1,000,506

PATENT SPECIFICATION

NO DRAWINGS

1,000,506

Date of Application and filing Complete Specification: Nov. 23, 1961.

No. 41928/61.

Application made in United States of America (No. 72844) on Dec. 1, 1960.

Complete Specification Published: Aug. 4, 1965.

© Crown Copyright 1965.

Index at acceptance:—C2 C(1E4K4, 1E4K6, 1E5K4, 1E5K6, 2B20, 3A12A4A, 3A12B3, 3A12C6, 3A13B3, 3A13C1C, 3A13C3C, 3A13C10B, 3A13C10F); C2 A(1C2A, 2C1)

Int. Cl.:—C 07 d

COMPLETE SPECIFICATION

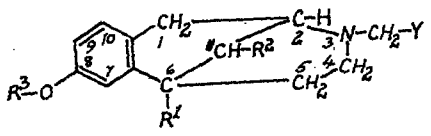
1,2,3,4,5,6-Hexahydro-2,6-Methano-3-Benzazocines

We, STERLING DRUG INC., a corporation organized under the laws of the State of Delaware, United States of America, of 1450 Broadway, New York, New York, 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 derivatives of 1,2,3,4,5,6 - hexahydro - 2,6 - methano - 3 - benzazocine and to the preparation thereof. More particularly, this invention relates to certain novel 1,2,3,4,5,6-hexahydro-3-substituted-8-hydroxy and alkoxy-2,6-methano-3-benzazocines and to their preparation.

The new compounds of this invention have pharmacodynamic activity and are useful as antagonists of certain strong analgesic agents, such as morphine and meperidine.

The compounds of the present invention are the 1,2,3,4,5,6 - hexahydro - 3 - (Y - CH_2 -) - 6 - (R^1) - 11 - (R^2) - 8 - hydroxy and alkoxy - 2,6-methano-3-benzazocines having the structural formula



Formula I

in which Y is an alkenyl group having three, four or five carbon atoms, a halo-lower alkenyl group having two to five carbon atoms and one or two chlorine or bromine atoms attached to ethylenic carbon, or a cyano, or cyano-lower alkenyl group, an alkynyl group having three, four or five carbon atoms, or a cycloalkyl group; R^1 is a hydrogen atom or a lower alkyl group; R^2 is a hydrogen atom, a methyl or ethyl group; and R^3 is a hydrogen atom or a lower alkyl group.

Y when it is an alkenyl group has three, four or five carbon atoms, for example

$-CH=CH-CH_3$, $-C(CH_3)=CH_2$,
$-CH_2-CH=CH_2$, $-CH=C(CH_3)_2$,
$-CH=CH-CH_2CH_2CH_3$ or
$-CH_2-CH=CH-CH_2CH_3$.

Y when it is a halo-lower alkenyl group has one or two chlorine or bromine atoms attached to ethylenic carbon, that is, either one or both of the two ethylenic carbon atoms involved in the $-\overset{|}{C}=\overset{|}{C}-$ double-bond bear chlorine or bromine, and has two to five carbon atoms, for example

$-CH=CH-Cl$, $-CH=CH-Br$,
$-CCl=CHCl$, $-CCl-CHBr$,
$-CH_2-CH=CCl-CH_3$,
$-CH_2-CCl=CCl-CH_3$,
$-CH=C(Cl)_2$, $-CBr=C(CH_3)_2$,
$-CH_2-CH=CCl_2$ or
$-CH_2CH_2-CH=CCl-CH_3$.

Y when it is a cyano-lower alkenyl group has three to six carbon atoms and one or two cyano groups, for example

$-CH=CH-CN$, $-C(CN)=CH_2$,
$-C(CH_3)=CH-CN$,
$-CH_2-CH=CH-CN$,
$-CH_2CH_2-CH=CH-CN$,
$-CH=CH-CH_2CH_2CH_2-CN$
or $-CH=C(CN)_2$.

Y when it is an alkynyl group has three, four or five carbon atoms, for example

$-C\equiv C-CH_3$, $-C\equiv C-CH_2-CH_3$,
$-CH_2-C\equiv C-CH_3$ or
$-C\equiv C-CH(CH_3)-CH_3$.

Y when it is a cycloalkyl group has 3 to 7 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl. R^1 or R^3 when it is a lower alkyl group contains one to four carbon atoms, including for example methyl, ethyl, *n*-propyl, isopropyl, and *n*-butyl.

[Price 4s. 6d.]

Due to the presence of a basic tertiary amino grouping, the compounds of this invention react with organic and inorganic acids to form acid-addition salts; and, due to the presence of both a basic tertiary amino grouping and an acidic phenolic grouping in their structure, the new 1,2,3,4,5,6 - hexahydro - 3 - (Y-CH_2 -) - 6 - (R^1) - 11 - (R^2) - 8 - hydroxy - 2,6 - methano - 3 - benzazocines of this invention have amphoteric properties; and therefore for a given compound, the particular molecular species which will predominate will depend on the pH of the environment. Thus, in strongly acidic media, the amino nitrogen will be protonated, and the predominant molecular species will be an acid-addition salt. On the other hand, in strongly alkaline madia, the predominant molecular species of the 8-hydroxy compounds, i.e. when R^3 is hydrogen, will be than of a phenolate ion, and under pH conditions intermediate between these extremes, the proportion of the un-dissociated molecular species will increase to reach a maximum as the isoelectric point is approached, the form which is isolatable at the isoelectric point being conveniently termed the isoelectric form.

The new compounds can exist in stereochemically isomeric forms, that is, optical isomers and geometric isomers. Unless otherwise designated, the starting materials and products of the present invention are all in the cis (or normal) form. If desired, the isolation or the production of a particular stereochemical form can be accomplished by application of the general principles known in the prior art.

The phenoxide and acid-addition salt forms of the new compounds are useful not only as antagonists of certain strong analgesic agents, as above-indicated, but are also useful for characterizing and identifying purposes, and in isolation or purification procedures. Moreover, the phenoxides and acid-addition salts are sources of the isoelectric forms, by reaction with acids or bases, respectively, and accordingly all of the phenoxides and acid-addition salts, regardless of considerations of solubility, toxicity, physical form, or the like of a particular compound are useful for the purposes of the invention.

It will be appreciated from the above that if one or more of the characteristics, such as solubility, molecular weight, physical appearance, toxicity, or the like of a given isoelectric, phenoxide, or acid-addition salt form of a particular compound render that form unsuitable for the purpose at hand, it can be readily converted to another, more suitable form.

The new 1,2,3,4,5,6 - hexahydro - 3 - (Y - CH_2 -) - 6 - (R^1) - 11 - (R^2) - 8 - hydroxy - and alkoxy-2,6-methano-3-benzazocines of the invention can be conveniently prepared in their isoelectric forms or free amino forms, as the case may be, by N-substituting the corresponding secondary amines, namely the 1,2,3,4,5,6 - hexahydro - 6 - (R^1) - 11 - (R^2) - 8 - hydroxy - and alkoxy-2,6-methano-3-benzazocines, by heating with an agent having the formula Y—CH_2—An, where Y has the same meaning indicated hereinabove and An is the anion of a strong organic or inorganic acid, for instance a reactive halide or an arylsulfonate, e.g., a tosylate, in the presence of an acid-absorbing medium, for instance an alkali metal carbonate or bicarbonate, for instance sodium bicarbonate. This reaction is preferably carried out in the presence of a suitable reaction medium such as a lower alkanol, for instance methanol or ethanol, or an N,N-(di-lower alkyl)-lower alkanamide, for instance N,N-dimethylformamide or N,N-dimethylacetamide.

Another method suitable for preparing the new compounds of this invention comprises: N-acylating the corresponding 1,2,3,4,5,6 - hexahydro - 6 - (R^1) - 11 (R^2) - 8 - hydroxy - or alkoxy-2,6-methano-3-benzazocines with an acid halide or acid anhydride of an acid having the formula Y—COOH; and reducing the resulting N—(CO—Y) derivative with a reducing agent such as lithium aluminum hydride which is effective to reduce the carbonyl group of said derivative without affecting any ethylenic linkages.

When an 8—OH compound is used as the starting material and it is desired to prepare an 8-alkoxy compound, the 8—OH group is etherified, for instance by treatment with a di-lower alkyl sulfate after treatment with the agent Y—CH_2—An, or acylation, and, in the latter case, either before or after reduction.

The acid-addition salt forms of the 1,2,3,4,5,6 - hexahydro - 3 - (Y - CH_2 -) - 6 - (R^1) - 11 - (R^2) - 8 - hydroxy - and alkoxy-2,6-methano-3-benzazocines of this invention are conveniently obtained by interacting the free base forms or the isoelectric forms which are obtained by the above alkylation or acylation-reduction methods with one equivalent of an organic or inorganic acid. The acid residues or anions in these salt forms are in themselves neither novel nor critical and therefore can be any acid anion or acid-like substance capable of salt formation with the isoelectric forms of the compounds.

The acid-addition salt forms of the compounds are prepared from any organic acid, inorganic acid (including organic acids having an inorganic group therein), or organo-metallic acid as exemplified by organic mono- and polycarboxylic acids such as found, for example, in Beilstein's Organische Chemie, 4th Ed., Volumes III, IV, IX, X, XIV, XVII, XIX, XXI, XXII, and XXV; organic mono- and polysulfonic acid-sulfinic acids such as found, for example in Beilstein Volumes VI, XI, XVI, and XXII; organic phosphonic and phosphinic acids such as found, for example, in Beilstein Volumes XI and XVI; organic acids of arsenic and antimony such as found,

for example, in Beilstein Volume XVI; organic heterocyclic carboxylic, sulfonic, and sulfinic acids such as found, for example in Beilstein Volumes XVIII, XXII, and XXV; acidic ion-exchange resins; and inorganic acids of any acid forming element or combination of elements such as found in Mellor, Comprehesive Treatise on Inorganic and Theoretical Chemistry, Longman's, Green and Co., New York, N.Y. Volumes I—XVI. In addition, other salt-forming compounds which are acidic in their chemical properties but which are not generally considered as acids in the same sense as carboxylic or sulfonic acids are also considered to be among the numerous acids which can be used to prepare the acid-addition salt forms of the compounds of this invention. Thus there are also included acidic phenolic compounds such as found, for example, in Volume VI of Beilstein, acidic compounds having "activated" or acidic hydrogen atoms, as for example, picrolonic acid, or barbituric acid derivatives having an acidic proton such as found, for example, in Cox et al. Medicinal Chemistry, Vol. IV, John Wiley and Sons, Inc., New York, N.Y. (1959). Also included as salt forming agents are so-called Lewis acids which lack a pair of electrons in the outer "electron shell" and react with basic compounds having an unshared pair of electrons to form salts, for example boron trifluoride.

Representative acids for the formation of the acid-addition salts include formic acid, acetic acid, isobutyric acid, alpha-mercaptopropionic acid, trifluoroacetic acid, malic acid, fumaric acid, succinic acid, succinamic acid, glutamic acid, tartaric acid, oxalic acid, pyromucic acid, citric acid, lactic acid, glycolic acid, gluconic acid, saccharic acid, ascorbic acid, penicillin, benzoic acid, phthalic acid, salicyclic acid, 3,5-dinitrobenzoic acid, anthranilic acid, cholic acid, 2-pyridinecarboxylic acid, 3-hydroxy-2-naphthoic acid, picric acid, quinic acid, tropic acid, 3-indoleacetic acid, barbituric acid, sulfamic acid, methane-sulfonic acid, ethanesulfonic acid, isethionic acid, benzenesulfonic acid, *p*-toluenesulfonic acid, butyl-arsonic acid, methanephosphonic acid, acidic resins, hydrofluoric acid, hydrochloric acid, hydrobromic acid, hydriodic acid, perchloric acid, nitric acid, sulfuric acid, phosphoric acid, hydrocyanic acid, phosphotungstic acid, molybdic acid, and arsenic acid. The acid-addition salts with lactic acid and with ethanesulfonic acid, for example, are water-soluble and are ~~specially~~ especially suitable forms for using the new compounds as antagonists.

The acid-addition salts are prepared in conventional fashion, for instance either by direct mixing of the acid and the free base form or the isoelectric form or, when this is not appropriate, by dissolving either or both of the acid and the free base form or isoelectric form separately in water or an organic solvent and mixing the two solutions, or by dissolving both the acid and the free base form of the isoelectric form together in a solvent. The resulting acid-addition salt is isolated by filtration, if it is insoluble in the reaction medium, or by evaporation of the reaction medium to leave the acid-addition salt as a residue.

The phenolate salt form of the new compounds where R^3 is hydrogen is readily obtained for example by treating the isoelectric form with a strong alkali, such as sodium hydroxide. The alkali metal phenolates are water-soluble.

The starting materials for the preparation of the compounds of this invention can be obtained by application of known procedures. Thus, a 3-(R^2)-4-(R^1)-pyridine methiodide is interacted with *p*-methoxybenzylmagnesium chloride; the resulting N-methyl-2-(*p*-methoxybenzyl)-3-(R^1)-4-(R^2)-1,2-dihydropyridine is reduced with sodium borohydride or by catalytic hydrogenation to produce an N-methyl - 2 - (*p* - methoxybenzyl) - 3 - (R^2) - 4 - (R^1) - 1,2,5,6 - tetrahydropyridine; and this latter product is heated with an appropriate cyclizing agent, such as concentrated hydrobromic or phosphoric acid to yield a 1,2,3,4,5,6 - hexahydro - 3 - methyl - 6 - (R^1) - 11 - (R^2) - 8 - hydroxy - 2,6 - methano - 3 - benzazocine. By acetylation of the 8-hydroxyl group in this cyclization product by treatment with acetic anhydride and treatment of the resulting 8-acetoxy compound with cyanogen bromide, there is produced a 1,2,3,4,5,6 - hexahydro - 3 - cyano - 6 - (R^1) - 11 - (R^2) - 8 - acetoxy - 2,6 - methano - 3 - benzazocine which by heating with dilute hydrochloric acid is converted to the desired 1,2,3,4,5,6 - hexahydro - 6 - (R^1) - 11 - (R^2) - 8 - hydroxy - 2,6 - methano - 3 - benzazocine.

By alternative system of nomenclature, the compounds of this invention are designated as benzomorphan derivatives, that is, as 2 - (Y - CH_2 -) - 2^1 - hydroxy - or alkoxy - 5 - (R^1) - 9 - (R^2) - 6,7 - benzomorphans.

The structures of the compounds of this invention followed from the methods of synthesis which were used and from the elementary analyses of the products obtained.

Our invention is illustrated by the following examples without, however, being limited thereto.

EXAMPLE 1

1,2,3,4,5,6 - Hexahydro - 3 - (3 - hexenyl) - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine

A mixture of 4.78 g. of 1,2,3,4,5,6 - hexahydro - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine (which is known also as 2^1 - hydroxy - 5,9 - dimethyl - 6,7 - benzomorphan), 3.58 g. of 1-bromo-3-hexene, 75 ml. of methanol, and 2.65 g. of sodium bicarbonate was stirred and refluxed for approxi-

mately five and one-half hours. The reaction mixture was then filtered and the filtrate was concentrated under reduced pressure to yield a syrupy residue. This residue was extracted with two 30 ml. portions of chloroform, and the extracts were combined and filtered. The filtrate was treated with charcoal and, after removal of the charcoal, was concentrated under reduced pressure. The resulting residue was dissolved in 30 ml. of diethyl ether. After the solution had stood overnight, more diethyl ether was added, and an amorphous precipitate formed. This precipitate was removed by filtration. The filtrate was concentrated and then a solution of hydrogen chloride in diethyl ether was added. The white precipitate which formed was collected on a filter and dried. This solid was dissolved in water and the solution was treated with decolorizing charcoal. The charcoal was removed by filtration and to the filtrate there was added ammonium hydroxide. The mixture thus obtained was extracted with chloroform and the chloroform extract was dried and concentrated to a red-brown syrup. This syrup was dissolved in 80 ml. of anhydrous ether, and the resulting solution was filtered using a diatomaceous earth filter aid to remove about 0.2 g. of insoluble amorphous solid. The filtrate was concentrated to a red-brown syrup. By triturating this syrup with acetone there was obtained a white crystalline solid. After chilling, this solid was collected on a filter. There is obtained 1,2,3,4,5,6 - hexahydro - 3 - (3 - hexenyl) - 6,11 - di - methyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine (Formula I: $Y=-CH_2-CH=CH-CH_2-CH_3$; $R^1=-CH_3$; $R^2=-CH_3$; $R^3=-H$), having the molecular formula $C_{20}H_{29}NO$.

EXAMPLE 2

1,2,3,4,5,6 - Hexahydro - 3 - (3 - methyl - 2 - butenyl) - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine

A mixture of 8.7 g. of 1,2,3,4,5,6 - hexahydro - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine, 6.0 g. of 1-bromo-3-methyl-2-butene, 5.0 g. of sodium bicarbonate, and 125 ml. of N,N-dimethylformamide was stirred and refluxed for approximately four and one-half hours. The reaction mixture was then filtered, and the solid on the filter was washed with ethanol. The filtrate and the wash liquor were combined, concentrated under reduced pressure, and then extracted with chloroform. The chloroform extract was concentrated under reduced pressure to yield a syrup which weighed 15.8 g. This syrup was dissolved in 120 ml. of diethyl ether and the resulting solution was filtered to remove approximately one-half gram of a brown amorphous solid. The filtrate was extracted with a mixture of 5 ml. of concentrated hydrochloric acid and 20 ml. of water. To the extract there was added 5 ml. of concentrated ammonium hydroxide solution and ice. A pale tan syrup separated from solution and after stirring, this syrup solidified. The resulting pale tan solid was collected and dried; it weighed 10.6 g. After two recrystallizations from a mixture of methyl alcohol and water, with charcoaling, this solid weighed 8.2 g. and melted at 145—147°C. The product thus obtained was 1,2,3,4,5,6 - hexahydro - 3 - (3 - methyl - 2 - butenyl) - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine (Formula I: $Y=-CH=C(CH_3)_2$; $R^1=-CH_3$; $R^2=-CH_3$; $R^3=-H$), having the molecular formula $C_{19}H_{27}NO$. This product was soluble in a mixture of 0.35 ml. of N/2 hydrochloric acid and 0.15 ml. of water to the extent of 10 per cent, the pH of the 1 per cent solution being 2.80; and when the pH of the 1 per cent solution was gradually raised by addition of N/10 sodium hydroxide solution, a precipitate formed at pH 5.4.

EXAMPLE 3

1,2,3,4,5,6 - Hexahydro - 3 - (3 - methyl - 2 - butenyl) - 6 - methyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine

Following the procedure described in Example 2 hereinabove but substituting 8.15 g. of 1,2,3,4,5,6 - hexahydro - 6 - methyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine for the 8.7 g. of the corresponding 6,11-dimethyl compound used in that example, there is obtained 1,2,3,4,5,6 - hexahydro - 3 - (3 - methyl - 2 - butenyl) - 6 - methyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine (Formula I: $Y=-CH=C(CH_3)_2$; $R^1=-CH_3$; $R^2=-H$; $R^3=-H$), having the molecular formula $C_{18}H_{25}NO$.

EXAMPLE 4

1,2,3,4,5,6 - Hexahydro - 3 - (3 - methyl - 2 - butenyl) - 8 - hydroxy - 2,6 - methano - 3 - benzazocine

Following the procedure described in Example 2 hereinabove but substituting 7.6 g. of 1,2,3,4,5,6 - hexahydro - 6 - methyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine for the 8.7 g. of the corresponding 6,11-dimethyl compound used in that example, there is obtained 1,2,3,4,5,6 - hexahydro - 3 - (3 - methyl - 2 - butenyl) - 8 - hydroxy - 2,6 - methano - 3 - benzazocine (Formula I: $Y=-CH=C(CH_3)_2$; $R^1=-H$; $R^2=-H$; $R^3=-H$), having the molecular formula $C_{17}H_{23}NO$.

EXAMPLE 5

1,2,3,4,5,6 - Hexahydro - 3 - (3 - methyl - 2 - butenyl) - 6 - ethyl - 11 - methyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine

A mixture of 9.25 g. of 1,2,3,4,5,6 - hexahydro - 6 - ethyl - 11 - methyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine, 6.0 g. of 1-bromo-3-methyl-2-butene, 125 ml. of N,N-dimethylformamide, and 5.0 g. of sodium

bicarbonate was stirred and refluxed for approximately four and one-half hours. The reaction mixture was then filtered, and the solid collected on the filter was washed with ethanol. The filtrate and the wash liquor were combined and concentrated under reduced pressure. To the resulting residue there was added 50 ml. of diethyl ether, and the mixture was filtered. Approximately 0.6 g. of solid was collected on the filter, and 8.2 g. of brown solid separated from the filtrate and was collected by filtration. These two crops of solid (8.8 g.) were combined, 25 ml. of methanol was added, and the mixture was boiled. Only a small portion of the solid dissolved. This mixture was mixed with 25 ml. of water and chilled. The mixture was filtered to collect 8.3 g. of pale tan solid which melted at 156—158°C. The product thus obtained was 1,2,3,4,5,6 - hexahydro - 3 - (3 - methyl - 2 - butenyl) - 6 - ethyl - 11 - methyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine (Formula I: Y=—CH=C(CH_3)$_2$; R^1=—C_2H_5; R^2=—CH_3; R^3=—H), having the molecular formula $C_{20}H_{29}NO$. The solubility of this product in a mixture of 0.34 ml. of N/2 hydrochloric acid and 19.66 ml. of water was less than 0.25 per cent; and its solubility in ethanol was less than 1 per cent (weight/volume).

EXAMPLE 6

1,2,3,4,5,6 - Hexahydro - 3 - (3 - methyl - 2 - butenyl) - 6 - *n* - butyl - 11 - methyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine

Following the procedure described in Example 5 hereinabove but substituting 9.9 g. of 1,2,3,4,5,6 - hexahydro - 6 - n - butyl - 11 - methyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine for the 9.25 g. of the corresponding 6-ethyl-11-methyl compound used in Example 5, there is obtained 1,2,3,4,5,6 - hexahydro - 3 - (3 - methyl - 2 - butenyl) - 6 - n - butyl - 11 - methyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine (Formula I: Y=—CH=C(CH_3)$_2$; R^1=—$(CH_2)_3$—CH_3; R^2=—CH_3; R^3=—H), having the molecular formula $C_{22}H_{33}NO$.

EXAMPLE 7

1,2,3,4,5,6 - Hexahydro - 3 - (3 - chloro - 2 - propenyl) - 6,11 - dimethyl - 8 - hydroxy-2,6 - methano - 3 - benzazocine

A mixture of 8.7 g. of 1,2,3,4,5,6 - hexahydro - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine, 4.4 g. of a mixture of the cis and trans forms of 1,3-dichloro-1-propene, 5.0 g. of sodium bicarbonate, and 125 ml. of N,N-dimethylformamide was stirred and refluxed for approximately five hours. The reaction mixture was then filtered, and the solid collected on the filter was washed with ethanol. The filtrate and the wash liquor were combined and concentrated under reduced pressure, and water and diethyl ether were added to the resulting brown syrupy residue. The ether layer was separated and extracted with dilute hydrochloric acid. Concentrated ammonium hydroxide was added to the acidic aqueous extract, thus causing separation of a gum. This gum was dissolved in diethyl ether, and the resulting solution was filtered to remove a small amount of insoluble brown amorphous solid. The filtrate was charcoaled to remove some of its color, was concentrated under reduced pressure, and was then cooled in a refrigerator. The solid which separated from solution was collected on a filter and dried. The white solid thus obtained weighed 2.6 g. and melted at 165—176°C. It was recrystallized from methano to yield 1.7 g. of white granules which melted at 174—186°C. The product thus obtained was 1,2,3,4,5,6-hexahydro - 3 - (3 - chloro - 2 - propenyl) - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine (Formula I: Y=—CH=CH—Cl; R^1=—CH_3; R^2=—CH_3; R^3=—H) in the form of a mixture of cis and trans isomers, having the molecular formula $C_{17}H_{22}ClNO$. This product was soluble in a mixture of 0.34 ml. of N/2 hydrochloric acid and 0.16 ml. of water to the extent of 10 per cent, the pH of the 1 per cent solution being 2.0; and when the pH of these solutions was gradually raised by addition of N/10 sodium hydroxide solution, a precipitate formed at pH 6.0.

When the above preparation was repeated using pure trans-1,3-dichloro-1-propene as the alkylating agent, the product obtained was trans - 1,2,3,4,5,6 - hexahydro - 3 - (3 - chloro - 2 - propenyl) - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine in the form of white crystals which melted at 156—158°C. The solubility of this product in water was less than 0.25 per cent, and its solubility in ethanol was less than 1 per cent (weight/volume).

When pure cis-1,3-dichloro-1-propene was used as the alkylating agent, there was obtained cis - 1,2,3,4,5,6 - hexahydro - 3 - (3 - chloro - 2 - propenyl) - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine in the form of pale yellow crystals which melted at 186—189°C. The solubility of this product in a mixture of 0.34 ml. of N/2 hydrochloric acid and 19.66 ml. of water was less than 0.25 per cent, and its solubility in ethanol was less than 1 per cent (weight/volume).

EXAMPLE 8

1,2,3,4,5,6 - Hexahydro - 3 - (3 - chloro - 2 - propenyl) - 6 - methyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine

Following the procedure described in Example 7 hereinabove but substituting 8.15 g. of 1,2,3,4,5,6 - hexahydro - 6 - methyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine for the 8.7 g. of the corresponding 6,11-dimethyl

compound used in that example, there is obtained 1,2,3,4,5,6 - hexahydro - 3 - (3 - chloro - 2 - propenyl) - 6 - methyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine (Formula I: Y=—CH=CH—Cl; R^1=—CH_3; R^2=H; R^3=—H) in the form of a mixture of cis and trans isomers, having the molecular formula $C_{16}H_{20}ClNO$.

EXAMPLE 9

1,2,3,4,5,6 - Hexahydro - 3 - (3 - chloro - 2 - propenyl) - 8 - hydroxy - 2,6 - methano - 3 - benzazocine

Following the procedure described in the first part of Example 7 hereinabove but substituting 7.6 g. of 1,2,3,4,5,6 - hexahydro - 8 - hydroxy - 2,6 - methano - 3 - benzazocine for the 8.7 g. of the corresponding 6,11-dimethyl compound used in that example, there is obtained 1,2,3,4,5,6 - hexahydro - 3 - (3-chloro - 2 - propenyl) - 6 - methyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine (Formula I: Y=—CH=CH—Cl; R^1=—H; R^2=—H; R^3=—H) in the form of a mixture of cis and trans isomers, having the molecular formula $C_{15}H_{18}ClNO$.

EXAMPLE 10

1,2,3,4,5,6 - Hexahydro - 3 - (3,3 - dichloro - propenyl) - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine

Following the procedure described in Example 7 hereinabove but using 1,3,3-trichloro-2-propene instead of 1,3-dichloro-1-propene as the alkylating agent, there was obtained 1,2,3,4,5,6 - hexahydro - 3 - (3,3 - dichloro-propenyl) - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine (Formula I: Y=—CH=$C(Cl)_2$; R^1=—CH_3; R^2=—CH_3; R^3=—H) having the molecular formula $C_{17}H_{21}Cl_2NO$, in the form of off-white crystals which melted at 145—147°C. The solubility of this compound in a mixture of 0.30 ml. of N/2 hydrochloric acid and 19.70 ml. of water was less than 0.25 per cent, and in ethanol was less than 1 per cent.

EXAMPLE 11

1,2,3,4,5,6 - Hexahydro - 3 - (2 - bromo - 3 - methyl - 2 - butenyl) - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine

Following the procedure described in Example 7 hereinabove but substituting 9.05 g. of 1,2-dibromo-3-methyl-2-butene for the 4.4 g. of 1,3-dichloro-1-propene used in that example, there is obtained 1,2,3,4,5,6 - hexahydro - 3 - (2 - bromo - 3 - methyl - 2 - butenyl) - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine (Formula I: Y=—CBr=$C(CH_3)_2$; R^1=—CH_3; R^2=—CH_3; R^3=—H), having the molecular formula $C_{19}H_{26}BrNO$.

EXAMPLE 12

1,2,3,4,5,6 - Hexahydro - 3 - (3 - cyanoallyl) - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine

Following the procedure described in Example 7 hereinabove but substituting 5.7 g. of 3-cyanoallyl bromide for the 4.4 g. of the 1,3-dichloro-1-propene used in that example, there is obtained 1,2,3,4,5,6 - hexahydro - 3 - (3 - cyanoallyl) - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine (Formula I: Y=—CH=CH—CN; R^1=—CH_3; R^2=—CH_3; R^3=—H), having the molecular formula $C_{18}H_{22}N_2O$.

EXAMPLE 13

1,2,3,4,5,6 - Hexahydro - 3 - (3,3 - dicyano - allyl) - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine

Following the procedure described in Example 6 hereinabove but substituting 5.5 g. of 1-chloro-3,3-di-cyano-1-propene for the 4.4 g. of the 1,3-dichloro-1-propene used in that example, there is obtained 1,2,3,4,5,6 - hexahydro - 3 - (3,3 - dicyanoallyl) - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine (Formula I: Y=—CH=$C(CN)_2$; R^1=—CH_3; R^2=—CH_3; R^3=—H), having the molecular formula $C_{19}H_{21}N_3O$.

EXAMPLE 14

1,2,3,4,5,6 - Hexahydro - 3 - cyclopropyl-methyl - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine

A mixture of 8.8 g. of 1,2,3,4,5,6 - hexahydro - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine and 100 ml. of methanol was warmed, and when almost all of the solid had dissolved there were added 15 ml. of water and 10 g. of pulverized potassium carbonate. The resulting mixture was cooled to room temperature and stirred while adding dropwise, over a period of approximately four hours, 7.9 g. of cyclopropanecarbonyl chloride. The reaction mixture was then filtered. The filtrate was concentrated, the resulting residue was mixed with water, and the mixture was extracted with a mixture of two parts of benzene and one part of butanol. The benzene-butanol extract was washed with dilute hydrochloric acid and then dried and concentrated to a small volume. The solid was isolated from the resulting suspension by filtering, and the collected solid was washed with diethyl ether. This solid was dissolved in chloroform and the resulting solution was extracted with a solution of 2.5 g. of sodium hydroxide in water. The alkaline aqueous extract was acidified to Congo Red paper by addition of hydrochloric acid. Blowing air through the acidified solution caused crystallization of an off-white solid which was collected on a filter and dried. This product, which was 1,2,3,4,5,6 - hexahydro - 3 - cyclopropanecarbonyl - 6,11 - dimethyl - 8 -

hydroxy - 2,6 - methano - 3 - benzazocine weighed 7.9 g. and melted at 179—180°C. A 1.9 g. sample of this compound was recrystallized from aqueous ethanol solution to yield 1.4 g. of off-white solid melting at 181—183°C. Its solubility in a mixture of 0.35 ml. of N/2 sodium hydroxide solution and 19.65 ml. of water was less than 0.25 per cent. In ethanol, this compound was soluble to the extent of 5 per cent (weight/volume), being precipitated from this solution by addition of four volumes of water.

A mixture of 6 g. of 1,2,3,4,5,6 - tetrahydro - 3 - cyclopropanecarbonyl - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine in 75 ml. of tetrahydrofuran and 2 g. of lithium aluminum hydride in tetrahydrofuran was stirred and refluxed for approximately three and one-half hours. To the reaction mixture there was added 6 ml. of water, and the mixture was filtered using a diatomaceous earth filter aid. The filtration proceeded very slowly. The filtrate was evaporated to dryness and the residue was stirred with hot water and filtered. There was thus obtained 2.0 g. of solid (crop 1) which melted at 188—195°C. with decomposition.

The solid which was collected on the filter with the diatomaceous earth filter aid was extracted with water, the aqueous extract being discarded, and the residue was extracted with tetrahydrofuran. The tetrahydrofuran extract was concentrated to yield 2.1 g. of white solid (crop 2) which melted at 190—200°C.

Crops 1 and 2 were separately treated as follows. Each crop was dissolved in dilute hydrochloric acid, the resulting solution was filtered, and the filtrate was made basic by addition of concentrated ammonium hydroxide, and the resulting precipitate was collected, and then was recrystallized from methanol. The two crops were then combined and recrystallized from methanol to yield 1.9 g. of shiny white crystals which melted at 201—204°C. The product thus obtained was 1,2,3,4,5,6-hexahydro - 3 - cyclopropyl - methyl - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine (Formula I: Y=—cyclopropyl; R^1=—CH_3; R^2=—CH_3; R^3=—H), having the molecular formula $C_{18}H_{25}NO$. This product was soluble in a mixture of 0.54 ml. of N/2 hydrochloric acid and 0.46 ml. of water to the extent of 5 per cent, the pH of the 1 per cent solution being 2.3; and when the pH of the 1 per cent solution was gradually raised by addition of N/10 sodium hydroxide solution, a precipitate formed at pH 2.9.

Example 15

1,2,3,4,5,6 - Hexahydro - 3 - cyclopropyl - methyl - 6 - methyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine

Following the procedure described in Example 14 hereinabove but substituting 8.2 g. of 1,2,3,4,5,6 - hexahydro - 6 - methyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine for the 8.8 g. of the corresponding 6,11-dimethyl compound used in that example, there is obtained 1,2,3,4,5,6 - hexahydro - 3 - cyclopropylmethyl - 6 - methyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine (Formula I: Y=—cyclopropyl; R^1=CH_3; R^2=—H; R^3=—H), having the molecular formula $C_{17}H_{23}NO$.

Example 16

1,2,3,4,5,6 - Hexahydro - 3 - cyclopropylmethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine

Following the procedure described in Example 14 hereinabove but substituting 7.7 g. of 1,2,3,4,5,6 - hexahydro - 8 - hydroxy - 2,6 - methano - 3 - benzazocine for the 8.8 g. of the corresponding 6,11-dimethyl compound used in that example, there is obtained 1,2,3,4,5,6 - hexahydro - 3 - cyclopropylmethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine (Formula I: Y=—cyclopropyl; R^1=—H; R^2=—H; R^3=—H), having the molecular formula $C_{16}H_{21}NO$.

Example 17

1,2,3,4,5,6 - Hexahydro - 3 - (3,3 - dichloro - 2 - propenyl) - 6 - ethyl - 11 - methyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine

Following a procedure similar to that described in Example 7 hereinabove but using 5.0 g. of 1-bromo-3,3-dichloro-2-propene and 6.2 g. of 1,2,3,4,5,6 - hexahydro - 6 - ethyl - 11 - methyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine as the reactants, there was obtained 5.8 g. of 1,2,3,4,5,6 - hexahydro - 3 - (3,3 - dichloro - 2 - propenyl) - 6 - ethyl - 11 - methyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine (Formula I: Y=—CH=$C(Cl)_2$; R^1=—C_2H_5; R^2=—CH_3; R^3=—H) having the molecular formula $C_{18}H_{23}Cl_2NO$, in the form of tan crystals which melted at 150—153°C. The solubility of this compound in a mixture of 0.30 ml. of N/2 hydrochloric acid and 19.70 ml. of water was less than 0.25 per cent, and its solubility in ethanol was less than 1 per cent (weight/volume).

Example 18

1,2,3,4,5,6 - Hexahydro - 3 - cyanomethyl - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine

Following a procedure similar to that described in Example 7 hereinabove but using 2.7 g. of chloroacetonitrile and 7.8 g. of 1,2,3,4,5,6 - hexahydro - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine as the reactants, there was obtained 4.8 g. of 1,2,3,4,5,6 - hexahydro - 3 - cyanomethyl - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine (Formula I: Y=—CN; R^1=—CH_3; R^2=—CH_3; R^3=—H) having the molecular formula $C_{16}H_{20}N_2O$, in the form

of white crystals which melted at 118—122°C. The solubility of this compound in water was less than 0.25 per cent, and in ethanol was less than 1 per cent (weight/volume).

EXAMPLE 19

1,2,3,4,5,6 - Hexahydro - 3 - (2 - methyl - 2 - propenyl) - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine

Using a procedure similar to that described in Example 7 hereinabove, 3.3 g. of 1-chloro-2-methyl-2-propene was interacted with 7.5 g. of 1,2,3,4,5,6 - hexahydro - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine (Formula I: Y=—$C(CH_3)=CH_2$; R^1=—CH_3; R^2=—CH_3; R^3=—H) having the molecular formula $C_{18}H_{25}NO$, which was treated with hydrochloric acid to yield 3.6 g. of the corresponding hydrochloride in the form of off-white crystals which melted at 260—261°C. (dec.). The solubility of the hydrochloride in water was less than 0.25 per cent, and in ethanol was less than 1 per cent (weight/volume).

EXAMPLE 20

1,2,3,4,5,6 - Hexahydro - 2 - chloro - 2 - propenyl - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine

Using a procedure similar to that described in Example 7 hereinabove, 3.3 g. of 1,2-dichloro-2-propene was interacted with 6.5 g. of 1,2,3,4,5,6 - hexahydro - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine to produce 1,2,3,4,5,6 - hexahydro - 2 - chloro - 2 - propenyl - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine (Formula I: Y=—$C(Cl)=CH_2$; R^1=—CH_3; R^2=—CH_3; R^3=—H) having the molecular formula $C_{17}H_{22}ClNO$, which was treated with hydrochloric acid to yield 4.5 g. of the corresponding hydrochloride in the form of white crystals which melted at 262—265°C. The solubility of the hydrochloride in water was less than 0.25 per cent, and in ethanol was less than 1 per cent (weight/volume).

EXAMPLE 21

1,2,3,4,5,6 - Hexahydro - 3 - cyclopropylmethyl - 6,11 - dimethyl - 8 - methoxy - 2,6 - methano - 3 - benzazocine

5.0 g. of 1,2,3,4,5,6 - hexahydro - 3 - cyclopropanecarbonyl - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine, obtained as described above in Example 14, was dissolved in 50 ml. of N sodium hydroxide solution, 10 ml. of dimethyl sulfate was added at room temperature, and the mixture was stirred vigorously for seven hours. The reaction mixture was then extracted with chloroform, and the chloroform layer was separated, washed with ammonium hydroxide solution, and dried. The chloroform solution was then concentrated on a steam bath to yield 6.9 g. of residue. This residue was further concentrated under reduced pressure (0.1 mm.). There was thus obtained 4.7 g. of 1,2,3,4,5,6 - hexahydro - 3 - cyclopropanecarbonyl - 6,11 - dimethyl - 8 - methoxy - 2,6 - methano - 3 - benzazocine as a yellow syrup. This product was dissolved in chloroform and the chloroform solution was washed with N sodium hydroxide solution and with dilute hydrochloric acid, and was then concentrated under reduced pressure. The residue thus obtained, which weighed 5.5 g., was reduced with lithium aluminum hydride (4.4 g.) in tetrahydrofuran for six hours. The reaction mixture was diluted with 8 ml. of water and filtered. The solid on the filter was washed with diethyl ether, and was then discarded. The filtrate and the wash liquid were combined and concentrated to yield 1,2,3,4,5,6 - hexahydro - 3 - cyclo - propylmethyl - 6,11 - dimethyl - 8 - methoxy - 2,6 - methano - 3 - benzazocine (Formula I: Y=cyclopropyl; R^1=—CH_3; R^2=—CH_3; R^3=—CH_3), having the molecular formula $C_{19}H_{27}NO$, as a yellow syrup. This product was dissolved in ether, and hydrogen chloride was added to convert the base to the hydrochloride salt. The hydrochloride was collected on a filter and dried. There was thus obtained 3.7 g. of the hydrochloride in the form of white crystals which melted at 219—220°C. This salt was soluble in water to the extent of 20 per cent. The pH of a 1 per cent aqueous solution of the salt was 6.1 and, when the pH of this solution was adjusted to 7.0 by addition of N/10 sodium hydroxide solution, a precipitate formed.

EXAMPLE 22

1,2,3,4,5,6 - Hexahydro - 3 - cyclobutylmethyl - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine

Following a procedure similar to that described in Example 14 hereinabove, 8.9 g. of cyclobutylcarbonyl chloride and 8.8 g. of 1,2,3,4,5,6 - hexahydro - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine were interacted to produce 6.7 g. of 1,2,3,4,5,6-hexahydro - 3 - cyclobutanecarbonyl - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine, m.p. 181—184°C. This amide (6.2 g.) was reduced with lithium aluminum hydride (3.0 g.) in tetrahydrofuran for two and one-half hours to yield 3.5 g. of 1,2,3,4,5,6-hexahydro - 3 - cyclobutylmethyl - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine (Formula I: Y=cyclobutyl; R^1=—CH_3; R^2=—CH_3; R^3=—H), having the molecular formula $C_{19}H_{27}NO$, as white crystals which melted at 167—169°C. This compound was soluble in a mixture of 0.34 ml. of N/2 hydrochloric acid and 0.66 ml. of water to the extent of 5 per cent. The pH of a 1% solution in this dilute aqueous acid was 1.0; and a precipitate formed when the pH was adjusted to 5.0 by addition of N/10 sodium hydroxide solution.

PATENT OFFICE

EXAMPLE 23

1,2,3,4,5,6 - Hexahydro - 3 - cyclobutylmethyl - 6 - ethyl - 11 - methyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine

Following a procedure similar to that described in Example 14 hereinabove, 1,2,3,4,5,6 - hexahydro - 6 - ethyl - 11 - methyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine was acylated with cyclobutanecarbonyl chloride. The yellow syrup (6 g.) obtained as the acylation product, which was a mixture of 1,2,3,4,5,6 - hexahydro - 3 - cyclobutanecarbonyl - 6 - ethyl - 11 - methyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine and 1,2,3,4,5,6 - hexahydro - 3 - cyclobutanecarbonyl - 6 - ethyl - 11 - methyl - 8 - cyclobutanecarbonyloxy - 2,6 - methano - 3 - benzazocine, was reduced with lithium aluminum hydride (4 g.) in tetrahydrofuran to produce 3.1 g. of 1,2,3,4,5,6 - hexahydro - 3 - cyclobutylmethyl - 6 - ethyl - 11 - methyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine (Formula I: Y=cyclobutyl; $R^1=C_2H_5$; $R^2=—CH_3$; $R^3=—H$), having the molecular formula $C_{20}H_{29}NO$, as white crystals which melted at 195—197°C. The solubiilty of this compound in water was less than 0.25 per cent, and in ethanol was less than 1 per cent (weight/volume).

EXAMPLE 24

1,2,3,4,5,6 - Hexahydro - 3 - cyclopentylmethyl - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine

Using a procedure similar to that described in Example 14 hereinabove, 8.8 g. of 1,2,3,4,5,6 - hexahydro - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine was acylated with 10.0 g. of cyclopentanecarbonyl chloride to produce 7.4 g. of 1,2,3,4,5,6 - hexahydro - 3 - cyclopentanecarbonyl - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine as white crystals which melted at 207—210°C. This amide (7 g.) was reduced with lithium aluminum hydride (4 g.) in tetrahydrofuran for about three hours to produce 3.8 g. of 1,2,3,4,5,6 - hexahydro - 3 - cyclopentylmethyl - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine (Formula I: Y=cyclopentyl; $R^1=—CH_3$; $R^2=—CH_3$; $R^3=—H$), having the molecular formula $C_{21}H_{31}NO$. This compound was treated with hydrochloric acid to convert it to the hydrochloride, a white crystalline solid which melted at 230—233°C. The hydrochloride was soluble in water to the extent of 0.5 per cent. The pH of the 0.5 per cent aqueous solution was 6.1, and a precipitate formed when the pH was adjusted to 6.4 by addition of N/10 sodium hydroxide solution.

Compounds of this invention which were prepared as described in the foregoing examples were found to be antagonists of certain strong analgesics. Thus, when tested in rats by a modified D'Amour-Smith test procedure and in dogs, they were found to be antagonists of the analgesic activity of morphine and meperidine. In this test procedure, when the compounds of this invention were ~~administerd~~ administered prior to or simultaneously with administration of morphine or meperidine, the expected analgesic effect of the latter was decreased with increasing dosage levels of the former to a point where no analgesic effect was obtained. And when the new compounds were administered after the administration of morphine or meperidine, the analgesic effect was diminished or terminated, depending on the dosage levels involved. The benzazocine derivatives of the invention are generally dispensed in pharmaceutical compositions or solutions comprising the derivative and an inert carrier or diluent. For example representative compounds of this invention, each in the form of an aqueous solution of the lactic acid acid-addition salt, were administered subcutaneously to rats to determine the dosage level, in terms of weight of antagonist per kilogram of body weight of the animal, which caused reduction of the analgesic effect of a 60 mg./kg. dose of meperidine hydrochloride by approximately 50 per cent, so that the analgesic effect produced by the combination of the antagonist and the meperidine hydrochloride was substantially the same as the analgesic effect produced by a 30 mg./kg. dose of meperidine hydrochloride alone. The results thus obtained for the lactic acid acid-addition salt of each of the indicated compounds were as follows: 1,2,3,4,5,6 - hexahydro - 3 - allyl - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine, 0.040 mg./kg.; 1,2,3,4,5,6 - hexahydro - 3 - allyl - 6 - ethyl - 11 - methyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine, 0.040 mg./kg.; 1,2,3,4,5,6 - hexahydro - 3 - (3 - methyl - 2 - butenyl) - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine, 10 mg./kg.; 1,2,3,4,5,6 - hexahydro - 3 - (3 - chloro - 2 - propenyl) - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine, 0.020 mg./kg.; 1,2,3,4,5,6 - hexahydro - 3 - propargyl - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine, 0.080 mg./kg.; and 1,2,3,4,5,6 - hexahydro - 3 - (3 - methyl - 2 - butenyl) - 6 - ethyl - 11 - methyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine, 20 mg./kg.

In addition to having antagonistic activity toward morphine and meperidine, 1,2,3,4,5,6-hexahydro - 3 - cyclopropylmethyl - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine was found to have muscle relaxant properties.

WHAT WE CLAIM IS:—

1. A process of preparing a benzazocine derivative of Formula I herein, which comprises either:

(a) treating the corresponding secondary amine with an agent having the formula

EXAMPLE 23

1,2,3,4,5,6 - Hexahydro - 3 - cyclobutylmethyl - 6 - ethyl - 11 - methyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine

Following a procedure similar to that described in Example 14 hereinabove, 1,2,3,4,5,6 - hexahydro - 6 - ethyl - 11 - methyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine was acylated with cyclobutanecarbonyl chloride. The yellow syrup (6 g.) obtained as the acylation product, which was a mixture of 1,2,3,4,5,6 - hexahydro - 3 - cyclobutanecarbonyl - 6 - ethyl - 11 - methyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine and 1,2,3,4,5,6 - hexahydro - 3 - cyclobutanecarbonyl - 6 - ethyl - 11 - methyl - 8 - cyclobutanecarbonyloxy - 2,6 - methano - 3 - benzazocine, was reduced with lithium aluminum hydride (4 g.) in tetrahydrofuran to produce 3.1 g. of 1,2,3,4,5,6 - hexahydro - 3 - cyclobutylmethyl - 6 - ethyl - 11 - methyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine (Formula I: Y=cyclobutyl; $R^1=C_2H_5$; $R^2=-CH_3$; $R^3=-H$), having the molecular formula $C_{20}H_{29}NO$, as white crystals which melted at 195—197°C. The solubiilty of this compound in water was less than 0.25 per cent, and in ethanol was less than 1 per cent (weight/volume).

EXAMPLE 24

1,2,3,4,5,6 - Hexahydro - 3 - cyclopentylmethyl - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine

Using a procedure similar to that described in Example 14 hereinabove, 8.8 g. of 1,2,3,4,5,6 - hexahydro - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine was acylated with 10.0 g. of cyclopentanecarbonyl chloride to produce 7.4 g. of 1,2,3,4,5,6 - hexahydro - 3 - cyclopentanecarbonyl - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine as white crystals which melted at 207—210°C. This amide (7 g.) was reduced with lithium aluminum hydride (4 g.) in tetrahydrofuran for about three hours to produce 3.8 g. of 1,2,3,4,5,6 - hexahydro - 3 - cyclopentylmethyl - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine (Formula I: Y=cyclopentyl; $R^1=-CH_3$; $R^2=-CH_3$; $R^3=-H$), having the molecular formula $C_{20}H_{29}NO$. This compound was treated with hydrochloric acid to convert it to the hydrochloride, a white crystalline solid which melted at 230—233°C. The hydrochloride was soluble in water to the extent of 0.5 per cent. The pH of the 0.5 per cent aqueous solution was 6.1, and a precipitate formed when the pH was adjusted to 6.4 by addition of N/10 sodium hydroxide solution.

Compounds of this invention which were prepared as described in the foregoing examples were found to be antagonists of certain strong analgesics. Thus, when tested in rats by a modified D'Amour-Smith test procedure and in dogs, they were found to be antagonists of the analgesic activity of morphine and meperidine. In this test procedure, when the compounds of this invention were ~~administered~~ administered prior to or simultaneously with administration of morphine or meperidine, the expected analgesic effect of the latter was decreased with increasing dosage levels of the former to a point where no analgesic effect was obtained. And when the new compounds were administered after the administration of morphine or meperidine, the analgesic effect was diminished or terminated, depending on the dosage levels involved. The benzazocine derivatives of the invention are generally dispensed in pharmaceutical compositions or solutions comprising the derivative and an inert carrier or diluent. For example representative compounds of this invention, each in the form of an aqueous solution of the lactic acid acid-addition salt, were administered subcutaneously to rats to determine the dosage level, in terms of weight of antagonist per kilogram of body weight of the animal, which caused reduction of the analgesic effect of a 60 mg./kg. dose of meperidine hydrochloride by approximately 50 per cent, so that the analgesic effect produced by the combination of the antagonist and the meperidine hydrochloride was substantially the same as the analgesic effect produced by a 30 mg./kg. dose of meperidine hydrochloride alone. The results thus obtained for the lactic acid acid-addition salt of each of the indicated compounds were as follows: 1,2,3,4,5,6 - hexahydro - 3 - allyl - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine, 0.040 mg./kg.; 1,2,3,4,5,6 - hexahydro - 3 - allyl - 6 - ethyl - 11 - methyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine, 0.040 mg./kg.; 1,2,3,4,5,6 - hexahydro - 3 - (3 - methyl - 2 - butenyl) - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine, 10 mg./kg.; 1,2,3,4,5,6 - hexahydro - 3 - (3 - chloro - 2 - propenyl) - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine, 0.020 mg./kg.; 1,2,3,4,5,6 - hexahydro - 3 - propargyl - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine, 0.080 mg./kg.; and 1,2,3,4,5,6 - hexahydro - 3 - (3 - methyl - 2 - butenyl) - 6 - ethyl - 11 - methyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine, 20 mg./kg.

In addition to having antagonistic activity toward morphine and meperidine, 1,2,3,4,5,6-hexahydro - 3 - cyclopropylmethyl - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine was found to have muscle relaxant properties.

WHAT WE CLAIM IS:—

1. A process of preparing a benzazocine derivative of Formula I herein, which comprises either:

(a) treating the corresponding secondary amine with an agent having the formula

PATENT OFFICE

* C L M S *

Y—CH_2—An where Y is as set forth in connection with Formula I and An is a reactive ester group corresponding to the anion of a strong organic or inorganic acid; or

(b) reducing the amide corresponding to the compound of Formula I, except that Y—CH_2 is replaced by Y—CO, with a reducing agent which is effective to reduce the carbonyl group to a methylene group without affecting any ethylenic linkages;

and, in either case if desired, forming a salt of the resulting derivative; and, where the starting material is an 8-hydroxy compound and it is desired to prepare the corresponding 8-alkoxy compound, etherifying the 8-hydroxy group.

2. A process according to claim 1, in which the reaction (a) is effected by heating the amine with the agent of the formula Y—CH_2—An in the presence of an acid-absorbing agent and preferably in the presence of a reaction medium or solvent.

3. A process according to claim 1, in which the reduction is effected by lithium aluminum hydride.

4. A process according to claim 1, in which the amide is prepared by acylating the secondary amine with a halide or anhydride of an acid having the formula Y—COOH where Y is as set forth in connection with Formula I.

5. A process according to claim 1, in which R^2 is methyl, R^3 is hydrogen, and R^1 is lower alkyl, preferably methyl.

6. A process according to claim 5, in which Y is lower alkenyl or cycloalkyl.

7. The processes of preparing benzazocine derivatives substantially as set forth in the Examples.

8. Benzazocine derivatives whenever prepared by a process according to any one of the preceding claims.

9. A benzazocine derivative of Formula I herein, or a salt thereof.

10. A compound according to claim 9, in which the salt is an acid-addition salt.

11. A compound according to claim 9, in which R^2 is methyl, R^3 is hydrogen, and R^1 is lower alkyl, preferably methyl.

12. A compound according to claim 11, in which Y is an alkenyl group having three, four or five carbon atoms.

13. A compound according to claim 11, in which Y is halo-lower alkenyl having 1 or 2 chlorine or bromine atoms attached to ethylenic carbon.

14. A compound according to claim 11, in which Y is an alkynyl group having three, four or five carbon atoms.

15. A compound according to claim 11, in which Y is cycloalkyl, preferably cyclopropyl.

16. 1,2,3,4,5,6 - Hexahydro - 3 - (3 - methyl - 2 - butenyl) - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine.

17. 1,2,3,4,5,6 - Hexahydro - 3 - (3 - methyl - 2 - butenyl) - 6 - ethyl - 11 - methyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine.

18. 1,2,3,4,5,6 - Hexahydro - 3 - (3 - chloro - 2 - propenyl) - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine.

19. 1,2,3,4,5,6 - Hexahydro - 3 - cyclopropylmethyl - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine.

20. 1,2,3,4,5,6 - Hexahydro - 3 - cyclobutylmethyl - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine.

21. 1,2,3,4,5,6 - Hexahydro - 3 - cyclopentylmethyl - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine.

22. The benzazocine derivatives as claimed in claim 9 set forth herein.

23. Pharmaceutical compositions or solutions including benzazocine derivatives according to any one of claims 8 to 22 and an inert carrier or diluent.

STEVENS, LANGNER, PARRY & ROLLINSON,
Chartered Patent Agents,
Agents for the Applicants.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press (Leamington) Ltd.—1965. Published by The Patent Office, 25 Southampton Buildings, London, W.C.2, from which copies may be obtained.

