

PATENT SPECIFICATION

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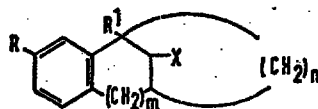
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(54) BENZOBICYCLOALKANE COMPOUNDS

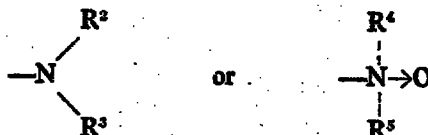
(71) We, AMERICAN HOME PRODUCTS CORPORATION, a corporation organised and existing under the laws of the State of Delaware, United States of America, of 685 Third Avenue, New York 10017, New York, United States of America, do hereby declare the invention for which we pray that a patent may be granted 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 benzobicycloalkane compounds. In particular the invention relates to amine and amine oxide derivatives of 5,8 - methano - benzocyclohexane, 5,8 - methano - benzocycloheptane, 5,9 - methano - benzocycloheptane, 5,9 - methano - benzocyclooctane, 5,10 - methano - benzocyclooctane, 5,10 - methano - benzocyclonane, 5,11 - methano - benzocyclononane, 5,11 - methano - benzocyclodecane, 5,12 - methano - benzocyclodecane, or 5,12 - methano - benzocycloundecane (including their pharmaceutically acceptable acid addition salts), to processes for preparing these derivatives, to pharmaceutical compositions containing the amine and amine oxide derivatives and to processes for using the derivatives and the pharmaceutical compositions. The amine and amine oxide derivatives, in general, exhibit pharmacological activity, e.g. analgesic or anti-inflammatory activity, in standard pharmacological tests in animals.

The new benzobicycloalkane derivatives of the invention can be represented by general formula (I)



wherein X is:



R is hydrogen, lower alkyl, lower alkyloxy, hydroxy, acyloxy, phen(lower)alkyloxy, halogen or trifluoromethyl; R1 is lower alkyl, phen(lower)alkyl, or when X is —NR2R3, hydroxymethyl or (lower)alkenyl; R2 is hydrogen, lower alkyl or phen(lower)alkyl; R3 is hydrogen, lower alkyl, phen(lower)alkyl, lower alkenyl or lower alkynyl; R4 is lower alkyl; R5 is lower alkyl; m is 0 or 1; and n is an integer of from 2 to 6 and the pharmaceutically acceptable acid addition salts thereof.

The compounds of general formula (I), in general, possess the inherent general

physical properties in the acid salt form of being high melting, white crystalline solids, substantially soluble in water and polar organic solvents such as lower aliphatic alcohols and the like. Examination of compounds produced according to the herein-after described processes reveals upon infrared and nuclear magnetic resonance spectroscopic analysis, infrared and nuclear magnetic resonance spectral data confirming the molecular structure hereinbefore set forth.

Many of the compounds of general formula (I) exert an analgesic effect in animals as evidenced by standard pharmacological tests. The analgesic activity of the compounds can be demonstrated by following a modification of the test procedure described by D'Amour and Smith in *Journal of Pharmacology* 72:74 (1941), an accepted test for analgesic agents. In this test rats are administered the compound orally, intraperitoneally or intramuscularly and the time required for response to a pain stimulus caused by a high intensity beam of light shining on the tail measured. The compounds of the invention in general exhibit analgesic activity in rats at a dose of from 3.15 mg. to 125 mg. per kilogram of body weight orally and intraperitoneally, and from 0.16 to 10.0 mg. per kilogram of body weight intramuscularly.

Particular compounds of general formula (I) are those wherein n is 4 or 5. As mentioned above these compounds, in general, possess the inherent applied use characteristic of exerting analgesic effects in warm-blooded animals as evidenced by pharmacological evaluation by standard test procedures.

Examples of such compounds are:

6,7,8,9,10,11 - Hexahydro - 3 - methoxy - 5 - methyl - 5,10 - methano - 5H - benzocyclononen-12-amine,

12 - Amino - 6,7,8,9,10,11 - hexahydro - 5 - methyl - 5,10 - methano - 5H - benzocyclononen-3-ol,

5 - Ethyl - 6,7,8,9,10,11 - hexahydro - 3 - methoxy - 5,10 - methano - 5H - benzocyclononen-12-amine,

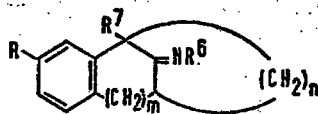
12 - Amino - 6,7,8,9,10,11 - hexahydro - 5 - ethyl - 5,10 - methano - 5H - benzocyclononen-3-ol,

3 - Methoxy - 5 - methyl - 5,6,7,8,9,10,11,12 - octahydro - 5,11 - methano - benzocyclodecen-13-amine,

13 - Amino - 5 - methyl - 5,6,7,8,9,10,11,12 - octahydro - 5,11 - methano - benzocyclodecen-3-ol including the isomers thereof e.g. (—)-syn-13-amino-5-methyl-5,6,7,8,9,10,11,12-octahydro-5,11-methano-benzocyclodecen-3-ol.

Other preferred compounds of general formula (I) are those wherein m is 1 and n is 2 or 3. These compounds, in general, possess the use characteristic of exerting analgesic effects in warm-blooded animals and in addition possess the use characteristic of exerting anti-inflammatory effects in animals as evidenced by standard pharmacologic tests. The anti-inflammatory activity of the compounds can be demonstrated by following a test procedure described by Winter *et al* in *Proceedings of the Society of Experimental Biology and Medicine*, 111:554, (1962) and by Buttle *et al* *Nature* 179:629, (1957), a generally accepted test for anti-inflammatory agents. In this test the compound is administered orally as a solution or suspension in distilled water to a group of six rats. After one hour edema in the paw of the rats is elicited by injection into the paw of a 1% solution of carrageenin. Paw volume is measured immediately and after 3 hours. The ability of the compounds to reduce the volume of the edema so produced when compared to a like number of control animals is a measure of anti-inflammatory activity. The above mentioned compounds of the invention generally exhibit anti-inflammatory activity in rats at a dose of from 50 mg. to 100 mg. per kilogram of body weight.

The novel benzobicycloalkane amines and amine oxides of the invention may be prepared by a process comprising reducing a compound of general formula (II)



(II)

wherein R⁶ is hydroxy, alkoxy, or has the meaning of R² given above except when R⁷ is alkoxy carbonyl R⁶ is not R²; R⁷ is alkoxy carbonyl, lower alkyl, lower alkenyl, hydroxy methyl or phen(lower)alkyl; and R, R², m and n are as hereinbefore described, and, if desired, lower alkylating, phen(lower)alkylating, lower alkenylating or

lower alkynylating a compound of general formula (I) in which R^3 is hydrogen to give a compound of general formula (I) in which R^3 is lower alkyl, phen(lower)alkyl, lower alkenyl or lower alkynyl, and/or lower alkylating or phen(lower)alkylating a compound in which R^2 is hydrogen and R^3 is lower alkyl, phen(lower)alkyl, lower alkenyl or lower alkynyl to give a corresponding compound in which R^2 is lower alkyl or phen(lower)alkyl, and/or oxidizing by known methods a compound in which R^2 and R^3 are lower alkyl to give the corresponding N-oxide, and/or converting by known methods a compound of general formula (I) in which R has one meaning into a compound of general formula (I) in which R has a different meaning and/or converting a free base of general formula (I) into a pharmaceutically acceptable acid addition salt.

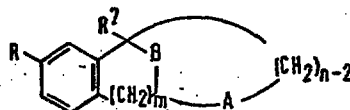
The compounds of general formula (II) may be reduced by standard reduction methods, e.g. with hydrogen using catalysts such as Raney nickel or platinum oxide; with hydrides of boron and aluminium and the complex metal hydrides derivable therefrom (e.g. with lithium aluminium hydride or with diborane); or with an alkali metal, preferably sodium, in an alcohol, for example, ethanol or isopropanol. When catalytically reducing an oximino compound the reaction proceeds stepwise, the imine of formula (II) in which R^2 is hydrogen may be isolated as an intermediate and this may be then reduced to the desired primary amine. Examples of methods of carrying out the various optional after-processes, for example, the hydrolysis of a compound in which R is lower alkoxy or phen(lower)alkoxy to give a compound in which R is hydroxy, are given hereinafter.

A primary amine in which both R^2 and R^3 are hydrogen may, for example, be converted into a secondary amine in which R^2 is hydrogen and R^3 is lower alkyl, phen(lower)alkyl, alkenyl or alkynyl by reaction with a halo compound of general formula



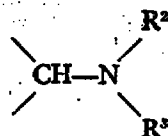
where Hal is chlorine or bromine and R'' is lower alkyl, phen(lower)alkyl, alkenyl or alkynyl, preferably in the presence of an organic base. A secondary amine in which R^2 is hydrogen and R^3 is lower alkyl, phen(lower)alkyl, lower alkenyl or lower alkynyl may be lower alkylated or phen(lower)alkylated to give a tertiary amine; for example, the secondary amine may be reacted with a haloformate ester and then reduced to give the tertiary amine in which R^2 is methyl. The haloformate ester may also be similarly reacted with the primary amine in which both R^2 and R^3 are hydrogen to give an N-methyl secondary amine. Other tertiary amines can be prepared by acylating the secondary amine to give a compound in which R^2 is acyl and then reducing the acylated amine. Oxidation of di(lower)alkyl tertiary amines to produce the corresponding N-oxides is conveniently accomplished by treatment with an organic peracid.

The novel benzobicyclicalkane amine and amine oxides of the invention may also be prepared by a process comprising the reduction of a compound having the formula (V)

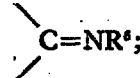


(V)

wherein A is: $-\text{CH}=\text{CH}-$, or $-\text{CH}(\text{OTosyl})-\text{CH}_2-$; B is:



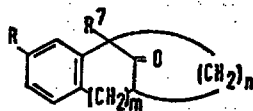
or



and R, R^2 , R^3 , R^6 , R^7 , m and n are as hereinbefore described, and if desired performing the previously described after-processes to prepare other compounds of formula (I) and their acid addition salts. The reduction may be accomplished by standard methods, for example, an olefinic bond may be reduced catalytically or by such borohydride reducing agents as sodium borohydride and aluminium chloride in diglyme, sodium borohydride and boron trifluoride in diglyme, diborane in tetra-

hydrofuran, and bis - 3 - methyl - 2 - butyl borane in tetrahydrofuran, and a tosyloxy group is conveniently reductively cleaved by lithium aluminium hydride. If present imino substituents will be simultaneously reduced to the corresponding amines, and alkoxy carbonyl substituents will be reduced to the corresponding alcohol.

The compounds of general formula (II) are disclosed and claimed in our co-pending application 35390/73 (Serial No. 1363660). They may be prepared by reacting a tricyclic ketone of general formula (III)



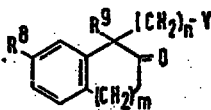
(III)

wherein R, R', m and n are as hereinbefore defined in connection with formula (II), with a compound of the formula



wherein R⁶ is as hereinbefore defined in connection with formula (II).

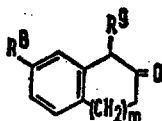
The tricyclic ketones of general formula (III) are disclosed and claimed in our co-pending application 35390/73 (Serial No. 1363660). They may be prepared by cyclising a halo(lower)alkylsulphonyl- or phenylsulphonyl-alkyl tetralone or indanone of general formula (IV)



(IV)

wherein m and n are as defined hereinabove, R⁸ is hydrogen, lower alkyl, lower alkoxy, acyloxy, phen(lower)alkoxy, halogen or trifluoromethyl, R⁹ is alkoxy-carbonyl, lower alkyl, lower alkenyl, hydroxymethyl or phen(lower)alkyl; Y is halo (preferably chloro or bromo), (lower) alkylsulphonyl or phenylsulphonyl and, if desired, converting a resulting compound of formula (III) in which R is lower alkoxy or phen(lower)alkoxy into a corresponding compound in which R is hydroxy, for example, by acid hydrolysis. The cyclisation is preferably effected with a strong base such as sodium hydride or an alkali metal alkoxide.

Most of the compounds of general formula (IV) are disclosed and claimed in our co-pending application 35389/73 (Serial No. 1363659). They may be prepared by alkylating a tetralone or indanone of general formula



where R⁸, R⁹ and m are as hereinabove defined preferably in the presence of a strong base (e.g. sodium hydride or an alkali metal alkoxide or when m is 0 preferably sodium hydroxide), with a compound of general formula



where n is as hereinabove defined, Y' has the meaning of Y as hereinabove defined or is tetrahydropyranyloxy and Z is halo (preferably chloro or bromo), (lower)alkylsulphonyl or phenylsulphonyl and where Y' is tetrahydropyranyloxy hydrolysing the product (preferably with aqueous mineral acid) and converting the resulting alcohol into a compound of general formula (IV), e.g. by treatment with a (lower)alkylsulphonyl or phenylsulphonyl halide (such as the chloride), preferably in pyridine.

As used herein the term "lower alkyl" means a saturated hydrocarbon radical, including the straight and branched radicals having from 1 to 4 carbon atoms, among which are for the purposes of illustration, but without limiting the generality of the foregoing, methyl, ethyl, n-propyl, n-butyl, and i-butyl. The term "lower alkenyl" means an unsaturated hydrocarbon radical, including straight and branched radicals, having from 3 to 5 carbon atoms, among which are for the purposes of illustration but without limiting the generality of the foregoing, allyl, 2-butenyl, 3-methyl-2-butenyl, 2-methyl-2-butenyl, and 2-pentyl. The term "lower alkynyl" means an unsaturated hydrocarbon radical, containing a triple bond, including straight and branched radicals, having from 3 to 6 carbon atoms, among which are for the purposes of illustration, but without limiting the generality of the foregoing 3-propynyl, 2-butylnyl, 1-butyln-3-yl, and 3-methyl-1-butyln-4-yl. The term "phen(lower)alkyl" means a lower alkyl radical as defined hereinabove substituted in a terminal position by a phenyl or a phenyl radical substituted by lower alkyl or lower alkyloxy, among which are for the purposes of illustration but without limiting the generality of the foregoing benzyl, phenethyl, *o*, *m*, or *p*-anisyl, *p* or *m*-cumenyl, veratryl, *o*, *m*, or *p*-xylyl. The term "phenylsulphonyl" means a phenyl or substituted phenyl sulphononic acid radical among which are, for the purposes of illustration, but without limiting the generality of the foregoing, phenyl sulphonyl, or *p*-toluene sulphonyl. The term "acyloxy" means either an aliphatic or aromatic carboxylic acid radical; if aliphatic, it may contain from 2 to 7 carbon atoms either straight chain, branched or concatenated to form a carbocyclic ring, among which are for the purposes of illustration but without limiting the generality of the foregoing acetic, propionic, butyric, i-butyric, cyclohexanecarboxylic, cyclopentanecarboxylic; if aromatic, it may contain an unsubstituted aromatic nucleus or the aromatic nucleus ring substituted by lower alkyl, among which are for the purposes of illustration but without limiting the generality of the foregoing, benzoic, *o*, *m*, or *p*-toluic, *p* or *m*-ethylbenzoic.

In describing the processes for the preparation of the specific embodiments of the invention, reference will be made to Figure A wherein the compounds are assigned Roman numerals for identification schematically, and wherein is illustrated schematically the reaction sequence for preparing specific primary amine embodiments of formula (I), namely 6,7,8,9,10,11 - hexahydro - 3 - methoxy - 5 - methyl - 5,10 - methano - 5H - benzocyclononen - 12 - amine (XI), 12 - amino - 6,7,8,9,10,11 - hexahydro - 5 - methyl - 5,10 - methano - 5H - benzocyclononen - 3 - ol (XIV), and 12 - amino - 6,7,8,9,10,11 - hexahydro - 5 - methyl - 5,10 - methano - 5H - benzocyclononen-3-ol, acetate (XV); specific secondary amine embodiments of formula (I), namely N - allyl - 6,7,8,9,10,11 - hexahydro - 3 - methoxy - 5 - methyl - 5,10 - methano - 5H - benzocyclononen - 12 - amine (X) and N,5 - dimethyl - 6,7,8,9,10,11 - hexahydro - 3 - methoxy - 5,10 - methano - 5H - benzocyclononen - 12 - amine (Xa); specific tertiary amine embodiments of formula (I), namely N - allyl - N,5 - dimethyl - 6,7,8,9,10,11 - hexahydro - 3 - methoxy - 5,10 - methano - 5H - benzocyclononen - 12 - amine (XII) and N - allyl - N - ethyl - 6,7,8,9,10,11 - hexahydro - 3 - methoxy - 5-methyl-5,10-methano-5H-benzocyclononen-12-amine (XIII).

Referring now to Figure A, the starting materials 1-alkyl, 1-alkenyl, or 1-phen(lower)alkyl-2-tetralones, may be prepared from commercially available 2-tetralones, by a well-known alkylation reaction as typically described by Stork and Schulenberg in the *Journal of the American Chemical Society*, 84, 284 (1962). The tetralones are treated with pyrrolidine in an inert solvent such as benzene, and then reacted with the appropriate lower alkyl, lower alkenyl, or phen(lower)alkyl halide in an inert solvent, such as benzene or dioxane, at elevated temperatures, conveniently the reflux temperature of the solvent employed. Substitution of an appropriate carbonylation reagent in this reaction will permit, if desired, the preparation of alkoxy carbonyl substituted tetralones. Lower alkyl, lower alkenyl, and phen(lower)alkyl tetralones may also be prepared from a suitable commercially available 1-tetralone which may be treated as described by Howell and Taylor in the *Journal of the Chemical Society*, 1958, 1249 with a Grignard reagent, prepared from the appropriate lower alkyl, lower alkenyl, or phen(lower)alkyl halide, and the resulting 1-substituted dihydronaphthalene oxidized with peracid.

Syntheses of non-commercially available tetralones are readily available in the literature, e.g. the synthesis of α -tetralone is described in *Organic Synthesis, Collective Volume IV*, page 898; the synthesis of β -tetralone is described in the same work on page 903; and a general synthesis of β -tetralones is described in *Netherlands Specification No. 67,09534*.

The first step in preparing the aforementioned embodiments is the portionwise addition, in the cold, of a strong base, such as a suspension of sodium hydride in

benzene, to a stirred solution of 1 - methyl - 7 - methoxy - 2 - tetralone (VI) and 1 - bromo - 4 - chloro - butane, in dimethyl formamide, followed by a period of stirring at room temperature, to produce 1 - (4 - chlorobutyl) - 1 - methyl - 7 - methoxy - 2 - tetralone (compound VII). Compound VII may be converted to the bridged tetralone, 6,7,8,9,10,11 - hexahydro - 3 - methoxy - 5 - methyl - 5,10 - methano - 5H - benzocyclononen - 12 - one (VIII) by treatment with a strong base, preferably sodium hydride, in an inert solvent, preferably dimethyl formamide. The bridged tetralone VIII so produced may then be used as an intermediate either for the production of 6,7,8,9,10,11 - hexahydro - 3 - methoxy - 5 - methyl - 5,10 - methano - 5H - benzocyclononen - 12 - one, oxime, IX, or if desired for the production of the secondary amine Xa.

FIGURE A

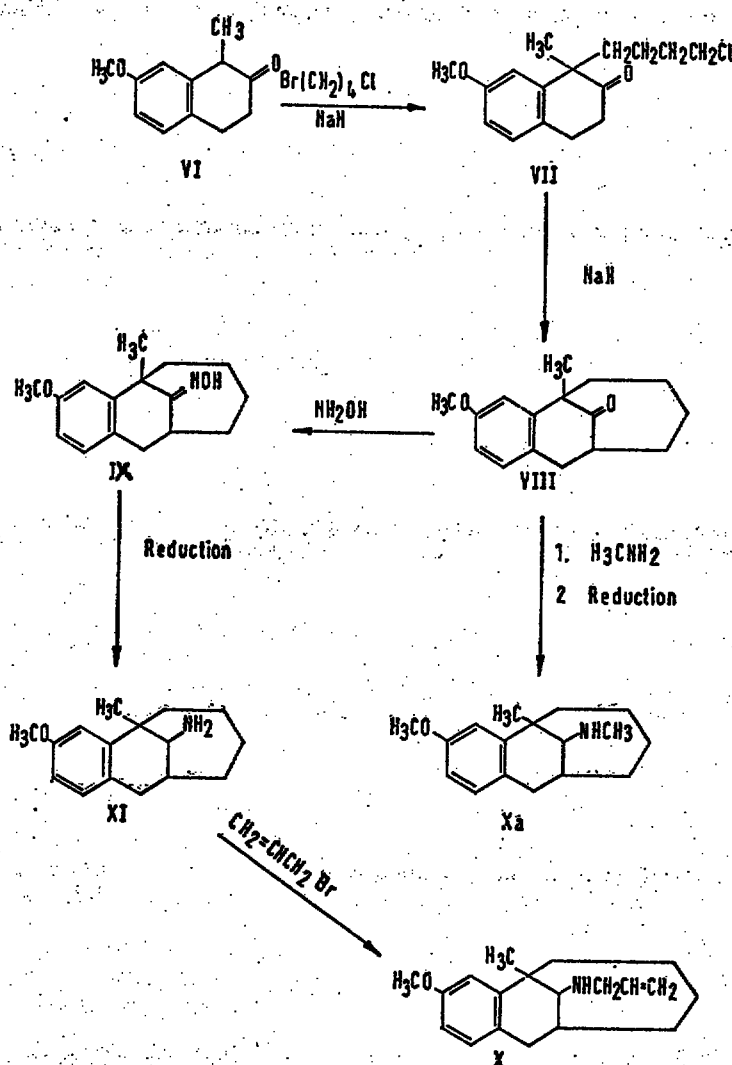
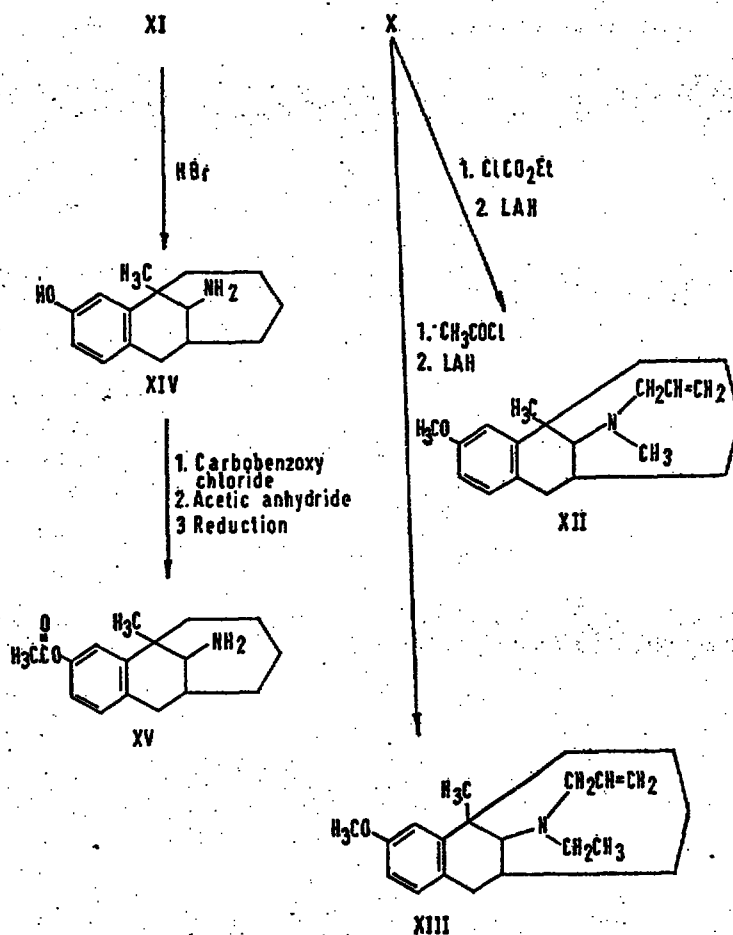


FIGURE A (Continued)



In order to prepare the oxime IX the bridged tetralone VIII is treated with hydroxylamine under basic conditions. The oxime IX may be isolated by conventional means and can be used as an intermediate for the production of the primary amine XI. To prepare the amine XI the oxime IX can be treated either with hydrogen in the presence of a catalyst, preferably Raney nickel, and ammonium hydroxide, at moderate pressure, preferably 40—50 psi; the hydride reducing agents, for example lithium aluminium hydride; diborane at elevated temperature; or an alkali metal, preferably sodium, in an alkanol, for example ethanol or isopropanol. When using catalytic reduction the reaction proceeds stepwise and the corresponding imine of formula (II) may be isolated as an intermediate, and they may be reduced to the desired primary amine. The amine XI can be isolated by conventional means. To prepare the amine Xa, the bridged tetralone VIII may be treated with an excess of methyl amine. The substitution may be carried out with removal of water, conveniently in the presence of calcium oxide, at an elevated temperature, preferably 180—190°C. When the amine has a boiling point below the desired temperature the reaction is conveniently carried out in a sealed pressure vessel. The intermediate imine so produced may be reduced as obtained directly from the substitution reaction. The amine Xa may be produced by treating this imine with either hydrogen in the presence of a catalyst, preferably platinum oxide, at moderate pressure, preferably 40—50 psi; the hydride reducing agents, for example lithium aluminium hydride or sodium borohydride; diborane at elevated temperature, or an alkali metal, preferably sodium, in an alkanol, for example ethanol or isopropanol. The primary amine XI may also be converted to the secondary amine X by substitution reactions well known in the art of organic chemistry. A convenient method is to treat with one mole equivalent of allyl bromide. The substitution may be carried out in the presence

of an organic acid acceptor, preferably di-isopropyl ethyl amine, in an organic solvent at a temperature of from about 60°C. to 140°C. Benzene and xylene are particularly useful solvents but it will be apparent to an organic chemist that any solvent can be used which will not interfere with the course of the reaction. For convenience the reflux temperature of the solvent selected can be employed. The secondary amine X can be isolated by conventional methods.

If desired the secondary amine X can be methylated to give the N-methyl tertiary amine XII. A preferred method for the methylation reaction is to first carbethoxylate the secondary amine by treatment with ethyl chloroformate in an unreactive organic solvent, such as methylene chloride or chloroform. For best results, a weak inorganic base, such as sodium bicarbonate or potassium carbonate, is added to the reaction mixture. The temperature of the carbethoxylation reaction is not critical and, for convenience, room temperature is used. It will be obvious to one skilled in organic chemistry that for the purposes of this reaction other halo formate esters would be equivalent to ethyl chloroformate. The carbethoxylated amine may then be reacted with a reducing agent, preferably lithium aluminium hydride, in an inert solvent, preferably ether or tetrahydrofuran, to afford the N-methyl tertiary amine XII which can be isolated by standard procedures.

A preferred method of preparation of the tertiary amine XIII is to first acylate the secondary amine X with acetyl chloride in a basic organic solvent, preferably pyridine, at an elevated temperature, conveniently the reflux temperature of the solvent selected. The acylated amine is then reacted with a reducing agent, preferably lithium aluminium hydride, in an inert solvent preferably ether or tetrahydrofuran, to afford the tertiary amine XIII which can be isolated by standard techniques.

The primary amine XI which bears a lower alkoxy substituent can be hydrolyzed to the phenolic compound XIV. A particularly useful method is to treat the primary amine with 48% aqueous hydrobromic acid at elevated temperature, conveniently reflux temperature. The crystalline product can be isolated by standard techniques. It will be obvious to one skilled in the art of organic chemistry that the hydrolysis reaction may be performed on the bridged tetralone VIII and that the phenolic compound so formed would then be the full equivalent of all other compounds not bearing such a substituent in all subsequent reactions.

The phenolic amine XIV may be acetylated to produce the acetyl derivative XV. A skilled organic chemist will recognize that in order to acetylate the phenolic function a primary or secondary amine must first be reacted with a suitable protecting group. Carbobenzoxy chloride is particularly convenient for this purpose. The protected derivative is then treated with acetic anhydride and the protecting group removed, conveniently, in the case of the carbobenzoxy group by hydrogenolysis. It will be obvious to a skilled organic chemist that any desired acylation reagent may be substituted for the acetic anhydride. The acylation reaction may also be accomplished by exposure of the phenolic amine, suitably distributed on an inert carrier, conveniently potassium bromide powder, to a suitably volatile acylating agent, in the vapour state, at temperatures moderately higher than room temperature, conveniently 40—70°C.

While the processes of the invention have been specifically described with reference to the drawing which illustrates their application to 1 - methyl - 7 - methoxy-2-tetralone it will be readily apparent to one skilled in the art of organic chemistry that the processes will be equally applicable to tetralones bearing, in the 1 and 7 positions, other substituents contemplated within the scope of the invention. Similarly it will be obvious to vary the chain length of the polymethylene compound in order to produce the variously sized ring systems encompassed by the invention. A skilled chemist will readily recognize that, in addition to the α,ω -dihalopolymethylene, and polymethylene compound of the desired chain length, which bears, as substituents in the terminal positions, suitable leaving groups, such as (lower) alkylsulfonyl or phenylsulfonyl, or one such leaving group and a group, such as tetrahydropyranyloxy which may be readily converted to a leaving group, may be utilized in the initial cycloalkylation process. The substitution of other strong bases, such as alkali metal alkoxides, in suitable solvents, for the illustrated sodium hydride will also be apparent to one skilled in the art. It will be obvious to one skilled in the art that, if the α,ω -disubstituted polymethylene does not bear a tetrahydropyranyl substituent, the complete cycloalkylation may be performed without isolation of the intermediate, compound VII. One skilled in the art will recognize that it is possible to substitute anhydrous ammonia for methyl amine in the imination of compound VIII and that reduction will then give compound XI. The substitution of other lower alkyl, and phen(lower)alkyl amines, for methylamine, to give secondary amines

analogous to compound Xa will similarly be apparent to one skilled in the art. Other lower alkyl halides, lower alkenyl halides, phen(lower)alkyl halides, or lower alkynyl halides may be substituted for allyl bromide in the treatment of compound XI to obtain the secondary amines encompassed by the invention. Similarly other lower alkanoyl, lower alkenoyl, phen(lower)alkanoyl or lower alkynyl halides may be used in the preparation of the tertiary amine embodiments of the invention.

The amines oxides of formula (I) are prepared by oxidation, conveniently with an organic peracid, of the di(lower)alkyl tertiary amine embodiments of formula (I).

One knowledgeable in the art of organic chemistry will recognize that 1-alkyl substituted 2-indanones can be cycloalkylated in a fashion similar to that described for the cycloalkylation of 1-alkyl substituted 2-tetralones. The compounds so formed can then be further treated by the processes described hereinabove to produce derivatives which are the full equivalents of the compounds of formula (I) described herein.

Preparation of the compounds formula (I) in which m is 0 may also be accomplished by cyclization of appropriate known o-phenylene dicarboxylic acid diesters to product 1 - alkoxy carbonyl - 2 - indanones. Alkylation to produce the 1 - alkoxy carbonyl - indanones of formula (IV) may be accomplished as described for the corresponding tetralones of formula (IV). Alternatively the keto group of the alkoxy carbonyl-indanone may be treated with a suitable ketone protecting reagent, such as ethylene glycol, a lower alkyl, lower alkenyl, or phen(lower)alkyl group may be introduced into the 1-position by standard alkylation techniques, the protective group removed from the ketone, the ester function hydrolyzed, and the carbonyl group eliminated by decarboxylation. The resulting lower alkyl, lower alkenyl, or phen(lower)alkyl - 2 - indanone may then be treated similarly to the corresponding tetralones to produce the lower alkyl, lower alkenyl or phen(lower)alkyl indanones of formula (IV). Cycloalkylation to the benzobicyclic system of formula (III) may also be accomplished as described for the corresponding tetralones of formula (IV). Preparation of the imino derivatives of the benzobicyclic ketones derived from the above described indanones may be accomplished in a fashion similar to that described for the preparation of the imino derivatives of the benzobicyclic ketones derived from tetralones. A skilled organic chemist will of course recognize that the alkoxy carbonyl substituted benzobicyclic ketones may be converted to oximino derivatives but that treatment with ammonia or primary amine will result in side reactions with the alkoxy carbonyl group.

Reduction of the imino compounds of the alkoxy carbonyl compound to the hydroxy alkyl amines of formula (I) may be accomplished by the same reduction methods as used to prepare the amines of formula (I).

The skilled organic chemist will of course not use catalytic reduction methods involving the use of ammonia or primary amines.

The alkoxy carbonyl benzobicyclic ketone may, if desired, be treated with a suitable ketone protecting reagent, such as ethylene glycol, the alkoxy carbonyl group may then be reduced to a hydroxy methyl group, and the keto group regenerated. This compound may then be converted into the hydroxy methyl imino compounds of formula (II) by the above described methods. If desired the hydroxyl group may be removed by standard means, such as tosylation and reduction with lithium aluminium hydride. The variously other substituted amines of formula (I) may be prepared from appropriate primary or secondary amines or embodiments of formula (I) by after-processes similar to those previously described for the preparation of the variously substituted amines of formula (I).

It will be obvious to one skilled in the art of chemistry that the benzobicyclic ketones of formula (III) will be produced as racemic mixtures, and that reduction of either imino compounds of formula (II) will yield the amines of formula (I) as diastereomers in which the amine function has a syn or anti relationship to the benzene ring. The separation of the diastereomeric pairs and their resolution into enantiomers, if desired, may be accomplished by well known procedures. The diastereomers, enantiomers and mixtures thereof are all included within the scope of this invention.

The synthesis of the amines and imines of formula (V) may be accomplished by methods similar to those described by Wiesner, Chau and Demerson in *Tetrahedron Letters*, 1965, page 2893.

The novel compounds of formula (I) may be isolated as their pharmaceutically acceptable acid addition salts during their preparation or the salts may be prepared by dissolving the specific compound of said formula (I), in a suitable organic solvent, and treating it with an alcoholic solution of the selected acceptable acid, in accordance

with conventional procedures for preparing acid-addition salts from base compounds generally. As such acids, there may be used any of hydrochloric, hydrobromic, tartaric, phosphoric, maleic, citric, acetic, benzoic, or other pharmacologically acceptable acid.

5 The invention further provides a pharmaceutical composition comprising a compound of general formula (I) or a pharmaceutically acceptable acid addition salt thereof in association with a pharmaceutical acceptable carrier. The invention also provides a method for inducing analgesia in warm-blooded animals other than humans which comprises administering to the warm-blooded animal a pharmaceutically effective amount of a compound of general formula (I) or an acid addition salt thereof. Preferably the compound administered is one in which n is an integer from 3 to 6.

10 When the compounds of this invention are employed pharmaceutically, e.g. as analgesic agents, or as anti-inflammatory agents, they may be administered alone or in combination with pharmaceutically acceptable carriers, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration and standard pharmacological practice. For example they may be administered orally in the form of tablets or capsules containing such excipients as starch, milk, sugar, and so forth. They may be administered orally in the form of solution or they may be injected parenterally, e.g. intramuscularly. For parenteral administration, they may be used in the form of a sterile solution or suspensions containing other solutes, for example, enough saline or glucose to make the solution isotonic.

15 The dosage of the present pharmacologically active agents will vary with the form of administration and the particular compound chosen. Furthermore, it will vary with the particular subject under treatment. Generally, treatment is initiated with small dosages substantially less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached.

20 It will generally be found that when the composition is administered orally, larger quantities of the active agent will be required to produce the same effect as a smaller quantity given parenterally. In general, the compounds of this invention are most desirably administered at a concentration level that will generally afford effective results without causing any harmful or deleterious side effects.

25 The following Examples illustrate the invention. The preparation of starting materials for these Examples is described in our co-pending applications 35390/73 (Serial No. 1363660) and 35389/73 (Serial No. 1363659).

EXAMPLE 1

6,7,8,9,10,11-Hexahydro-3-Methoxy-5-Methyl-5,10-Methano-5H-Benzocyclononen-12-Amine

40 A. 6,7,8,9,10,11 - Hexahydro - 3 - methoxy - 5 - methyl - 5,10 - methano - 5H - benzocyclononen - 12 - one, oxime (15 g. 0.058 m.) Raney nickel (3 tsps.) ethanol (100 ml.) and concentrated ammonium hydroxide (50 ml.) are shaken with hydrogen at 45 psi and 45°C. The catalyst is removed by filtration and the filtrate concentrated to remove solvent. The residue is distilled under reduced pressure to afford the title product (11 g.), b.p. 140°—142°C. (0.2 mm.) HCl salt, m.p. 298—299°C.

45 Analysis for: $C_{16}H_{24}ClNO$
Calculated: C, 68.21; H, 8.58; N, 4.96.
Found: C, 67.96; H, 8.63; N, 4.92.

50 B. Undistilled 6,7,8,9,10,11 - hexahydro - 3 - methoxy - 5 - methyl - 5,10 - methano - 5H - benzocyclononen - 12 - amine (31 g.) in dry ether (200 ml.) is treated with dry hydrogen chloride in ether until the solution is acidic. The precipitated salt is collected, washed with ether and dried to afford a product (32 g.), m.p. 257—267°C.

55 This product is dissolved in water (1,000 ml.) and methanol (180 ml.). Addition of concentrated hydrochloric acid (2 ml.), concentration at atmospheric pressure to 500 ml., collection of the precipitate obtained on cooling, followed by washing and drying gives a product (20.0 g.), m.p. 302—305°C. On the basis of infrared and nuclear magnetic resonance spectra this product is assigned a configuration having the amine group in the anti-configuration.

60 Concentration of the mother liquors obtained after isolation of the anti product gives a product (2 g.), m.p. 262—273°C. Further concentration to about 65 ml. clarifying and chilling gives crystals (5.9 g.), m.p. 231—236°C. which are collected with the aid of additional cold water (50 ml.). Recrystallization is accomplished by dis-

solving in acetone-methanol (2:1), concentrating to one-half volume then making up to the original volume with acetone. Repetition of the concentration-dilution process three additional times followed by chilling gives a product (4.5 g.), m.p. 237—240°C.

Analysis for: $C_{16}H_{24}ClNO$
Calculated: C, 68.21; H, 8.58; N, 4.96; Cl, 12.54.
Found: C, 68.40; H, 8.72; N, 5.02; Cl, 12.04.

On the basis of infrared and nuclear magnetic resonance spectra this product is assigned a configuration having the amine group in the syn configuration.

EXAMPLE 2

Anti-5-Methyl-5,6,7,8,9,10,11,12-Octahydro-5,11-Methano-Benzocyclodecen-13-Amine

5 - Methyl - 5,6,7,8,9,10,11,12 - octahydro - 5,11 - methano 5H - benzocyclodecen-13-one, oxime (2.5 g.), Raney nickel (2 g.), ammonium hydroxide (4 ml.) and ethanol (50 ml.) are shaken with hydrogen at 45 psi. After hydrogen uptake ceases (approximately 7 pounds versus 14 pounds theory) the solution is removed from the apparatus, filtered and concentrated. The residue (pink oil) is combined with fresh Raney Nickel, ammonium hydroxide, and ethanol and hydrogenated at 50 psi and 50—50°C. When completed the solution is worked up as above. The residue, a colorless oil is converted to the hydrochloride salt, filtered, washed and dried. The salt is recrystallized from water to give the title compound, as the hydrochloride, 1.15 g., m.p. >335°C.

Analysis for: $C_{16}H_{24}ClN$
Calculated: C, 72.29; H, 9.10; N, 5.27.
Found: C, 72.12; H, 9.45; N, 5.28.

EXAMPLE 3

Anti-6,7,8,9,10,11-Hexahydro-5-Methyl-5,10-Methano-5H-Benzocyclononen-12-Amine

6,7,8,9,10,11 - Hexahydro - 5 - Methyl - 5,10 - methano - 5H - benzocyclononen-12-one, oxime (2.5 g.), Raney nickel catalyst (6 g.) in 25 ml. of concentrated ammonium hydroxide and 50 ml. of ethanol are shaken with hydrogen at 50 psi and 45°C. After hydrogen uptake stops the catalyst is filtered off, the filtrate concentrated, and the residue converted to the hydrochloride salt (2.8 g.); recrystallization from water gives the title product as its hydrochloride, m.p. >315°C.

Analysis for: $C_{16}H_{22}ClN$
Calculated: C, 71.62; H, 8.81; N, 5.53.
Found: C, 71.62; H, 8.81; N, 5.86.

EXAMPLE 4

5-Ethyl-6,7,8,9,10,11-Hexahydro-3-Methoxy-5,10-Methano-5H-Benzocyclononen-12-Amine

Using a procedure analogous to that described in Example 1A for the preparation of 5 - methyl - 5,6,7,8,9,10,11,12 - octahydro - 5,11 - methano - benzocyclodecen - 13 - amine there is obtained from 3.5 g. of 5 - ethyl - 6,7,8,9,10,11 - hexahydro - 3 - methoxy - 5,10 - methano - 5H - benzocyclononen - 12 - one, oxime 1.6 g. of the title product, b.p. 150—160°C. (0.5 mm.).

I.R. Analysis: 6.1 μ .

Addition of ethereal hydrogen chloride to the title product in ether gives the hydrochloride salt, m.p. 252—255°C. (dec.).

Analysis for: $C_{17}H_{24}NOCl$
Calculated: C, 69.48; H, 8.23; N, 4.77.
Found: C, 69.25; H, 8.28; N, 4.72.

EXAMPLE 5

5-Ethyl-6,7,8,9,10,11-Hexahydro-3-Methoxy-5,10-Methano-5H-Benzocyclononen-12-Amine

A. Using a procedure analogous to that described in Example 1A for the preparation of 5 - methyl - 5,6,7,8,9,10,11,12 - octahydro - 5,11 - methano - benzocyclodecen -

13-amine there is obtained from 5 - ethyl - 6,7,8,9,10,11 - hexahydro - 3 - methoxy - 5,10 - methano - 5H - benzocyclononen - 12 - amine (4.0 g.) approximately 3.5 g. of title product which is converted to its solid hydrochloride salt, m.p. 226—231°C.

5 On the basis of infrared and nuclear magnetic resonance spectra this product is assigned a configuration having the amine group in the anti configuration. 5 5

Analysis for: $C_{17}H_{26}NOCl$
 Calculated: C, 69.01; H, 8.86; N, 4.73.
 Found: C, 68.76; H, 8.94; N, 4.72.

10 B. Using a procedure analogous to that described in Example 1A for the preparation of 6,7,8,9,10,11-hexahydro-3-methoxy-5,10-methano-5H-benzocyclononen-12-amine, from 5 - ethyl - 6,7,8,9,10,11 - hexahydro - 3 - methoxy - 5,10 - methano - 5H - benzocyclononen-12-one, oxime there is obtained distilled title product which is shown by gas chromatography-mass spectra data to be approximately a 8 to 1 mixture of epimeric amines. Dissolving 70 g. of this mixture in 1100 ml. of dilute aqueous hydrochloric acid, filtering the solution through diatomaceous earth and allowing it to stand 1 day at room temperature and for 2 days at 10° gives 64 g. of the hydrogen chloride, hydrate salt of anti - 5 - ethyl - 6,7,8,9,10,11 - hexahydro - 3 - methoxy - 5,10 - methano - 5H - benzocyclononen - 12 - amine with m.p. 253—256°C. 10 10

15
 20 Analysis for: $C_{17}H_{26}NO \cdot HCl \cdot H_2O$
 Calculated: C, 65.05; H, 8.99; N, 4.46.
 Found: C, 65.26; H, 9.01; N, 4.50.

25 C. The filtrate recovered from B above is made basic with aqueous sodium hydroxide, extracted with ether and the ether extracts dried and concentrated to an oil. This oil is chromatographed on 300 g. of silica gel. Elution with a solution of 3 parts benzene, 1 part chloroform gives 3.0 g. of pure syn - 5 - ethyl - 6,7,8,9,10,11 - hexahydro - 3 - methoxy - 5,10 - methano - 5H - benzocyclononen - 12 - amine. Conversion of the amine to its hydrogen chloride salt in ether gives a crystalline salt with m.p. 182—185°. 25 25

30 Analysis for: $C_{17}H_{26}NOCl$
 Calculated: C, 69.01; H, 8.86; N, 4.73.
 Found: C, 68.73; H, 8.91; N, 4.75.

EXAMPLE 6

35 5,6,7,8,9,10-Hexahydro-3-Methoxy-5-Methyl-5,9-Methano-Benzocycloocten-11-Amine 35 35

A. Using a procedure analogous to that described in Example 1A for the preparation of 6,7,8,9,10,11 - hexahydro - 3 - methoxy - 5 - methyl - 5,10 - methano - 5H - benzocyclononen - 12 - amine there is obtained from 5,6,7,8,9,10 - hexahydro - 3 - methoxy - 5 - methyl - 5,9 - methano - benzocycloocten - 11 - one, oxime (4.2 g.), 2.7 g. of the title compound, b.p. 125—129°C. (0.1 mm.). 40 40

A sample is converted to the hydrochloride salt which crystallizes from ethanol: ether, m.p. 262—264°C.

45 Analysis for: $C_{15}H_{22}ClNO$
 Calculated: C, 67.27; H, 8.28; N, 5.23.
 Found: C, 67.16; H, 8.48; N, 5.14.

50 B. Using a procedure analogous to that described in Example 1A for the preparation of 6,7,8,9,10,11 - hexahydro - 3 - methoxy - 5 - methyl - 5,10 - methano - 5H - benzocyclononen - 12 - amine, from 5,6,7,8,9,10 - hexahydro - 3 - methoxy - 5 - methyl - 5,10 - methano - 5H - benzocyclooctene - 11 - one, oxime, there is obtained distilled title product which is shown by gas chromatography, mass spectral data to be a 3 to 2 mixture of amino epimers. By repeated recrystallization of hydrogen chloride salt of 27 g. of the epimeric amine mixture from ethanol-ether, there is obtained 16.3 g. of product, m.p. 270—272°, which is assigned the syn configuration. 50 50

55 Analysis for: $C_{15}H_{22}NOCl$
 Calculated: C, 67.27; H, 8.28; N, 5.23.
 Found: C, 67.17; H, 8.48; N, 5.14.

C. Concentration of the combined mother liquors from B gives a residue which is crystallized from acetonitrile and then repetitively recrystallized from ethanol ether to give a product, m.p. 300—302°, which is assigned the anti configuration.

Analysis for: $C_{11}H_{22}NOCl$
 Calculated: C, 67.27; H, 8.28; N, 5.23.
 Found: C, 67.14; H, 8.24; N, 5.24.

EXAMPLE 7

Anti-3-Methoxy-5-Methyl-5,6,7,8,9,10,11,12-Octahydro-5,11-Methano-Benzocyclodecen-13-Amine

Using a procedure analogous to that described in Example 2 for the preparation of 5 - methyl - 5,6,7,8,9,10,11,12 - octahydro - 5,11 - methano - benzocyclodecen - 13 - amine there is obtained from 3 - methoxy - 5 - methyl - 5,6,7,8,9,10,11,12 - octahydro - 5,11 - methanobenzocyclodecen - 13 - one, oxime (18.5 g.) Raney nickel (3 tablespoons), 100 ml. of ethanol and 50 ml. of concentrated ammonium hydroxide; after distillation 11.1 g. [b.p. 140—145°C. (1.2 mm.)] of the title product which is converted to the hydrochloride salt which recrystallizes from water, m.p. 311—312°C.

Analysis for: $C_{17}H_{26}ClNO$
 Calculated: C, 69.13; H, 8.86; N, 4.73.
 Found: C, 69.17; H, 9.16; N, 4.70.

EXAMPLE 8

To prepare: 6,7,8,9,10,11 - hexahydro - 5 - benzyl - 5,10 - methano - 5H - benzocyclononen - 12 - amine (hydrochloride salt, m.p. 154—158°C.) reduce 6,7,8,9,10,11 - hexahydro - 5 - benzyl - 5,10 - methano - 5H - benzocyclononen - 12-one, oxime as taught in Example 1.

To prepare: 5 - benzyl - 6,7,8,9,10,11 - hexahydro - 3 - methoxy - 5,10 - methano - 5H - benzocyclononen - 12 - amine (hydrochloride salt, m.p. 152—156°C.) reduce 5 - benzyl - 6,7,8,9,10,11 - hexahydro - 3 - methoxy - 5,10 - methano - 5H - benzocyclononen - 12 - one, oxime as taught in Example 1.

EXAMPLE 9

Syn-6,7,8,9,10,11-Hexahydro-3-Methoxy-N,5-Dimethyl-5,10-Methano-5H-Benzocyclononen-12-Amine

Syn - 6,7,8,9,10,11 - hexahydro - 3 - methoxy - 5 - methyl - 5,10 - methano - 5H - benzocyclononen - 12 - amine, hydrochloride (2.5 g.), saturated aqueous sodium bicarbonate (50 ml.), methylene chloride (50 ml.) and ethylchloroformate (3 ml.) are stirred, at room temperature, for 4 hours. The organic layer is separated, washed successively with aqueous sodium carbonate, hydrogen chloride and sodium chloride, dried and concentrated to give 2.6 g. of oil. This oil is added to a mixture of 1 g. of lithium aluminium hydride in tetrahydrofuran and the resulting mixture is refluxed overnight. Two ml. of water is added and the mixture is filtered. Concentration of the filtrate gives 2.1 g. of oil which is converted to 1.8 g. of hydrogen chloride salt with m.p. 249—250° after recrystallization from ethanol-ether.

Analysis for: $C_{17}H_{26}NOCl$
 Calculated: C, 69.01; H, 8.86; N, 4.73.
 Found: C, 68.53; H, 9.08; N, 5.13.

EXAMPLE 10

Syn-6,7,8,9,10,11-Hexahydro-3-Methoxy-N,N,5-Trimethyl-5,10-Methano-5H-Benzocyclononen-12-Amine

In a manner analogous to that described in Example 9 for the preparation of syn - 6,7,8,9,10,11 - hexahydro - 3 - methoxy - N,5 - dimethyl - 5,10 - methano - 5H - benzocyclononen - 12 - amine, from 1.2 g. of 6,7,8,9,10,11 - hexahydro - 3 - methoxy - N,5 - dimethyl - 5,10 - methano - 5H - benzocyclononen - 12 - amine there is obtained 0.90 g. of the hydrogen chloride salt of the title product with m.p. 200—202°.

Analysis for: $C_{18}H_{26}NOCl$
 Calculated: C, 69.76; H, 9.11; N, 4.52.
 Found: C, 69.28; H, 9.12; N, 4.69.

EXAMPLE 11

Anti-6,7,8,9,10,11-Hexahydro-3-Methoxy-N,N,5-Trimethyl-5,10-Methano-5H-Benzocyclononen-12-Amine

5 In a manner analogous to that described in Example 9 for the preparation of syn - 6,7,8,9,10,11 - hexahydro - 3 - methoxy - N,5 - dimethyl - 5,10 - methano - 5H - benzocyclononen - 12 - amine, from 1.2 g. of anti - 6,7,8,9,10,11 - hexahydro - 3 - methoxy - N,5 - dimethyl - 5,10 - methano - 5H - benzocyclononen - 12 - amine there is obtained 1.0 g. of the hydrogen chloride salt of the title product with m.p. 207—209°.

10 Analysis for: $C_{18}H_{26}NOCl \cdot 1/4 H_2O$
Calculated: C, 68.79; H, 9.14; N, 4.46.
Found: C, 68.83; H, 9.36; N, 4.69.

EXAMPLE 12

Anti-5-Ethyl-6,7,8,9,10,11-Hexahydro-3-Methoxy-N-Methyl-5,10-Methano-5H-Benzocyclononen-12-Amine

15 In a manner analogous to that described in Example 9 for the preparation of syn - 6,7,8,9,10,11 - hexahydro - 3 - methoxy - N,5 - dimethyl - 5,10 - methano - 5H - benzocyclononen - 12 - amine, from 8.0 g. of anti - 5 - ethyl - 6,7,8,9,10,11 - hexahydro - 3 - methoxy - 5,10 - methano - 5H - benzocyclononen - 12 - amine there is obtained 5.5 g. of the hydrogen chloride salt of the title product with m.p. 282—284° dec. on recrystallization from ethanol-ether.

20 Analysis for: $C_{18}H_{26}NOCl$
Calculated: C, 69.76; H, 9.11; N, 4.52.
Found: C, 69.29; H, 9.22; N, 4.61.

EXAMPLE 13

Anti-5-Ethyl-6,7,8,9,10,11-Hexahydro-N,N-Dimethyl-3-Methoxy-5,10-Methano-5H-Benzocyclononen-12-Amine

25 In a manner analogous to that described in Example 9 for the preparation of syn - 6,7,8,9,10,11 - hexahydro - 3 - methoxy - N,5 - dimethyl - 5,10 - methano - 5H - benzocyclononen - 12 - amine, from 4.0 g. of anti - 5 - ethyl - 6,7,8,9,10,11 - hexahydro - 3 - methoxy - N - methyl - 5,10 - methano - 5H - benzocyclononen - 12 - amine there is obtained 2.65 g. of the hydrogen chloride salt of the title product with m.p. 162—165° on recrystallization from ethanol-ether.

EXAMPLE 14

Anti-3-Methoxy-N,5-Dimethyl-5,6,7,8,9,10,11,12-Octahydro-5,11-Methanobenzocyclodecen-13-Amine

35 In a manner analogous to that described in Example 9 for the preparation of syn - 6,7,8,9,10,11 - hexahydro - 3 - methoxy - N,5 - dimethyl - 5,10 - methano - 5H - benzocyclononen - 12 - amine, from 8.0 g. of anti - 3 - methoxy - 5 - methyl - 5,6,7,8,9,10,11,12 - octahydro - 5,11 - methanobenzocyclodecen - 13 - amine there is obtained 5.5 g. of the hydrogen chloride salt of the title product with m.p. 303—305° dec. on recrystallization from ethanol-ether.

40 Analysis for: $C_{18}H_{26}NOCl$
Calculated: C, 69.76; H, 9.11; N, 4.52.
Found: C, 69.27; H, 8.99; N, 4.66.

EXAMPLE 15

Anti-3-Methoxy-N,N,5-Trimethyl-5,6,7,8,9,10,11,12-Octahydro-5H-Methanobenzocyclodecen-13-Amine

45 In a manner analogous to that described in Example 9 for the preparation of syn - 6,7,8,9,10,11 - hexahydro - 3 - methoxy - N,5 - dimethyl - 5,10 - methano - 5H - benzocyclononen - 12 - amine, from 4.0 g. of anti - 3 - methoxy - N,5 - dimethyl - 5,6,7,8,9,10,11,12 - octahydro - 5H - methanobenzocyclodecen - 13 - amine there is obtained 2.0 g. of the hydrogen chloride salt of the title product with m.p. 195—198° on recrystallization from ethanol-ether.

50 Analysis for: $C_{19}H_{28}NOCl \cdot H_2O$
Calculated: C, 66.74; H, 9.43; N, 4.10.
Found: C, 66.61; H, 9.39; N, 3.96.

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EXAMPLE 16

Anti-5,6,7,8,9,10-Hexahydro-3-Methoxy-N,5-Dimethyl-5,9-Methanobenzocyclooctene-11-Amine

In a manner analogous to that described in Example 9 for the preparation of syn - 6,7,8,9,10,11 - hexahydro - 3 - methoxy - N,5 - dimethyl - 5,10 - methano - 5H - benzocyclononen - 12 - amine, from 1.5 g. of anti - 5,6,7,8,9,10 - hexahydro - 3 - methoxy - 5 - methyl - 5,9 - methano - benzocyclooctene - 11 - amine there is obtained 1.2 g. of the hydrogen chloride salt of the title product with m.p. 266—267°.

Analysis for: $C_{16}H_{24}NOCl$
Calculated: C, 68.19; H, 8.58; N, 4.97.
Found: C, 67.88; H, 8.88; N, 4.80.

EXAMPLE 17

Syn-5-Ethyl-6,7,8,9,10,11-Hexahydro-3-Methoxy-N-Methyl-5,10-Methano-5H-Benzocyclononen-12-Amine

In a manner analogous to that described in Example 9 for the preparation of anti - 6,7,8,9,10,11 - hexahydro - 3 - methoxy - N,5 - dimethyl - 5,10 - methano - 5H - benzocyclononen - 12 - amine, from 1.2 g. of syn - 5 - ethyl - 6,7,8,9,10,11 - hexahydro - 3 - methoxy - 5,10 - methano - 5H - benzocyclononen - 12 - amine there is obtained 0.90 g. of the hydrogen chloride salt of the title product with m.p. 284—285° dec. on recrystallization from ethanol-ether.

Analysis for: $C_{17}H_{28}NOCl \cdot 1/4H_2O$
Calculated: C, 68.77; H, 9.14; N, 4.46.
Found: C, 69.69; H, 9.19; N, 4.42.

EXAMPLE 18

Anti-N-Allyl-6,7,8,9,10,11-Hexahydro-3-Methoxy-5-Methyl-5,10-Methano-5H-Benzocyclononen-12-Amine

Anti - 6,7,8,9,10,11 - Hexahydro - 3 - methoxy - 5 - methyl - 5,10 - methano - 5H - benzocyclononen - 12 - amine (1.7 g.), allylbromide (0.85 g.), diisopropyl ethyl amine (1.3 g.) and benzene (10 ml.) are heated at reflux for 3 hours. The mixture is cooled, diluted with ether and filtered. The solvents are removed under reduced pressure and the residue distilled to give the title product (1.3 g.), b.p. 144—146°C. (0.2 mm.). The distilled product is taken up in ether and treated with a slight excess of hydrogen chloride in ether to give the hydrochloride addition salt of the title product (1.3 g.), m.p. 200—202°C.

Analysis for: $C_{17}H_{26}ClNO$
Calculated: C, 70.95; H, 8.74; N, 4.35.
Found: C, 70.50; H, 8.77; N, 4.46.

EXAMPLE 19

Syn-N-Allyl-5,6,7,8,9,10-Hexahydro-3-Methoxy-5-Methyl-5,9-Methanobenzocyclooctene-11-Amine

Using a procedure analogous to that described in Example 8 for the preparation of N - allyl - 6,7,8,9,10,11 - hexahydro - 3 - methoxy - 5 - methyl - 5,10 - methano-5H-benzocyclononen-12-amine there is obtained from syn-5,6,7,8,9,10-hexahydro - 3 - methoxy - 5 - methyl - 5,9 - methano - benzocycloocten - 11 - amine (1.4 g.), 1.3 g. of the title product, b.p. 148—153°C. (0.3 mm.). A sample is converted to the hydrochloride.

Analysis for: $C_{18}H_{26}ClNO$
Calculated: C, 70.22; H, 8.51; N, 4.55.
Found: C, 69.75; H, 8.73; N, 4.47.

EXAMPLE 20

Anti-6,7,8,9,10,11-Hexahydro-3-Methoxy-5-Methyl-N-Phenethyl-5,10-Methano-5H-Benzocyclononen-12-Amine

A mixture of anti - 6,7,8,9,10,11 - hexahydro - 3 - methoxy - 5,10 - methano - 5H - benzocyclononen - 12 - amine (2.4 g.), phenethyl bromide (3 g.), and diisopropyl ethylamine (1.3 g.) in xylene (20 ml.) is heated at reflux for 18 hours. After cooling ether is added (100 ml.) and the solid material is filtered off and washed

with ether. The combined filtrate is extracted with dilute hydrochloric acid. The solid residue is dissolved in warm water, and added to the acid extract. The solution is basified with 10% sodium hydroxide and the oily layer which separates is taken into ether. After removal of solvent the residue is distilled and the fraction boiling at 190—198°/2 mm. is collected. This is converted to the hydrochloride salt in ether which is recrystallized from i-propanol to give the title product as its hydrochloride salt, m.p. 243—245°C.

Analysis for: $C_{24}H_{32}ClNO$
 Calculated: C, 74.80; H, 8.36; N, 3.63.
 Found: C, 74.55; H, 8.74; N, 3.55.

EXAMPLE 21

Anti-6,7,8,9,10,11-Hexahydro-3-Methoxy-5-Methyl-N-(3-Methyl-2-Butenyl)-5,10-Methano-5H-Benzocyclononen-12-Amine

6,7,8,9,10,11 - Hexahydro - 3 - Methoxy - 5 - methyl - 5,10 - methano - 5H - benzocyclononen - 12 - amine (4.5 g.), 3,3 - dimethylallyl - bromide (4.5 g.), diisopropyl ethylamine (5.75 g.) and xylene (60 ml.) are heated at reflux for 4 hours. The mixture is cooled, diluted with ether and filtered. The solvent is removed under vacuum and the residue is distilled to give the title product (1.2 g.), b.p. 166—170°C. (0.2 mm.). A sample is converted to the hydrochloride and recrystallized from ethanol, m.p. 295—298°C.

Analysis for: $C_{17}H_{26}ClNO$
 Calculated: C, 69.01; H, 8.86; N, 4.73.
 Found: C, 68.90; H, 8.92; N, 4.83.

EXAMPLE 22

Syn-5,6,7,8,9,10-Hexahydro-3-Methoxy-5-Methyl-N-(3-Methyl-2-Butenyl)-5,9-Methano-Benzocycloocten-11-Amine

Syn - 5,6,7,8,9,10 - hexahydro - 3 - methoxy - 5 - methyl - 5,9 - methano - benzocycloocten - 11 - amine (1.4 g.), diisopropylethylamine (1.3 g.), and 1 - chloro - 3 - methyl - 2 - butene (0.7 g.) are refluxed 7 hours in xylene. The reaction is cooled to room temperature, filtered and the filtrate extracted with 2N hydrochloric acid. The aqueous extract is basified and extracted with ether. The ether extract is then washed with water, dried over sodium sulphate, concentrated *in vacuo*, and the residue distilled under reduced pressure to give the title product (1.5 g.), b.p. 150—155°C. (0.5 mm.). Treatment of the product in ether with hydrogen chloride gives the hydrochloride, m.p. 166—169°C.

Analysis for: $C_{20}H_{30}ClNO$
 Calculated: C, 71.51; H, 9.00; N, 4.17.
 Found: C, 71.58; H, 9.09; N, 4.20.

EXAMPLE 23

Anti-12-Amino-6,7,8,9,10,11-Hexahydro-5-Methyl-5,10-Methano-5H-Benzocyclononen-3-ol

A solution of anti - 12 - amino - 6,7,8,9,10,11 - hexahydro - 3 - methoxy - 5 - methyl - 5,10 - methano - 5H - benzocyclononen (1.19 g.) in 48% hydrobromic acid (15 ml.) is refluxed 30 minutes under nitrogen. The mixture is cooled, diluted with water (50 ml.), filtered and evaporated to dryness under reduced pressure. The residue is dissolved in ethanol (50 ml.) and again taken to dryness. Redissolving in ethanol (25 ml.) addition of ether (50 ml.) and standing in the cold gives crystals which are recrystallized from i-propanol to give the hydrobromide salt of the title product as the i-propanolate (0.72 g.), m.p. 246—248°C.

Analysis for: $C_{19}H_{28}BrNO_2$
 Calculated: C, 58.10; H, 8.07; N, 3.76.
 Found: C, 57.52; H, 8.71; N, 3.69.

EXAMPLE 24

Anti-13-Amino-5-Methyl-5,6,7,8,9,10,11,12-Octahydro-5,11-Methano-Benzocyclodecen-3-ol

Anti - 3 - methoxy - 5 - methyl - 5,6,7,8,9,10,11,12 - octahydro - 5,11 - methano - benzocyclodecen - 13 - amine (3 g.) is refluxed in 60 ml. 48% aqueous

hydrobromic acid for one hour. The mixture is poured into ice (100 g.) and stirred. The precipitate is then filtered off, washed with cold water, then with ether and dried. Recrystallisation from water (after treating with activated charcoal) gives the hydrogen bromide salt of the title product, 1.85 g., m.p. 269—270°C.

Analysis for: $C_{16}H_{24}BrNO \cdot 1/2H_2O$
 Calculated: C, 57.18; H, 7.52; N, 3.97.
 Found: C, 57.22; H, 7.61; N, 4.14.

EXAMPLE 25

Anti-12-Amino-6,7,8,9,10,11-Hexahydro-5-Ethyl-5,10-Methano-5H-Benzocyclononen-3-Ol

A mixture of anti - 5 - ethyl - 6,7,8,9,10,11 - hexahydro - 5,10 - methano - 5H - benzocyclononen - 12 - amine (2.0 g.) and 75 ml. of 48% hydrobromic acid is refluxed for one-half hour, then concentrated to a viscous oil. The oil is dissolved in water and treated with concentrated aqueous ammonia. Filtration gives 1.7 g. of a crude product, m.p. 170—191°C. Recrystallization from ethyl acetate gives the title product, m.p. 201—204°C.

Analysis for: $C_{16}H_{23}NO$
 Calculated: C, 78.31; H, 9.45; N, 5.71.
 Found: C, 77.93; H, 9.68; N, 5.88.

EXAMPLE 26

Syn-11-(Dimethylamino)-5,6,7,8,9,10-Hexahydro-5-Methyl-5,9-Methano-Benzocycloocten-3-Ol

Syn - 5,6,7,8,9,10 - hexahydro - 3 - methoxy - N,N - 4 - trimethyl - 5,9 - methano - benzocycloocten - 11 - amine (1.2 g.) is refluxed for one hour under a dry nitrogen atmosphere in 13 ml. of aqueous 48% hydrobromic acid. Concentration of the solution affords a residue which on crystallization from ethanol-ether gives the title product as its hydrobromic acid salt, m.p. 268—271°.

Analysis for: $C_{16}H_{24}NOBr$
 Calculated: C, 58.89; N, 7.41; H, 4.29.
 Found: C, 58.80; N, 7.52; H, 4.22.

EXAMPLE 27

Syn-11-Amino-5,6,7,8,9,10-Hexahydro-5-Methyl-5,9-Methanobenzocycloocten-3-Ol

In a manner analogous to that described in Example 23 for the preparation of anti - 12 - amino - 6,7,8,9,10,11 - hexahydro - 5 - methyl - 5,10 - methano - 5H - benzocyclononen - 3 - ol, from 2.0 g. of syn - 5,6,7,8,9,10 - hexahydro - 3 - methoxy - 5 - methyl - 5,9 - methanobenzocyclooctene - 11 - amine there is obtained 2.3 g. of the hydrogen bromide, ethanolate salt of the title product with m.p. 277—280° on recrystallization from ethanol-ether.

Analysis for: $C_{17}H_{29}NOBr \cdot 1/2C_2H_5OH$
 Calculated: C, 56.07; H, 7.22; N, 4.36.
 Found: C, 55.86; H, 7.37; N, 4.10.

EXAMPLE 28

Anti-11-Amino-5,6,7,8,9,10-Hexahydro-5-Methyl-5,9-Methanobenzocycloocten-3-Ol

In a manner analogous to that described in Example 51 for the preparation of anti - 12 - amino - 6,7,8,9,10,11 - hexahydro - 5 - methyl - 5,10 - methano - 5H - benzocyclononen - 3 - ol, from 1.25 g. of anti - 5,6,7,8,9,10 - hexahydro - 3 - methoxy - 5 - methyl - 5,9 - methanobenzocyclooctene - 11 - amine there is obtained 1.05 g. of the hydrogen bromide salt of the title product with m.p. 305—310° dec. on recrystallization from ethanol-ether.

Analysis for: $C_{17}H_{29}NOBr$
 Calculated: C, 56.38; H, 6.76; N, 4.70.
 Found: C, 56.01; H, 6.79; N, 4.63.

EXAMPLE 29

Syn-12-Amino-6,7,8,9,10,11-Hexahydro-5-Methyl-5,10-Methano-5H-Benzocyclononen-3-Ol

5 In a manner analogous to that described in Example 51 for the preparation of anti - 12 - amino - 6,7,8,9,10,11 - hexahydro - 5 - methyl - 5,10 - methano - 5H - benzocyclononen - 3 - ol, from 1.2 g. of syn - 6,7,8,9,10,11 - hexahydro - 3 - methoxy - 5 - methyl - 5,10 - methano - 5H - benzocyclononen - 12 - amine there is obtained 1.1 g. of the hydrogen bromide salt of the title compound with m.p. 130—134° on recrystallization from acetonitrile.

10 Analysis for: $C_{15}H_{21}NO \cdot HBr \cdot 1/4CH_3CN$
Calculated: C, 57.72; H, 7.11; N, 5.43.
Found: C, 57.47; H, 7.00; N, 5.57.

EXAMPLE 30

Syn-12-Amino-6,7,8,9,10,11-Hexahydro-5-Ethyl-5,10-Methano-5H-Benzocyclononen-3-Ol

15 In a manner analogous to that described in Example 23 for the preparation of anti - 12 - amino - 6,7,8,9,10,11 - hexahydro - 5 - methyl - 5,10 - methano - 5H - benzocyclononen - 3 - ol, from 1.0 g. of syn - 5 - ethyl - 6,7,8,9,10,11 - hexahydro - 3 - methoxy - 5,10 - methano - 5H - benzocyclononen - 12 - amine, there is obtained 0.72 g. of the hydrogen bromide salt of the title product with m.p. 266—270° on recrystallization from ethanol-ether.

20 Analysis for: $C_{16}H_{24}NOBr$
Calculated: C, 58.89; H, 7.41; N, 4.29.
Found: C, 58.50; H, 7.47; N, 4.10.

EXAMPLE 31

Anti-6,7,8,9,10,11-Hexahydro-3-Methoxy-N,5-Dimethyl-5,10-Methano-5H-Benzocyclononen-12-Amine

25 6,7,8,9,10,11 - Hexahydro - 3 - methoxy - 5 - methyl - 5,10 - methano - 5H - benzocyclononen - 12 - one (3 g.), calcium oxide (2 g.), and liquid methyl amine (10 ml.) are heated in a sealed vessel at 180—190°C. for 18 hours. After cooling the mixture is diluted with ether and filtered to separate the hydrated calcium oxide. The filtrate is concentrated to an oil which is taken up in ethanol and shaken with hydrogen at 45 psi in the presence of platinum dioxide catalyst. The catalyst is removed by filtration, rinsed thoroughly with ethanol and combined filtrate is concentrated *in vacuo*. The residue was distilled under reduced pressure to give the title product (1.8 g.), b.p. 138—144°C. (0.2 mm.). For analytical purposes a sample is converted to the hydrochloride which crystallizes from ethanol, m.p. 295—298°C.

30 Analysis for: $C_{17}H_{22}ClNO$
Calculated: C, 69.01; H, 8.86; N, 4.73.
Found: C, 68.90; H, 8.92; N, 4.83.

EXAMPLE 32

5,6,7,8,9,10-Hexahydro-3-Methoxy-5-Methyl-N-Phenethyl-5,9-Methano-Benzocycloocten-11-Amine

45 Using a procedure analogous to that described in Example 31 for the preparation of N,5 - dimethyl - 6,7,8,9,10,11 - hexahydro - 3 - methoxy - 5,10 - methano - 5H - benzocyclononen - 12 - amine there is obtained from 5,6,7,8,9,10 - hexahydro - 3 - methoxy - 5 - methyl - 5,9 - methanobenzocycloocten - 11 - one (2.3 g.) 1.80 g. of the title product, b.p. 170—200°C. (0.5 mm.). A sample is converted to the hydrochloride salt.

50 Analysis for: $C_{23}H_{30}ClNO$
Calculated: C, 74.27; H, 8.12; N, 3.77.
Found: C, 74.23; H, 8.29; N, 3.59.

EXAMPLE 33

Syn-5,6,7,8,9,10-Hexahydro-3-Methoxy-N,5-Dimethyl-5,9-Methano-Benzocycloocten-11-Amine

55 Using a procedure analogous to that described in Example 31 for the preparation of anti - 6,7,8,9,10,11 - hexahydro - 3 - methoxy - N,5 - dimethyl - 5,10 -

methano - 5H - benzocyclononen - 12 - amine there is obtained from 5,6,7,8,9,10-hexahydro - 3 - methoxy - 5 - methyl - 5,9 - methano - benzocycloocten - 11 - one (9.5 g.), 5.4 g. of the title product as the hydrochloride salt, m.p. 232—236°C.

Analysis for: $C_{16}H_{24}ClNO$
Calculated: C, 68.19; H, 8.58; N, 4.97.
Found: C, 67.83; H, 8.45; N, 4.91.

EXAMPLE 34

Syn-N-Allyl-N,5-Dimethyl-5,6,7,8,9,10-Hexahydro-3-Methoxy-5,9-Methano-Benzocycloocten-11-Amine

Syn - N - allyl - 5,6,7,8,9,10 - hexahydro - 3 - methoxy - 5 - methyl - 5,9 - methano - benzocycloocten - 11 - amine (3 g.), ethylchloroformate (3 ml.), saturated aqueous sodium bicarbonate (50 ml.) and methylene chloride (25 ml.) are stirred vigorously overnight at room temperature. The layers are then separated, the methylene chloride washed with 2N hydrochloric acid, dried over potassium carbonate and concentrated *in vacuo*. The residue obtained (3.3 g.) is dissolved in tetrahydrofuran (100 ml.), stirred and refluxed under nitrogen with lithium aluminium hydride (1 g.) for 20 hours. The mixture is cooled, water (1.5 ml.) added to destroy excess hydride, and aluminium salts removed by filtration. The filtrate is dried and concentrated *in vacuo* and the residue distilled to give the title product (1.4 g.), b.p. 130—135°C. (0.5 mm.). A portion is dissolved in ether, treated with hydrogen chloride, the crystals recovered by filtration and recrystallized from ethyl acetate to give a hydrochloride salt, m.p. 164—166°C.

Analysis for: $C_{17}H_{26}ClNO$
Calculated: C, 70.89; H, 8.77; N, 4.35.
Found: C, 71.06; H, 9.07; N, 4.53.

EXAMPLE 35

5,6,7,8,9,10-Hexahydro-3-Methoxy-N,N,5-Trimethyl-5,9-Methano-Benzocycloocten-11-Amine

Using a procedure analogous to that described in Example 34 for the preparation of N - Allyl - N,5 - dimethyl - 5,6,7,8,9,10 - hexahydro - 3 - methoxy - 5,9 - methano - benzocycloocten - 11 - amine there is obtained from N,5 - dimethyl - 5,6,7,8,9,10 - hexahydro - 3 - methoxy - 5,9 - methano - benzocycloocten - 11 - amine (11.1 g.), 8.1 g. of the title product, b.p. 125—130°C. (0.3 mm.). The product in solution in ether is converted by treatment with hydrogen chloride to a crystalline hydrochloride salt. Recrystallization from ethanol-ether gives a product, A, m.p. 180—190° which is recrystallized from ethanol-ether to give a product having needle-shaped crystals, m.p. 225—226°C.

Analysis for: $C_{17}H_{26}ClNO$
Calculated: C, 69.01; H, 8.86; N, 4.74.
Found: C, 68.89; H, 8.92; N, 4.70.

On the basis of infrared and nuclear magnetic resonance spectra this product is assigned a structure as the isomers wherein the amino grouping is positioned in the anti-configuration.

From the mother liquors remaining after crystallization of product A, after concentration, is obtained a second product, m.p. 218—223°C., recrystallization from ethanol-ether gives a product having hexagonal crystals, m.p. 221—223°C.

Analysis for: $C_{17}H_{26}ClNO$
Calculated: C, 69.01; H, 8.86; N, 4.74.
Found: C, 68.89; H, 8.64; N, 4.74.

On the basis of infrared and nuclear magnetic resonance spectra this product is assigned a structure as the isomers wherein the amino grouping is positioned in the syn configuration.

EXAMPLE 36

N,5-Dimethyl-N-Phenethyl-5,6,7,8,9,10-Hexahydro-3-Methoxy-5,9-Methano-Benzocycloocten-11-Amine

Using a procedure analogous to that described in Example 34 for the preparation of N - Allyl - N,5 - dimethyl - 5,6,7,8,9,10 - hexahydro - 3 - methoxy - 5,9 -

methano - benzocycloocten - 11 - amine there is obtained from 5,6,7,8,9,10 - hexahydro - 3 - methoxy - 5 - methyl - N - phenethyl - 5,9 - methano - benzocycloocten-11-amine (3.8 g.) 3.1 g. of the title product, b.p. 185—190°C. (0.3 mm.). Treatment of a portion of the product in acetone with one equivalent of fumaric acid gives the fumarate salt which is recrystallized from acetone as a hydrate, m.p. 149—151°C.

Analysis for: $C_{28}H_{38}NO_6 \cdot 1/4H_2O$
 Calculated: C, 71.53; H, 7.61; N, 2.98.
 Found: C, 71.58; H, 7.73; N, 2.98.

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EXAMPLE 37

N,5-Dimethyl-5,6,7,8,9,10-Hexahydro-3-Methoxy-N-(3-Methyl-2-Butenyl)-5,9-Methano-Benzocycloocten-11-Amine

Using a procedure analogous to that described in Example 34 for the preparation of N - allyl - N,5 - dimethyl - 5,6,7,8,9,10 - hexahydro - 3 - methoxy - 5,9 - methano - benzocycloocten - 11 - amine, there is obtained from 5,6,7,8,9,10 - hexahydro - 3 - methoxy - 5 - methyl - N - (3 - methyl - 2 - butenyl) - 5,9 - methano - benzocycloocten-11-amine (3.6 g.) 2.6 g. of the title product, b.p. 150—155°C. (0.4 mm.). Treatment of a portion of the product in acetone with fumaric acid gives the crystalline fumaric acid salt as a hydrate, m.p. 136—138°C.

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Analysis for: $C_{28}H_{38}NO_6 \cdot 1/4H_2O$
 Calculated: C, 69.19; H, 8.24; N, 3.22.
 Found: C, 69.20; H, 8.11; N, 3.32.

EXAMPLE 38

N,5-Dimethyl-6,7,8,9,10,11-Hexahydro-3-Methoxy-N-(3-Methyl-2-Butenyl)-5,10-Methano-5H-Benzocyclononen-12-Amine

6,7,8,9,10,11 - Hexahydro - 3 - methoxy - 5 - methyl - N - (3 - methyl) - 2 - butenyl) - 5,10 - methano - 5H - benzocyclononen - 12 - amine (3.5 g.), ethyl chloroformate (6 g.), saturated aqueous sodium bicarbonate (100 ml.) and methylenedichloride (50 ml.) are stirred vigorously at room temperature for 24 hours. The layers are then separated and the organic layer is washed with 2N hydrochloric acid, dried over potassium carbonate and concentrated *in vacuo*. The residue (3 g.) is dissolved in tetrahydrofuran (50 ml.) and added to a suspension of lithium aluminium hydride in tetrahydrofuran (50 ml.) stirred and heated to reflux for 18 hours. After cooling, water (4.5 ml.) is added and the reaction mixture is stirred 30 minutes and filtered. The filtrate is dried over anhydrous sodium sulphate and concentrated. The residue (2 g.) is treated with fumaric acid in acetone to give the fumarate salt of the title product as the hemihydrate (1.8 g.), m.p. 108—110°C.

Analysis for: $C_{28}H_{38}NO_6 \cdot 1/2H_2O$
 Calculated: C, 69.02; H, 8.47; N, 3.08.
 Found: C, 68.82; H, 8.54; N, 2.94.

EXAMPLE 39

12-Amino-6,7,8,9,10,11-Hexahydro-5-Methyl-5,10-Methano-5H-Benzocyclononen-3-Ol, Acetate

A. A mixture of 12 - amino - 6,7,8,9,10,11 - Hexahydro - 5 - methyl - 5,10 - methano - 5H - benzocyclononen - 3 - ol (15.0 g.), carbobenzyloxy chloride (11.6 g.) and 100 ml. of saturated aqueous sodium bicarbonate are stirred for 30 minutes. Methylene chloride (100 ml.) is added and the mixture stirred for 1 hour. The organic layer is separated, dried and concentrated. The residue is triturated with ethyl acetate and pentane, then filtered to give 24 g. of crude product. Recrystallization from ethylacetate-cyclohexane gives 18.3 g. of carbobenzyloxyated amine with m.p. 103—110°.

B. A solution of the carbobenzyloxyated amine (5.0 g.) of part A above, acetic anhydride (10 ml.) and pyridine (50 ml.) is allowed to stand overnight. The solution is diluted with water and extracted with ether. The ether extracts are washed with 2% aqueous hydrochloric acid, dried and concentrated to give 5.1 g. of o-acetylated product shown to be pure by thin layer chromatography.

C. A solution of the o-acetyl product of part B above (2.5 g.) and hydrogen chloride

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gas (0.75 g.) in tetrahydrofuran (50 ml.) is hydrogenated in a Parr apparatus over 250 mg. of 10% palladium on carbon under 40 lbs. of hydrogen pressure for 90 minutes. The catalyst is filtered and concentration of the filtrate gives 2.2 g. of title product as a viscous glass. Crystallization of the glassy product from tetrahydrofuran-ether gives crystalline 12 - amino - 6,7,8,9,10,11 - hexahydro - 5 - methyl - 5,10 - methano-5H-benzocyclononen-3-ol, acetate, hydrochloride with m.p. 268° dec.

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Analysis for: $C_{17}H_{24}NO_2Cl$
Calculated: C, 65.90; H, 7.81; N, 4.52.
Found: C, 65.38; H, 7.82; N, 4.48.

EXAMPLE 40

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12-Amino-6,7,8,9,10,11-Hexahydro-5-Methyl-5,10-Methano-5H-Benzocyclononen-3-ol, Cyclopropane Carboxylate

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A. A solution of 2.0 g. of the carbobenzyloxylated amine, described in Example 39 part A, and 2.0 ml. of cyclopropane carboxoyl chloride in 10 ml. of pyridine is allowed to stand overnight. The solution is diluted with water and extracted with ether. The ether extracts are washed with 2% aqueous hydrochloric acid, dried and concentrated to an oil. The oil is chromatographed on 70 g. of activity III Woelm alumina. Elution with ether gives 1.5 g. of oil which is crystallised from ethyl acetate hexane to give 1.2 g. of *o*-cyclopropane carboxylate derivative with m.p. 104—109°.

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B. In a manner analogous to that described in Example 39, part C, for the preparation of 12 - amino - 6,7,8,9,10,11 - hexahydro - 5 - methyl - 5,10 - methano - 5H-benzocyclononen-3-ol, acetate, from 1.0 g. of the *o*-cyclopropane carboxylate derivative of part A of above there is obtained 0.45 g. of the hydrogen chloride salt of the title product with m.p. 255—57° dec. on crystallisation from tetrahydrofuran-ether.

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Analysis for: $C_{17}H_{26}NO_2Cl \cdot 1/4H_2O$
Calculated: C, 67.04; H, 7.85; N, 4.12.
Found: C, 66.79; H, 7.68; N, 4.14.

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EXAMPLE 41
Resolution of Anti-5-Ethyl-6,7,8,9,10,11-Hexahydro-3-Methoxy-5,10-Methano-5H-Benzocyclononen-12-Amine

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A solution of anti - 5 - ethyl - 6,7,8,9,10,11 - hexahydro - 3 - methoxy - 5,10 - methano - 5H - benzocyclononen - 12 - amine (64.6 g., 0.249 mole) in 300 ml. of methanol is added to a solution of 41.5 g. (0.275 mole) of *l*-tartaric acid in 1400 ml. of methanol. The resulting solution is warmed, filtered and diluted to 2000 ml. and allowed to stand for 3 days. Filtration then gives 36.1 g. of salt with m.p. 200—203° dec. and $[\alpha]_D = -27^\circ$ (1% in dimethyl formamide). Recrystallisation of the salt from methanol gives 29.1 g. with m.p. 212—214° and $[\alpha]_D = -32.8^\circ$. This salt is converted to the free base by treating it with aqueous sodium hydroxide extracting the aqueous mixture with ether and drying the ether extracts over anhydrous magnesium sulfate. On removal of the drying agent and the ether solvent 17.6 g. of resolved base is obtained. This is converted to its hydrogen chloride, hydrate salt which has a m.p. 115—119° dec. and $[\alpha]_D = -44.1^\circ$ (2% in methanol).

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To obtain the opposite rotating isomer, the mother liquors from the first crystallisations of above are concentrated, the residue treated with aqueous sodium hydroxide and extracted with ether. On drying the ether extracts over anhydrous magnesium sulphate and concentrating the extracts, 41.5 g. of base is obtained. This is dissolved in 500 ml. of methanol and the solution is added to a solution of 26.4 g. of *d*-tartaric acid in 1000 ml. of methanol. This solution is diluted to 1600 ml. and allowed to stand for 5 days. Filtration gives 36.7 g. of salt with m.p. 205—209° dec. and $[\alpha]_D = +30.3^\circ$ (1% in dimethylformamide). Recrystallisation of this salt from methanol gives 30.0 g. of salt with m.p. 209—211° dec. and $[\alpha]_D = +31.9^\circ$. Conversion of this salt to free base by the same procedure as for the minus rotating isomer described above gives 16.8 g. of base. This is converted to its hydrogen chloride hydrate salt which has m.p. 115—119° dec. and $[\alpha]_D = +44.5^\circ$ (2% in methanol).

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EXAMPLE 42

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Preparation of Plus and Minus Rotating Isomers of Anti-12-Amino-6,7,8,9,10,11-Hexahydro-5-Ethyl-5,10-Methano-5H-Benzocyclononen-3-ol

A. A mixture of optically pure minus rotating anti - 5 - ethyl - 6,7,8,9,10,11 - hexa-

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hydro - 3 - methoxy - 5,10 - methano - 5H - benzocyclononen - 12 - amine (9.5 g.) and 80 ml. of 48% aqueous hydrobromic acid are heated at the reflux temperature under a dry nitrogen atmosphere for 30 minutes. The resulting solution is concentrated to 40 ml., diluted to 150 ml. with water and basified with concentrated aqueous ammonia. After allowing to stand one hour, the mixture is filtered to give 8.9 g. of product with m.p. 185—191°. Recrystallisation of the product from ethyl acetate gives 7.5 g. with m.p. 194—196° and $[\alpha]_D = -51.3^\circ$ (2% in methanol).

B. When optically pure plus rotating anti - 5 - ethyl - 6,7,8,9,10,11 - hexahydro - 3 - methoxy - 5,10 - methano - 5H - benzocyclononen - 12 - amine (9.3 g.) is treated with aqueous 48% hydrobromic acid as in A, there is obtained 9.3 g. of crude product with m.p. 178—190°. Recrystallisation of this from ethyl acetate gives 7.0 g. of product with m.p. 194—196° and $[\alpha]_D = -52.0^\circ$ (2% in methanol).

EXAMPLE 43

10-Amino-6,7,8,9-Tetrahydro-5,9-Methano-5H-Benzocycloheptene-5-Methanol
A mixture of 1 - ethoxycarbonyl - 1,3 - propano - 2 - indanone oxime (1.9 g.) and lithium aluminium hydride (1.6 g.) and 100 ml. of tetrahydrofuran is heated at its reflux temperature under dry nitrogen for 40 hours and allowed to stand for 3 days at room temperature. A few ml. of concentrated aqueous ammonia is added and after 15 minutes stirring the mixture is filtered. The filter cake is washed twice with isopropanol containing a little ammonia. The combined filtrates are concentrated to give 1.6 g. of oil which when treated with hydrogen chloride in ether and ethanol gives 1.2 g. of crystalline hydrochloride salt of title product with m.p. 217—220°.

Analysis for: $C_{13}H_{18}NOCl$
Calculated: C, 65.12; H, 7.57; N, 5.84.
Found: C, 64.99; H, 7.80; N, 5.73.

EXAMPLE 44

5-Methyl-6,7,8,9-Tetrahydro-5,9-Methano-5H-Benzocycloheptene-10-Amine
To a cold (5°) mixture of pyridine (50 ml.) and 10 - amino - 6,7,8,9 - tetrahydro - 5,9 - methano - 5H - benzocycloheptane - 5 - methanol, hydrochloride (5.1 g.) is added, in portions, 8.0 g. of p-toluenesulfonyl chloride in 20 ml. of pyridine. After keeping on ice for 3 hours, 8.0 g. of p-toluenesulphonyl chloride in 20 ml. of pyridine is again added. The resulting solution is allowed to stand overnight then is poured into ice water and extracted with ether. The ether extracts are washed with dilute hydrochloric acid, dried and concentrated to give 11 g. of crude product. Trituration of the crude product with ether and recrystallisation from ethyl acetate-heptane gives 8.1 g. of product (A) with m.p. 157—159°.

Analysis for: $C_{27}H_{23}NO_4S_2$
Calculated: C, 63.39; H, 5.71; N, 2.74.
Found: C, 63.33; H, 5.82; N, 2.43.

A mixture of the ditosylate (A) (4.0 g.), lithium aluminium hydride (1.5 g.) and tetrahydrofuran is allowed to stir at room temperature for 1 hour under nitrogen then is refluxed overnight. Four ml. of water is added and the mixture is filtered. The collected solid is treated with dilute hydrochloric acid and extracted with ether. The ether extracts are combined with the filtrate of above and concentrated to give an oily solid (3.4 g.). Crystallisation of the solid from ethanol-water gives 1.4 g. of product (B) with m.p. 173—175°.

Analysis for: $C_{20}H_{23}NO_2S$
Calculated: C, 70.36; H, 6.79; N, 4.10.
Found: S, 70.29; H, 6.65; N, 4.39.

Sodium metal (2.8 g.) is dissolved in a solution of naphthalene (15.4 g.) and dimethoxyethane (130 ml.) under a nitrogen atmosphere with stirring. After 1.5 hours, product (B) (4.6 g.), in 45 ml. of dimethoxyethane, is added and the mixture is stirred for 2 hours. Water (1 ml.) is added and the mixture concentrated. The residue is dissolved in ether-water and the ether separated. The ether layer is extracted with dilute hydrochloric acid. The acid layer is basified with concentrated sodium hydroxide and extracted with ether and dried. Addition of ethereal hydrogen

line (9.5 g.)
temperature
is concen-
red aqueous
e 8.9 g. of
hyl acetate

exahydro -
(9.3 g.) is
g. of crude
ives 7.0 g.

hanol
e (1.9 g.)
heated at
nd for 3
dded and
wice with
centrated
d ethanol
7—220°.

ne
- tetra-
(5.1 g.)
e. After
pyridine
poured
dilute
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e gives

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chloride gives 2.3 g. of the hydrogen chloride salt of the title product with m.p. 225—227° which is collected by filtration.

Analysis for: $C_{12}H_{18}NCl \cdot 1/4 H_2O$
Calculated: C, 68.41; H, 8.16; N, 6.14.
Found: C, 68.62; H, 8.10; N, 5.92.

EXAMPLE 45

Resolution of Anti-5,6,7,8,9,10,11,12-Octahydro-3-Methoxy-5 α -Methyl-5,11-Methanobenzocyclodecen-13-Amine

Part A

A solution of racemic anti - 5,6,7,8,9,10,11,12 - octahydro - 3 - methoxy - 5 α - methyl - 5,11 - methanobenzocyclodecen - 13 - amine (83 g.) in 200 ml. of methanol is added to a solution of d-tartaric acid (57 g.) in 500 ml. of methanol. The solution is diluted to 1 litre and allowed to stand for 2 days. Filtration gives 83.5 g. of salt with m.p. 200—208° dec. Three recrystallisations of this salt from methanol give 21 g. of optically pure tartrate salt with m.p. 213—215°. This is converted to optically pure base by treatment of the salt with dilute sodium hydroxide and extraction with ether. Exactly 1/2 of the dried ether extracts (225 ml.) are treated with 15 ml. of ethanol and acidified with ethereal hydrogen chloride. Filtration gives 5.8 g. of the hydrochloride salt of the plus rotating enantiomorph with m.p. 234—237°.

Analysis for: $C_{17}H_{26}NOCl$
Calculated: C, 69.01; H, 8.86; N, 4.73.
Found: C, 68.90; H, 9.10; N, 4.42.

Part B

The mother liquors of the tartrate crystallisation of above are concentrated and the residue is converted to base by treatment with dilute aqueous sodium hydroxide and extraction with ether. Removal of the ether gives 58 g. of base which is dissolved in methanol and treated with 38 g. of l-tartaric acid in methanol. The final solution has a volume of 800 ml. Filtration after 4 days of standing gives 41.3 g. of tartrate salt with m.p. 204—209° dec. Two recrystallisations of this salt give optically pure tartrate salt with m.p. 216—218°. Conversion to optically pure base and subsequently hydrogen chloride salt as in part A yields 6.0 g. of hydrochloride salt of the minus rotating enantiomorph with m.p. 234—237° and $[\alpha]_D^{25} = -46.0^\circ$.

Analysis for: $C_{17}H_{26}NOCl$
Calculated: C, 69.01; H, 8.86; N, 4.73.
Found: C, 68.63; H, 9.10; N, 4.35.

EXAMPLE 46

(+)-Anti-13-Amino-5,6,7,8,9,10,11,12-Octahydro-5-Methyl-5,11-Methanobenzocyclodecen-3-Ol

The second half of the ethereal solution of optically pure plus rotating base described in Example 45, Part A is concentrated to give 6.5 g. of base. This is treated with 100 ml. of 48% aqueous hydrogenbromide and heated at reflux under dry nitrogen for 1/2 hour then concentrated. The residual oil is crystallised from water to give 5.4 g. of hydrogen bromide salt of the title product with m.p. 268—272° and $[\alpha]_D^{25} = +41.4^\circ$.

Analysis for: $C_{16}H_{24}NOBr \cdot 1/4 H_2O$
Calculated: C, 58.09; H, 7.46; N, 4.23.
Found: C, 58.20; H, 7.61; N, 4.23.

(-)-Anti-13-Amino-5,6,7,8,9,10,11,12-Octahydro-5-Methyl-5,11-Methanobenzocyclodecen-3-Ol

In the same manner as described for the preparation of the plus rotating isomer, from the ethereal solution of minus rotating base described in Example 45, Part B there is obtained 5.5 g. of hydrogen bromide salt of the title product with m.p. 269—271° and $[\alpha]_D^{25} = -41.7^\circ$.

Analysis for: $C_{16}H_{24}NOBr \cdot 1/4 H_2O$
Calculated: C, 58.09; H, 7.46; N, 4.23.
Found: C, 58.47; H, 7.41; N, 4.26.

EXAMPLE 47

Syn-13-(Dimethylamino)-5,6,7,8,9,10,11,12-Octahydro-5 α -Methyl-5,11-Methanobenzocyclodecen-3-Ol

A solution of syn - 5,6,7,8,9,10,11,12 - Octahydro - 3 - methoxy - *N,N*,5 α - trimethyl - 5,11 - methanobenzocyclodecen - 13 - amine, hydrochloride (5.0 g.) in 80 ml. of 48% hydrobromic acid is heated at reflux under dry nitrogen for 20 minutes then concentrated. The residue is crystallised from ethanol-ether to give 4.4 g. of the hydrobromide salt of the title product with m.p. 243—245°.

Analysis for: $C_{18}H_{24}NOBr$
 Calculated: C, 61.01; H, 7.96; N, 3.95.
 Found: C, 61.06; H, 8.10; N, 3.85.

EXAMPLE 48

Syn-5,6,7,8,9,10,11,12-Octahydro-3-Methoxy-*N,N*,5 α -Trimethyl-5,11-Methanobenzocyclodecen-13-Amine *N*-Oxide

To a cold (0°) solution of syn - 5,6,7,8,9,10,11,12 - octahydro - 3 - methoxy - *N,N*,5 α - trimethyl - 5,11 - methanobenzocyclodecen - 13 - amine (1.5 g.) in 20 ml. of dry tetrahydrofuran is added 1.0 g. of meta chloroperbenzoic acid in 10 ml. of tetrahydrofuran. The solution is stirred at 0 to 10° for 30 minutes. Two ml. of a saturated solution of hydrogen chloride in ethanol is added. After crystallisation occurs, 30 ml. of ether is added and the mixture is filtered to give 1.7 g. of the hydrogen chloride salt of the title product with m.p. 170—173° dec.

Analysis for: $C_{19}H_{25}NO_2Cl$
 Calculated: C, 67.13; H, 8.90; N, 4.13.
 Found: C, 66.61; H, 9.04; N, 3.98.

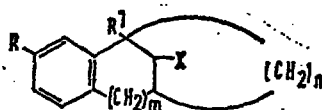
EXAMPLE 49

When the following compounds are administered to rats by the routes indicated, for evaluation of analgesic potential by the procedure described hereinabove, they exhibit the effective dose-50 values tabulated.

Compound	Mode of Administration	Effective dose-50 (mg/kg body weight)
6,7,8,9,10,11-hexahydro-3-methoxy-5-methyl-5,10-methano-5H-benzocyclononen-12-amine	intraperitoneal oral	25 30
12-amino-6,7,8,9,10,11-hexahydro-5-methyl-5,10-methano-5H-benzocyclononen-3-ol	intraperitoneal intramuscular oral	7.5 1.8 23
5-ethyl-6,7,8,9,10,11-hexahydro-3-methoxy-5,10-methano-5H-benzocyclononen-12-amine	intraperitoneal intramuscular oral	3.5 13.5 11
12-amino-6,7,8,9,10,11-hexahydro-5-ethyl-5,10-methano-5H-benzocyclononen-3-ol	intraperitoneal intramuscular oral	3.5 0.25 12
3-methoxy-5-methyl-5,6,7,8,9,10,11,12-octahydro-5,11-methanobenzocyclodecen-13-amine	intraperitoneal intramuscular oral	4.5 15 9
13-amino-5-methyl-5,6,7,8,9,10,11,12-octahydro-5,11-methanobenzocyclodecen-3-ol	intraperitoneal intramuscular oral	1.1 0.47 9

WHAT WE CLAIM IS:—

1. A benzobicycloalkane compound of the general formula



wherein X is $-NR^2R^3$ or

(1)



EXAMPLE 47

Syn-13-(Dimethylamino)-5,6,7,8,9,10,11,12-Octahydro-5 α -Methyl-5,11-Methanobenzocyclodecen-3-Ol

A solution of syn - 5,6,7,8,9,10,11,12 - Octahydro - 3 - methoxy - *N,N,5 α* - trimethyl - 5,11 - methanobenzocyclodecen - 13 - amine, hydrochloride (5.0 g.) in 80 ml. of 48% hydrobromic acid is heated at reflux under dry nitrogen for 20 minutes then concentrated. The residue is crystallised from ethanol-ether to give 4.4 g. of the hydrobromide salt of the title product with m.p. 243—245°.

Analysis for: $C_{11}H_{28}NOBr$
Calculated: C, 61.01; H, 7.96; N, 3.95.
Found: C, 61.06; H, 8.10; N, 3.85.

EXAMPLE 48

Syn-5,6,7,8,9,10,11,12-Octahydro-3-Methoxy-*N,N,5 α* -Trimethyl-5,11-Methanobenzocyclodecen-13-Amine *N*-Oxide

To a cold (0°) solution of syn - 5,6,7,8,9,10,11,12 - octahydro - 3 - methoxy - *N,N,5 α* - trimethyl - 5,11 - methanobenzocyclodecen - 13 - amine (1.5 g.) in 20 ml. of dry tetrahydrofuran is added 1.0 g. of meta chloroperbenzoic acid in 10 ml. of tetrahydrofuran. The solution is stirred at 0 to 10° for 30 minutes. Two ml. of a saturated solution of hydrogen chloride in ethanol is added. After crystallisation occurs, 30 ml. of ether is added and the mixture is filtered to give 1.7 g. of the hydrogen chloride salt of the title product with m.p. 170—173° dec.

Analysis for: $C_{11}H_{28}NO_2Cl$
Calculated: C, 67.13; H, 8.90; N, 4.13.
Found: C, 66.61; H, 9.04; N, 3.98.

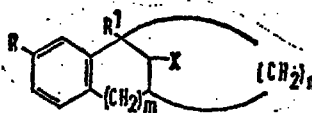
EXAMPLE 49

When the following compounds are administered to rats by the routes indicated, for evaluation of analgesic potential by the procedure described hereinabove, they exhibit the effective dose-50 values tabulated.

Compound	Mode of Administration	Effective dose-50 (mg/kg body weight)
6,7,8,9,10,11-hexahydro-3-methoxy-5-methyl-5,10-methano-5H-benzocyclononen-12-amine	intraperitoneal	25
	oral	30
12-amino-6,7,8,9,10,11-hexahydro-5-methyl-5,10-methano-5H-benzocyclononen-3-ol	intraperitoneal	7.5
	intramuscular	1.8
	oral	23
5-ethyl-6,7,8,9,10,11-hexahydro-3-methoxy-5,10-methano-5H-benzocyclononen-12-amine	intraperitoneal	3.5
	intramuscular	13.5
	oral	11
12-amino-6,7,8,9,10,11-hexahydro-5-ethyl-5,10-methano-5H-benzocyclononen-3-ol	intraperitoneal	3.5
	intramuscular	0.25
	oral	12
3-methoxy-5-methyl-5,6,7,8,9,10,11,12-octahydro-5,11-methanobenzo-cyclodecen-13-amine	intraperitoneal	4.5
	intramuscular	15
	oral	9
13-amino-5-methyl-5,6,7,8,9,10,11,12-octahydro-5,11-methanobenzo-cyclodecen-3-ol	intraperitoneal	1.1
	intramuscular	0.47
	oral	9

WHAT WE CLAIM IS:—

1. A benzobicycloalkane compound of the general formula



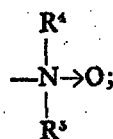
wherein X is $-NR^2R^3$ or

(I)



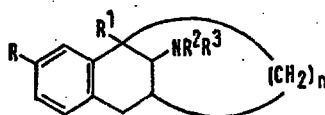
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R is hydrogen, lower alkyl, lower alkyloxy, hydroxy, acyloxy, phen(lower)alkyloxy, halogen or trifluoromethyl; R¹ is lower alkyl, phen(lower)alkyl or, when X is —NR²R³, hydroxymethyl or lower alkenyl; R² is hydrogen, lower alkyl or phen(lower)alkyl; R³ is hydrogen, lower alkyl, phen(lower)alkyl, (lower)alkenyl or (lower)alkynyl; R⁴ and R⁵ are each lower alkyl; m is 0 or 1 and n is an integer of from 2 to 6 or a pharmaceutically acceptable acid addition salt thereof.

2. A benzobicycloalkane compound as claimed in Claim 1 having the general formula



wherein R, R², R³ and n have the meanings given in Claim 1 and R¹ is lower alkyl or phen(lower)alkyl or a pharmaceutically acceptable acid addition salt thereof.

3. A benzobicycloalkane compound as claimed in Claim 2 wherein R is hydroxy, lower alkyl, lower alkyloxy, hydroxy, acyloxy, benzyloxy, halogen or trifluoromethyl.

4. A benzobicycloalkane compound as claimed in Claim 1 wherein n is 3 or 4.

5. A benzobicycloalkane compound as claimed in Claim 2 wherein n is 3 or 4.

6. A benzobicycloalkane compound as claimed in Claim 3 wherein n is 3 or 4.

7. A benzobicycloalkane compound as claimed in Claim 2 wherein n is 5.

8. 6,7,8,9,10,11 - Hexahydro - 3 - methoxy - 5 - methyl - 5,10 - methano - 5H-benzocyclononen-12-amine.

9. 12 - Amino - 6,7,8,9,10,11 - hexahydro - 5 - methyl - 5,10 - methano - 5H - benzocyclononen-3-ol.

10. 5 - Ethyl - 6,7,8,9,10,11 - hexahydro - 3 - methoxy - 5,10 - methano - 5H - benzocyclononen-12-amine.

11. 12 - Amino - 6,7,8,9,10,11 - hexahydro - 5 - ethyl - 5,10 - methano - 5H - benzocyclononen-3-ol.

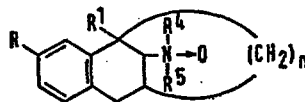
12. 13 - Amino - 5 - methyl - 5,6,7,8,9,10,11,12 - octahydro - 5,11 - methano - benzocyclodecen-3-ol.

13. 3 - Methoxy - 5 - methyl - 5,6,7,8,9,10,11,12 - octahydro - 5,11 - methano - benzocyclodecen-13-amine.

14. (—) - Anti - 13 - amino - 5 - methyl - 5,6,7,8,9,10,11,12 - octahydro - 5,11 - methanobenzocyclodecen - 3 - ol or a pharmaceutically acceptable salt thereof.

15. A pharmaceutically acceptable acid addition salt of a compound claimed in any one of Claims 8 to 13.

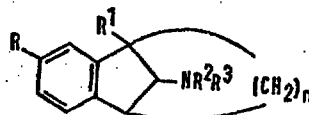
16. A benzobicycloalkane compound as claimed in Claim 1 having the general formula



wherein R, R⁴, R⁵ and n are as defined in Claim 1 and R¹ is lower alkyl or phen(lower)alkyl or a pharmaceutically acceptable acid addition salt thereof.

17. A compound as claimed in Claim 15 wherein n is 3, 4 or 5.

18. A benzobicycloalkane compound as claimed in Claim 1 having the general formula



wherein R, R², R³ and n have the meanings given in Claim 1 and R¹ is (lower)



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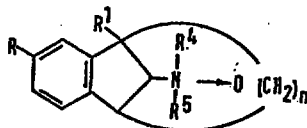
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alkyl, hydroxymethyl, (lower)alkenyl or phen(lower)alkyl or a pharmaceutically acceptable acid addition salt thereof.

19. A compound as claimed in Claim 18 wherein n is 3, 4 or 5.

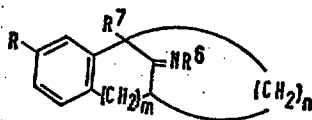
20. A benzobicycloalkane compound as claims in Claim 1 having the general formula



wherein R, R⁴, R⁵ and n have the meanings given in Claim 1 and R¹ is (lower) alkyl or phen(lower)alkyl or a pharmaceutically acceptable acid addition salt thereof.

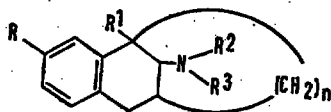
21. A compound as claimed in Claim 20 wherein n is 3, 4 or 5.

22. A process for preparing a compound claimed in Claim 1 which comprises reducing a compound of general formula (II)

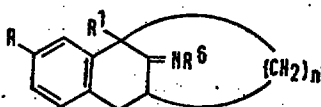


wherein R⁶ is hydroxy, alkoxy, or has the meaning of R² given in Claim 1 except when R⁷ is alkoxy carbonyl R⁶ is not R²; R⁷ is alkoxy carbonyl, lower alkyl, lower alkenyl, hydroxy methyl or phen(lower)alkyl; and R, R², m and n are as defined in Claim 1 and, if desired, lower alkylating, phen(lower)alkylating, lower alkenylating or lower alkynylating a resulting compound of general formula (I) in which R³ is hydrogen to give a compound of general formula (I) in which R³ is lower alkyl, phen(lower) alkyl, lower alkenyl or lower alkynyl, and/or lower alkylating or phen(lower)alkylating a compound in which R² is hydrogen and R³ is lower alkyl, phen(lower)alkyl, lower alkenyl or lower alkynyl to give a corresponding compound in which R² is lower alkyl or phen(lower)alkyl, and/or oxidizing by known methods a compound in which R² and R³ are lower alkyl to give the corresponding N-oxide, and/or converting by known methods a compound of general formula (I) in which R has one meaning into a compound of general formula (I) in which R has a different meaning and/or converting a free base of general formula (I) into a pharmaceutically acceptable acid addition salt.

23. A process as claimed in Claim 22 for preparing a benzobicycloalkane amine of general formula



wherein R, R², R³ and n have the meanings given in Claim 1 and R¹ is lower alkyl or phen(lower)alkyl; R² is hydrogen, lower alkyl or phen(lower)alkyl; or a pharmaceutically acceptable acid addition salt thereof which comprises reducing a compound of general formula



wherein R⁶ is hydroxy or has the meaning of R² and, if desired, lower alkylating, phen(lower)alkylating, alkenylating or alkynylating a resulting compound in which R³ is hydrogen to give a compound in which R³ is lower alkyl, phen(lower)alkyl, alkenyl or alkynyl, and/or lower alkylating or phen(lower)alkylating a product in which R² is hydrogen and R³ is lower alkyl, phen(lower)alkyl, alkenyl or alkynyl to give a corresponding compound in which R² is lower alkyl or phen(lower)alkyl, and/or converting by known methods a product in which R has one meaning into a com-



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pound in which R has a different meaning and/or converting a free base into a pharmaceutically acceptable acid addition salt.

24. A process as claimed in Claim 22 wherein the reduction is effected by catalytic reduction or with a hydride of boron or aluminium or a complex metal hydride derivable therefrom or with an alkali metal in an alkanol.

25. A process as claimed in Claim 23 wherein the reduction is effected by catalytic reduction or with a metal hydride.

26. A process as claimed in Claim 25 wherein the metal hydride is lithium aluminium hydride.

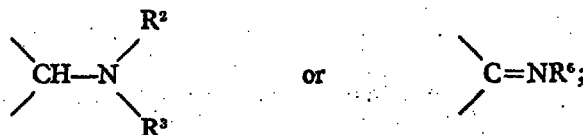
27. A process as claimed in Claim 22 or Claim 24 in which n is 3, 4 or 5.

28. A process as claimed in anyone of Claims 23, 25 and 26 in which n is 3, 4 or 5.

29. A process for preparing a compound claimed in Claim 1 which comprises reducing a compound of general formula (V)



wherein A is: $-\text{CH}=\text{CH}-$, or $-\text{CH}(\text{OTosyl})-\text{CH}_2-$; B is



and R, R², R³, m and n are as defined in Claim 1 and R⁶ and R⁷ are as defined in Claim 22 and, if desired, lower alkylating, phen(lower)alkylating, lower alkenylating or lower alkynylating a resulting compound of general formula (I) in which R³ is hydrogen to give a compound of general formula (I) in which R³ is lower alkyl, phen(lower)alkyl, lower alkenyl or lower alkynyl, and/or lower alkylating or phen(lower)alkylating a compound in which R² is hydrogen and R³ is lower alkyl, phen(lower)alkyl, lower alkenyl or lower alkynyl to give a corresponding compound in which R² is lower alkyl or phen(lower)alkyl, and/or oxidizing by known methods a compound in which R² and R³ are lower alkyl to give the corresponding N-oxide, and/or converting by known methods a compound of general formula (I) in which R has one meaning into a compound of general formula (I) in which R has a different meaning and/or converting a free base of general formula (I) into a pharmaceutically acceptable acid addition salt.

30. A process as claimed in Claim 29 wherein n is 2.

31. A process as claimed in Claim 29 wherein n is 3, 4 or 5.

32. A process as claimed in Claim 29 wherein n is 6.

33. A process as claimed in any one of Claims 29 to 32 wherein the compound of general formula (V) is reduced catalytically.

34. A process as claimed in any one of Claims 29 to 32 wherein the compound of general formula (V) in which B is $-\text{CH}(\text{OTosyl})-\text{CH}_2-$ is reduced with lithium aluminium hydride.

35. A process as claimed in any one of Claims 29 to 32 wherein the compound of general formula (V) in which B is $-\text{CH}=\text{CH}-$ is reduced with sodium borohydride and aluminium chloride in diglyme, sodium borohydride and boron trifluoride in diglyme, diborane in tetrahydrofuran, or bis-3-methyl-2-butylborane in tetrahydrofuran.

36. A process for preparing a benzobicycloalkane compound as claimed in claim 1, substantially as hereinbefore described with reference to any one of Examples 1A, 2, 3, 4, 5A, 6A, 7, 8 18 to 26 and 31 to 38.

37. A process for preparing a benzobicycloalkane compound as claimed in claim 1, substantially as hereinbefore described with reference to any one of Examples 1B, 5B, 6B, 9 to 17, 27 to 30 and 39 to 48.

38. A benzobicycloalkane compound whenever prepared by the process claimed in any one of the Claims 22, 24, 27, 29 to 35 and 37.

39. A benzobicycloalkane compound whenever prepared by the process claimed in Claim 36.



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40. A benzobicycloalkane compound whenever prepared by the process claimed in any one of Claims 23, 25, 26 and 28.

41. A benzobicycloalkane compound as defined in Claim 1 substantially as here-
inbefore described with reference to any one of Examples 1A, 2, 3, 4, 5A, 6A, 7, 8,
18 to 26 and 31 to 38.

42. A benzobicycloalkane compound as defined in Claim 1 substantially as here-
inbefore described with reference to any one of Examples 1B, 5B, 6B, 9 to 17, 27 to
30 and 39 to 48.

43. A pharmaceutical preparation comprising a compound claimed in any one
of Claims 1, 4, 14, 16 to 21, 38 and 42 in association with a pharmaceutically accept-
able carrier.

44. A pharmaceutical preparation comprising a compound claimed in any one
of Claims 2, 5, 7 and 40 in association with a pharmaceutically acceptable carrier.

45. A pharmaceutical preparation comprising a compound claimed in any one
of Claims 3, 6, 8 to 13, 15, 39 and 41 in association with a pharmaceutically accept-
able carrier.

46. A method of inducing analgesia in warm-blooded animals other than humans
which comprises administering to the warm-blooded animal a pharmaceutically effec-
tive amount of a compound claimed in any one of Claims 1, 2, 4, 5, 7, 14, 16 to 21,
38, 40 and 42.

47. A method of inducing analgesia in warm-blooded animals other than humans
which comprises administering to the warm-blooded animal a pharmaceutically effec-
tive amount of a compound claimed in any one of Claims 3, 6, 8 to 13, 15, 39
and 41.

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