-tetrahydro-6,14-endoethenonoripavine	2.5	2.5	10
	Lactose	90	90	
	Magnesium stearate	1.5	1.5	
15		94	94	15

The active ingredient, lactose and magnesium stearate are blended together. The mixture is used to fill hard shell capsules of a suitable size at a fill weight of 94 mg. per capsule.

EXAMPLE 70

20 Pharmaceutical Preparation containing N-cyclopropylmethyl-7 α -(1-phenyl-5-pyrazolyl)-6,7,8,14-tetrahydro-6,14-endoethenonoripavine 20

The active component, N-cyclopropylmethyl-7 α -(1-phenyl-5-pyrazolyl)-6,7,8,14-tetrahydro-6,14-endoethenonoripavine may be incorporated into an injectable solution according to the following formulation: 25

25	Ingredient			
	N-cyclopropylmethyl-7 α -(1-propyl-5-pyrazolyl)-6,7,8,14-tetrahydro-6,14-endoethenonoripavine		0.1 g.	
30	Polyethylene Glycol 4000 U.S.P.		4.0 g.	
	Sodium Chloride U.S.P.		0.90 g.	30
	Benzyl Alcohol, Reagent Grade		0.90 g.	
	Water for injection qs ad		100.0 ml.	

35 The vehicle is prepared by mixing together all of the above ingredients except N-cyclopropylmethyl-7 α -(1-phenyl-5-pyrazolyl)-6,7,8,14-tetrahydro-6,14-endoethenonoripavine. The vehicle and active ingredient are rendered sterile by suitable means. A solution of the active ingredient in the vehicle is prepared by dissolving the active ingredient first with a portion of the vehicle and then adding the remaining portion of the vehicle while stirring. 35

A one ml. dose of this solution therefore, provides 1 mg. of active ingredient. 40

EXAMPLE 71

40 Pharmaceutical Preparation containing N-cyclopropylmethyl-7 α -[1-(*m*-chlorophenyl)-5-pyrazolyl]-6,7,8,14-tetrahydro-6,14-endoethenonoripavine

45 The active component, N-cyclopropylmethyl-7 α -[1-(*m*-chlorophenyl)-5-pyrazolyl]-6,7,8,14-tetrahydro-6,14-endoethenonoripavine may be incorporated into an injectable solution according to the following formulation: 45

	Ingredient			
50	N-cyclopropylmethyl-7 α -[1-(<i>m</i> -chlorophenyl)-5-pyrazolyl]-6,7,8,14-tetrahydro-6,14-endoethenonoripavine		0.1 g.	
	Polyethylene Glycol 4000 U.S.P.		4.0 g.	50
	Sodium Chloride U.S.P.		0.90 g.	
	Benzyl Alcohol, Reagent Grade		0.90 g.	
	Water for injection qs ad		100.0 ml.	

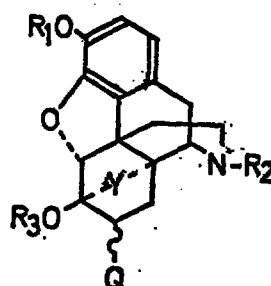
The vehicle is prepared by mixing together all of the above ingredients except N-

cyclopropylmethyl - 7 α - [1 - (*m* - chlorophenyl) - 5 - pyrazolyl] - 6,7,8,14 - tetrahydro - 6,14 - *endo*ethenonoropavine. The vehicle and active ingredient are rendered sterile by suitable means. A solution of the active ingredient in the vehicle is prepared by dissolving the active ingredient first with a portion of the vehicle and then adding the remaining portion of the vehicle while stirring.

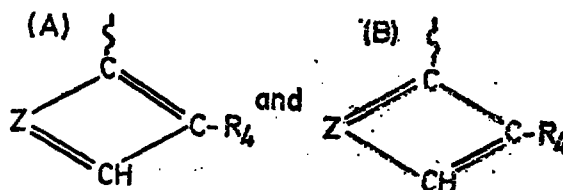
A one ml. dose of this solution therefore, provides 1 mg. of active ingredient.

WHAT WE CLAIM IS:—

1. A compound of the formula:

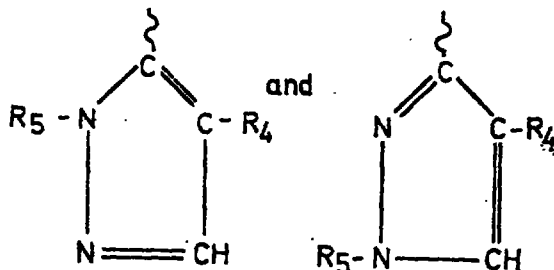


wherein R_1 is hydrogen, (C_1-C_4) alkyl or (C_2-C_6) alkanoyl; R_2 is hydrogen, cyano, propargyl, (C_1-C_4) alkyl, phenyl (C_1-C_4) alkyl, (C_2-C_6) alkenyl or (C_4-C_7) cycloalkylmethyl; R_3 is hydrogen or methyl; Y is etheno or ethano; and Q is a moiety selected from those of the formulae:



wherein R_4 is hydrogen or (C_1-C_7) alkyl, and Z is $-N(R_5)-N=$, $-O-N=$ or $-N=C(NH_2)-N=$, wherein R_5 is hydrogen, (C_1-C_4) alkyl, phenyl, halophenyl, (C_1-C_4) alkylphenyl, (C_1-C_4) alkoxyphenyl, trifluoro-methylphenyl, pyridyl, quinolyl, benzothiazolyl, dimethylpyrimidyl or dimethyl-*s*-triazinyl; or a non-toxic acid addition salt thereof; or an alkali metal phenolate thereof when R_4 is hydrogen.

2. A compound according to Claim 1, wherein Q is a moiety selected from those of the formula:



wherein R_4 and R_5 are as defined in Claim 1, except that R_5 is not (C_1-C_4) alkoxyphenyl or trifluoromethylphenyl.

3. A compound according to Claim 1, wherein Z is $-N=C(NH_2)-N=$.

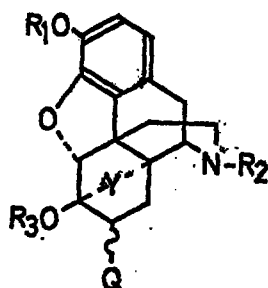
4. A compound according to Claim 1, wherein Q is a moiety of the formula:

cyclopropylmethyl - 7 α - [1 - (*m* - chlorophenyl) - 5 - pyrazolyl] - 6,7,8,14 - tetrahydro - 6,14 - *endo*ethenonoripavine. The vehicle and active ingredient are rendered sterile by suitable means. A solution of the active ingredient in the vehicle is prepared by dissolving the active ingredient first with a portion of the vehicle and then adding the remaining portion of the vehicle while stirring.

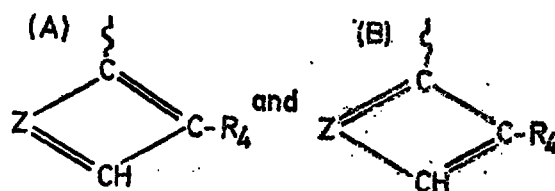
A one ml. dose of this solution therefore, provides 1 mg. of active ingredient.

WHAT WE CLAIM IS:—

1. A compound of the formula:

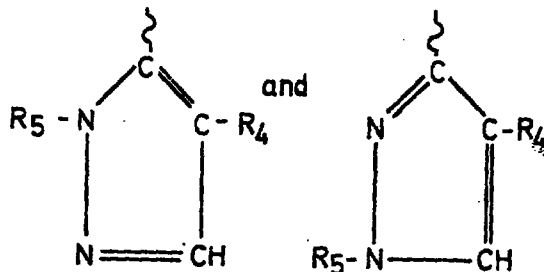


wherein R_1 is hydrogen, (C_1-C_4) alkyl or (C_2-C_6) alkanoyl; R_2 is hydrogen, cyano, propargyl, (C_1-C_4) alkyl, phenyl (C_1-C_6) alkyl, (C_2-C_6) alkenyl or (C_4-C_7) cycloalkylmethyl; R_3 is hydrogen or methyl; Y is etheno or ethano; and Q is a moiety selected from those of the formulae:



wherein R_4 is hydrogen or (C_1-C_7) alkyl, and Z is $-N(R_5)-N=$, $-O-N=$ or $-N=C(NH_2)-N=$, wherein R_5 is hydrogen, (C_1-C_4) alkyl, phenyl, halophenyl, (C_1-C_4) alkylphenyl, (C_1-C_4) alkoxyphenyl, trifluoro-methylphenyl, pyridyl, quinolyl, benzothiazolyl, dimethylpyrimidyl or dimethyl-*s*-triazinyl; or a non-toxic acid addition salt thereof; or an alkali metal phenolate thereof when R_1 is hydrogen.

2. A compound according to Claim 1, wherein Q is a moiety selected from those of the formula:

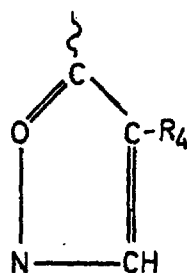


wherein R_4 and R_5 are as defined in Claim 1, except that R_5 is not (C_1-C_4) alkoxyphenyl or trifluoromethylphenyl.

3. A compound according to Claim 1, wherein Z is $-N=C(NH_2)-N=$.

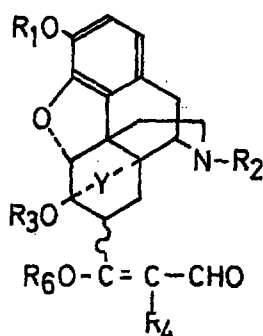
4. A compound according to Claim 1, wherein Q is a moiety of the formula:





wherein R_4 is as defined in Claim 1.

5. A process of preparing a compound according to Claim 1, comprising contacting a compound of the formula:



wherein R_1 , R_2 , R_3 , R_4 and Y are as defined in Claim 1 and R_6 is (C_1-C_4) alkyl, with a heterocycle-forming reagent selected from hydrazine, a substituted hydrazine of the formula $HN(R_5)-NH_2$, wherein R_5 is as defined in Claim 1, hydroxylamine, guanidine, and salts thereof, in a protic solvent at a temperature of from 50°C . to 125°C .; and, if desired, forming an acid addition salt, or, when R_1 is hydrogen, an alkali metal phenolate, of the codide or morphide product.

6. A process according to Claim 5, wherein R_6 is other than (C_1-C_4) alkoxy-phenyl and trifluoromethylphenyl.

7. A process of preparing a compound according to any one of Claims 2—4 and substantially as hereinbefore described.

8. A process of preparing a compound according to Claim 1 and substantially as hereinbefore described.

9. A compound whenever prepared by a process according to Claim 6 or Claim 7.

10. A compound whenever prepared by a process according to Claim 5 or Claim 8.

11. A compound according to any one of Claims 2—4 and substantially as hereinbefore described.

12. A compound according to Claim 1 and substantially as hereinbefore described.

13. A pharmaceutical preparation comprising a compound according to Claim 1 and a pharmaceutically acceptable carrier or diluent.

14. A pharmaceutical preparation comprising a compound according to any one of Claims 2—4 and a pharmaceutically acceptable carrier or diluent.

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