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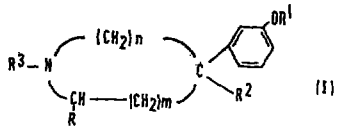
(54) HEXAHYDROAZEPINES

(71) We, JOHN WYETH & BROTHER LIMITED, of Huntercombe Lane South, Taplow, Maidenhead, Berkshire, a British Company, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to novel hexahydro-1H-azepine derivatives, to processes for their preparation and to pharmaceutical compositions containing them.

Compounds containing an azepine ring have been known for some time to have pharmaceutical activity, particularly analgesic activity. For example one well-known non-addictive analgesic of this type on the market is ethyl 1 - methyl - 4 - phenyl - hexahydroazepine-4-carboxylate which is known as ethoheptazine. We have now found that a new series of hexahydroazepines, which are substituted at either position 3 or 4 by both a lower alkyl group and a phenyl radical substituted at the *meta* position by a hydroxy, lower alkoxy, benzyloxy or lower alkanoyloxy generally exhibit pharmacetical activity, more specifically analgesic activity or analgesic antagonism. Some of the compounds, in particular that of Example 34, show a novel but highly interesting combination of analgesic and analgesic antagonistic activities. Furthermore, some of the novel compounds of the invention can be used as intermediates in the preparation of similar compounds.

The novel compound provided by the invention are hexahydroazepine derivatives of the general formula



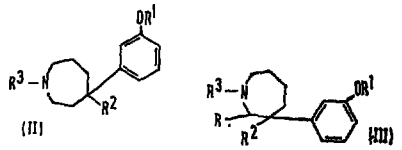
(I)

and acid addition and quaternary ammonium salts thereof, in which R^1 is a hydrogen atom, a lower alkyl radical, a benzyl radical or a lower alkanoyl radical, R^2 is a lower alkyl radical, R^3 is a hydrogen atom, a lower alkyl, lower alkenyl, lower alkynyl, cyclopropylmethyl, lower alkanoyl, lower alkoxycarbonyl, formyl, phenacyl or phenethyl group both of which may substituted in the benzene ring or a β-benzoylethyl radical which may be substituted in the benzene ring, n is the integer 3 or 4, m is 0 or the integer 1 with the proviso that n+m is always equal to 4, R is a hydrogen atom or lower alkyl radical when m is 0 or a hydrogen atom only when m is the integer 1. The term "lower" whenever used throughout the specification, means that the radical contains up to 6 preferably up to 4 carbon atoms.

When R is a hydrogen atom, there is only one asymmetric carbon atom in the molecule,

and so the invention provides both optically active isomers as well as the racemate, but when R is a lower alkyl radical there are two asymmetric carbon atoms and the invention provides all the optical isomers as well as the racemates. If an optically active isomer is desired, then a resolution can be carried out using methods known *per se*.

When n is 3 and m is 1, the compounds are 1,4,4-trisubstituted hexahydroazepines of general formula II, and when n is 4 and m is 0 the compounds are 1,3,3-trisubstituted hexahydroazepines possibly also substituted in the 2-position of general formula III, wherein R, R^1, R^2 and R^3 have the meanings defined above.



(II) (III)

We have named the compounds of the above general formulae using the hexahydro-1H-azepine ring as the basic unit and numbering from the nitrogen atom of this ring. Examples of such compounds are:

3 - (*m* - methoxyphenyl) - 1 - methyl - 3 - propylhexahydro-1H-azepine,

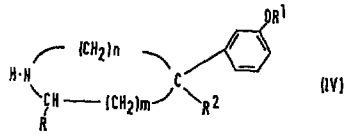
3 - (*m* - methoxyphenyl) - 1,3 - dimethyl - hexahydro-1H-azepine,

3 - (*m* - hydroxyphenyl) - 1 - methyl - 3 - propylhexahydro-1H-azepine and

3 - (*m* - hydroxyphenyl) - 1,3 - dimethyl - hexahydro-1H-azepine, though it is realised that the last two compounds could alternatively be named using *m*-hydroxyphenol as the basic unit. For example, the last compound could be named according to Chemical Abstracts nomenclature as *m*-(hexahydro-1,3-dimethyl-1H-azepin-3-yl)phenol.

Preferred compounds of the above general formulae (II) and (III) are hexahydro-1H-azepines in which R is hydrogen or methyl, R^1 is hydrogen, methyl or acetyl, R^2 is methyl, ethyl, *n*-propyl, *iso*-propyl or *n*-butyl and R^3 is hydrogen, methyl, ethyl, *n*-propyl, allyl, 3 - methyl - but - 2 - enyl (i.e. commonly known as dimethylallyl), propynyl, cyclopropylmethyl, phenacyl, phenethyl, *p*-aminophenethyl, *β*-benzoylethyl, *β*-(*p*-chlorobenzoylethyl), ethoxycarbonyl or formyl.

Compound of the above general formula (I) in which R^1 is other than lower alkanoyl, and R^3 is other than hydrogen or a lower alkonyl, formyl or lower alkoxycarbonyl, radical can be prepared by "alkylating", as hereinafter defined a compound of the general formula



(IV)

The term "alkylating" as used herein means introducing onto the nitrogen atom of the hexahydroazepine ring a radical R^3 selected from lower alkyl, lower alkenyl, lower alkynyl, cyclopropylmethyl, phenacyl or phenethyl (both of which may be substituted in the benzene ring) or *β*-benzoylethyl (which may be substituted in the benzene ring) radicals. Many methods of alkylating compounds are known and the most suitable method to give a desired product can be used, the following methods generally being preferred.

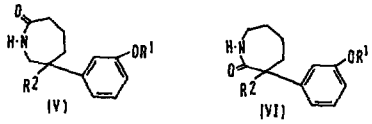
A compound of general formula (IV) in which R^1 is other than lower alkanoyl can be reacted with a halide of the general formula

$$R^3 - Hal$$

(where R^3 has the meanings defined above for formula (I) but is other than hydrogen, lower alkoxycarbonyl, lower alkanoyl or formyl, and Hal is a halogen atom) in the presence of an acid acceptor such as an alkali metal carbonate (e.g. potassium carbonate) preferably in solution in an organic solvent at e.g. 25°—100°C, preferably 80—100°C.

A 1-methyl group can be introduced into a compound of general formula (IV) in which R, R^1, R^2, n and m have the meanings defined above for formula (I) by reductive methylation, for example, using formaldehyde and hydrogen in the presence of a hydrogenation catalyst.

Furthermore, the compounds of general formula (I) in which n is 4, m is 0, R^1 is a lower alkyl or benzyl radical, R^2 is a lower alkyl radical, R^3 is lower alkyl, lower alkenyl, lower alkynyl, cyclopropylmethyl or phenethyl and R is a hydrogen atom can be prepared by "alkylating" (as hereinbefore defined with the proviso that the R^3 group introduced is other than phenacyl or *β*-benzoylethyl both of which may be substituted in the benzene ring) a hexahydro - 2H - azepin - 2 - one of the general formulae



(V) (VI)

wherein R^1 and R^2 have the meanings defined immediately above, and reducing the oxo group

to a methylene group by means of a hydride transfer agent such as lithium aluminium hydride. For example, the hexahydro-2H-azepin-2-one may be converted to an alkali metal salt (e.g. by reaction with sodium, sodamide or sodium hydride), the alkali metal salt reacted with a halide of the general formula

$$R^3 — Hal$$

wherein R^3 is a lower alkyl, lower alkenyl, lower alkynyl, cyclopropylmethyl or phenethyl, and the 1 - alkylated hexahydro - 2H - azepin-2-one subsequently reduced.

When it is desired to prepare the compounds of general formula (I) in which n is 4, m is 0, R^1 is a lower alkyl or benzyl radical, R^2 is a lower alkyl radical and R and R^3 are hydrogen atoms, then a compound of formula (V) or (VI) may be reduced without prior alkylation (as hereinbefore defined).

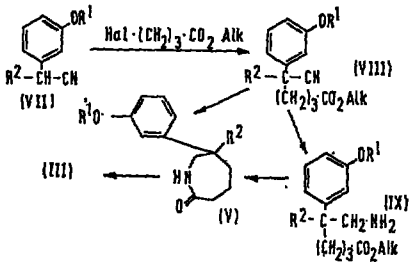
Compounds of the general formula (I) in which R^1 is other than hydrogen and R^3 is a lower alkanoyl radical, can be prepared by acylating a corresponding compound of the general formula (IV) in which R^1 is other than hydrogen.

Compounds of the general formula (I) in which R^3 is a formyl radical, can be prepared by formylating a corresponding compound of the general formula (IV). Of the many methods which are known for formylation, it is preferred to heat under reflux a compound of formula (IV) with formic acid.

Compounds of the general formula (I) in which R^1 is lower alkanoyl can be prepared by acylating a corresponding compound in which R^1 is hydrogen.

The compounds of general formula (I) in which R, R^2, R^3, n and m have the meanings already defined and R^1 is a hydrogen atom can be obtained from the corresponding compounds of general formula (I) in which R^1 is lower alkyl or benzyl by splitting off the ether group in known manner, e.g. by treating the lower alkyl or benzyl ethers with hydrogen bromide or boron tribromide or by subjecting the benzyl ethers to hydrogenolysis. If desired, the product obtained can then be acylated (e.g. with acetic anhydride) to give the corresponding compound in which R^1 is a lower alkanoyl radical.

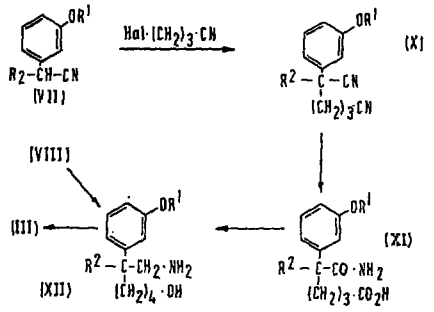
A preferred method for the preparation of compounds of general formula (III) in which R is hydrogen, R^1 is a lower alkyl radical and R^3 is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, cyclopropylmethyl or phenethyl group which may be substituted in the benzene ring, is illustrated below. In this method, R^2 and Hal have the meanings defined above, R^1 is lower alkyl and Alk is a lower alkyl radical which preferably is ethyl.



A substituted aliphatic nitrile of formula (VII) can be reacted with sodium in liquid ammonia followed by an alkyl halobutyrate (preferably ethyl 4-iodobutyrate) to give a nitrile-ester of formula (VIII); this nitrile ester can be reduced, (e.g. by catalytic hydrogenation at a temperature of up to 80°C, preferably with hydrogen in the presence of palladium on charcoal at room temperature in a solvent such as methyl alcohol containing sulphuric acid, and under a pressure of about 50 lbs/sq. inch, or by catalytic hydrogenation at a temperature above 100°C, preferably with hydrogen in the presence of Raney nickel at temperatures of 100—150°C in a solvent such as cyclohexane and under pressures of 800 to 1200 lbs/sq. inch). The low temperature reduction tends to give the open chain product of formula (IX), while the higher temperature reduction tends to give the product of formula (V); accordingly, the product of formula (IX) can be heated (e.g. in a solvent, such as refluxing toluene or decahydronaphthalene or with sodium ethoxide in absolute alcohol) to give the hexahydro - 2H - azepin - 2 - one of formula (V) which can be reduced (e.g. with a hydride transfer agent such as with sodium dihydro - bis - (2 - methoxyethoxy)aluminate or with lithium aluminium hydride) to give a compound of formula (III) wherein R and R^3 are hydrogen, or can be "alkylated" (as hereinbefore defined with the proviso that the group R^3 introduced is other than phenacyl or β-benzoylethyl both of which may be substituted in the benzene ring) directly with subsequent reduction to give a hexahydroazepine of general formula (III) wherein R is hydrogen and R^3 is lower alkyl, lower alkenyl, lower alkynyl, cyclopropylmethyl or phenethyl group which may be substituted in the benzene ring.

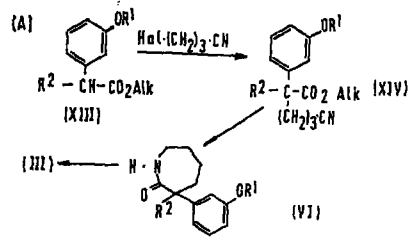
Once a compound of formula (III) in which R^1 is lower alkyl has been prepared the corresponding compound in which R^1 is hydrogen can be obtained therefrom by splitting the ether group following the information given above.

A less preferred method for the preparation of compounds of general formula (III) in which R and R^3 are hydrogen is next illustrated. In this method R^1 can be a lower alkyl or benzyl radical.

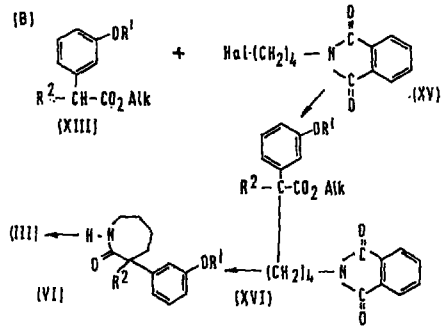


A substituted aliphatic nitrile of formula (VII) can be reacted in a similar manner to that of the previous method, but using, for example, 4-iodobutyronitrile to give a dinitrile of formula (X), which on hydrolysis (e.g. with an aqueous alkali metal hydroxide) gives the amido-acid of formula (XI); the amido-acid can be reduced (e.g. with a hydride transfer agent such as with lithium aluminium hydride) to the amino hydroxy compound of formula (XII) which may be halogenated (e.g. by heating with an halogenating agent such as with thionyl chloride) and then cyclised by heating in a solvent with or without the presence of a base (e.g. an alkali metal carbonate) to give the desired compound of formula (III). As a modification of this route, a compound of formula (VIII) may be reduced (e.g. with a hydride transfer agent such as with lithium aluminium hydride) to a compound of formula (XII).

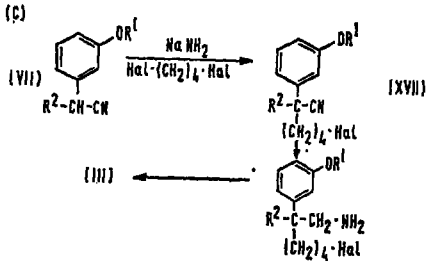
The following three methods can also be used for the preparation of compounds of the general formula III in which R is a hydrogen atom, R^2 is a lower alkyl radical and R^3 is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, cyclopropylmethyl or phenethyl (which may be substituted in the benzene ring). In the first and third method R^1 is a lower alkyl radical, whereas in the second method R^1 can also be a benzyl radical. In all three methods, Alk is a lower alkyl radical and Hal is a halogen atom.



One can start with a substituted aliphatic ester of formula (XIII) and react it with, for example, sodium in liquid ammonia followed by 4-iodobutyronitrile to give the nitrile ester of formula (XIV); the nitrile ester may be cyclised as described in the preferred method above, to give the hexahydro - 2H - azepin - 2-one of formula (VI) which may be reduced with a hydride transfer agent such as lithium aluminium hydride, to give a compound of formula (III) wherein R and R^3 are hydrogen, or "alkylated" (as hereinbefore defined with the proviso that the group R^3 introduced is other than phenacyl or β-benzoylethyl both of which may be substituted in the benzene ring), with subsequent reduction with a hydride transfer agent such as lithium aluminium hydride, to give a compound of formula (III) wherein R is hydrogen and R^3 is lower alkyl, lower alkenyl, lower alkynyl, cyclopropylmethyl or phenethyl.



A substituted aliphatic ester of formula (XIII) is reacted with for example, N-(4-iodobutyl) phthalimide of formula (XV) to give a compound of general formula (XIV) which can be cyclised, after removal of the phthaloyl protecting group, to give a compound of formula (VI). Reduction of (VI) gives compounds of formula (III) wherein R and R^3 are hydrogen, or "alkylation" (as hereinbefore defined with the proviso that the group R^3 introduced is other than phenacyl or β-benzoylethyl both of which may be substituted in the benzene ring), of (VI) followed by reduction gives compounds of formula III wherein R is hydrogen and R^3 is lower alkyl, lower alkenyl, lower alkynyl, cyclopropylmethyl, or phenethyl (which may be substituted in the benzene ring).

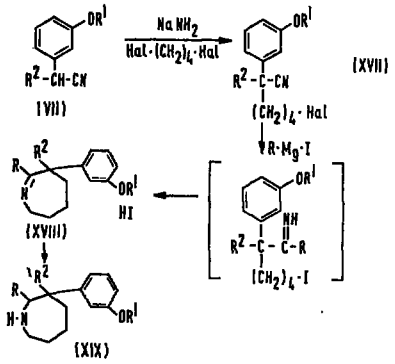


A substituted aliphatic nitrile of formula (VII) is converted to an alkali metal derivative thereof (for example, by reaction with an alkali metal amide) and then reacted with a dihalobutane (for example, 1 - bromo - 4 - chlorobutane) to give the halo-nitrile of formula (XVII). Reduction of this to the halo-amine is effected by catalytic hydrogenation, which

in turn is cyclised to compounds of general formula (III) by heating in a suitable solvent with or without the presence of a base.

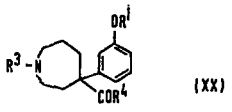
If the hexahydroazepine obtained by any of the above methods is not that desired, then it can optionally be treated in any of the ways hereinbefore or hereinafter described to give the one desired.

A preferred method of preparation of a compound of general formula (III) in which R is a lower alkyl radical, R^1 is a lower alkyl or benzyl radical and R^3 is a hydrogen atom is given below



As can be seen, a compound of general formula (VII), which may be prepared by methods known in the art, is converted to an alkali metal derivative thereof (e.g. by reaction with an alkali metal amide) and then reacted with a dihalo-butane (e.g. 1 - bromo - 4 - chlorobutane) to give a compound of general formula (XVII). Cyclisation of this compound to the unsaturated compound of general formula (XVIII) can be effected through reaction with a Grignard reagent. Subsequent reduction preferably with a hydride transfer agent such as aluminium lithium hydride or sodium borohydride, yields a compound of general formula (III) in which R^3 is hydrogen i.e. a compound of formula (XIX). If the hexahydroazepine produced by this method is not that desired, then it can optionally be treated in any of the ways hereinbefore or hereinafter described to give the one desired.

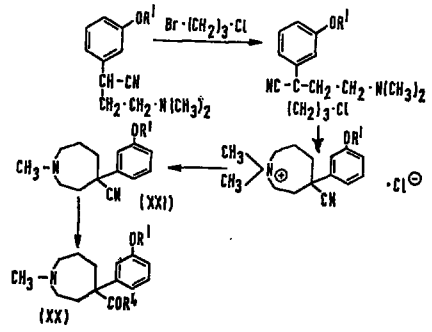
The compounds of general formula (II), wherein R^1 is a lower alkyl radical and R^3 is other than hydrogen, can be prepared by reducing a hexahydro-1H-azepine of the general formula



(where R^1 and R^3 have the meanings defined above and R^4 is a hydrogen atom or an alkyl radical containing 1 to 5 carbon atoms). The reduction may for example be carried out by heating with hydrazine in an alkaline solution, (for example, in the presence of an alkali metal hydroxide) in an organic solvent, such as diethylene glycol. Other methods of reduction which are known *per se* for reducing a keto group to a methylene group can be used, and examples are (a) reaction of the compound of general formula (II) with ethanedithiol followed by hydrogenolysis of the mercaptal group in the presence of Raney nickel or (b) reaction of the compound of general formula (II) with *p*-toluene-sulphonyl hydrazine followed by reduction, for example, with sodium borohydride or lithium aluminium hydride.

A compound of general formula (II) in which R^1 is a lower alkyl radical and R^3 is a methyl radical may be demethylated at the nitrogen atom to give the corresponding compound in which R^3 is hydrogen. For example, demethylation may be carried out using cyanogen bromide or ethyl chloroformate. If desired, this product may be converted to another compound of the same general formula by any of the methods hereinbefore described.

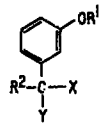
The starting materials of general formula (XX) in which R^4 is an alkyl radical containing 1 to 5 carbon atoms can be prepared following the information given in U.S.A. patent specifications Nos. 2,775,583 and 2,740,779, a summary of which is given below



The starting materials of general formula (XX) in which R^4 is a hydrogen atom, can be prepared by reducing the corresponding compounds of formula (XX) in which the radical COR^4 is replaced by CN (which may be prepared following the information given in the above-mentioned U.S.A. patent specifications), for example by partial reduction with lithium aluminium hydride, di-isobutyl aluminium hydride or a lithium trialkoxyaluminium hydride [see for example Quarterly Reviews *20*, 177 (1966)].

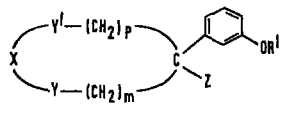
It is to be understood that the compounds of the invention produced by the foregoing reactions are racemic mixtures. If the pure optically active isomers are required, then these can be obtained by resolution of a racemic mixture using standard methods known in the art.

The invention provides a general process for the preparation of the compounds of formula (I) wherein R^1, R^2, R^3, n and m have the meanings defined in connection with formula (I), and R is a hydrogen atom, in which a precursor of the general formula



(wherein R^1 and R^2 have the meanings defined above, X is $—CH_2.NH_2$ when Y is $—(CH_2)_4.Hal$, $—(CH_2)_4.OH$ or $—(CH_2)_3.COOAlk$, or X is —CN when Y is $—(CH_2)_3.COOAlk$, or X is —COOAlk when Y is $—(CH_2)_4.NH_2$ or $—(CH_2)_3.CN$; Hal is a halogen atom and Alk is a lower alkyl radical) is cyclised by a method of the kind in actual use or described in the literature on the subject, followed if neccessary by reduction. It may be necessary to carry out a further step such as "alkylation" (as hereinbefore defined) or acylation in order to obtain the desired compound. Such further steps are described above.

The invention also provides a process for the preparation of a hexahydro-1H-azepine derivative of the general formula (I) as defined above or an acid addition or quaternary ammonium salt thereof, in which a compound of formula



wherein X—Y is $—N=CR—$, $R^3.N—CH_2—$, or $R^3.N—C—$ (with =O), R and R^3 being as defined above and Y^1 is $—CH_2—$, or X—Y is $R^3.N—CH_2—$ and Y^1 is C=O, Z is R^2 or COR^4, R^2 being as defined above and R^4 being hydrogen or lower alkyl, p is 2 or 3 and m is 0 or 1 and m + p is 3; is reduced.

This reduction process is described above and in the examples below.

If it is desired to prepare an acid addition salt, a compound of general formula (I) can be treated with a pharmaceutically acceptable acid, e.g. hydrochloric, sulphuric or maleic acid. Similarly, the free base can be prepared by neutralising an acid addition salt, for example, with an alkali metal carbonate. A quarternary ammonium salt can be prepared by reacting the free base with an alkyl halide

The reactants employed in the foregoing reactions either are known compounds, which are commercially available or can be prepared by methods known in the art, or are derivatives thereof which can be prepared by well-known chemical procedures from appropriate starting materials following the methods described in the art for the known compounds.

The invention also provides a pharmaceutical composition which comprises a compound of general formula (I), or an acid addition or quaternary ammonium salt thereof, and a pharmaceutically acceptable carrier. The carrier can be solid, liquid or cream-like and any suitable carrier known in the art can be used. The composition may be in the form of a tablet, capsule or solution.

The novel compounds of the present invention possess valuable pharmacological activity and/or are intermediates in the preparation of similar compounds. In particular, the novel compounds in standard pharmacological procedures generally demonstrate an ability to reduce pain and so may be useful as analgesics. In addition some of the compounds demonstrate the ability to antagonise narcotic analgesics.

In the pharmacological evaluation of the properties of the compounds of this invention the effects *in vivo* of the compounds are tested on mice by the Haffner tail clip method (see F. Haffner, Deutsch. Med. Wschr. *55,* 731 (1929)) or by the radiant heat on tail method of D'Amour-Smith (J. Pharmacol, *72,* 74 (1941). The analgesic antagonism may be tested for by the method of Casy *et al* disclosed in J. Pharm. Pharmacol, *20,* 768 (1968).

The compounds of this invention in the above test procedures when administered orally and/or i.p. at a dosage of about 10 to about 200 mg/kg. generally demonstrated analgesic activity.

When the compounds of this invention are employed as analgesic agents they may be administered to warm-blooded animals e.g. mice, rats, rabbits, dogs, cats or monkeys alone or in combination with pharmacologically acceptable carriers, the proportion of which is determined by the solubility and chemical nature of the compounds, chosen route of administration and standard biological practice. For example, they may be administered orally in the form containing such excipients as for example starch, milk or sugar. They may also be administered orally in the form of solutions or they may be injected parenterally. For parenteral administration they may be used in the form of a sterile solution or suspension containing other solutes, for example enough saline or glucose to make the solution isotonic.

The dosage of the present 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 dosage 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. 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.

The following non-limiting Examples illustrate the invention:

EXAMPLE 1

3 - (m - Methoxyphenyl) - 1 - methyl - 3 - propylhexahydro-1H-azepine

(a) 2-(*m*-Methoxyphenyl)pentanenitrile (18.9 g.,) in dry ether (20 ml.) was added to a stirred suspension of sodium amide (from 2.35 g. sodium) in liquid ammonia (250 ml.). The resulting solution was stirred for 30 minutes and 4-iodobutyronitrile (20.5 g.) in ether (40 ml.) added dropwise. On completion of the addition the reaction mixture was stirred for 4 hours. Ether (100 ml.) was added and the ammonia allowed to evaporate off overnight. Water (100 ml.) was added, the organic layer separated, dried over magnesium sulphate and the ether removed by distillation. The viscous oily residue was distilled at 158—164°C/0.3 mm. to yield 5 - cyano - 5 - (*m*-methoxyphenyl)octanenitrile as a viscous colourless liquid.

(b) The above dinitrile (7.9 g.) was heated under reflux with a mixture of ethylene glycol (30 ml), water (2.3 ml.) and potassium hydroxide (17 g.) for 3.5 hours. The reaction mixture was poured into water (100 ml.) and extracted with ether. After acidifying, the aqueous layer was extracted with ether, dried over magnesium sulphate and the ether was evaporated to small bulk when 5-carbamoyl-5 - (*m* - methoxyphenyl)octanoic acid crystallised yielding colourless needles 5.9 g., m.p. 172—4°C.

(c) This acid (6.2 g.) in dry tetrahydrofuran was added dropwise with stirring, to a solution of lithium aluminium hydride (7.0 g.) in dry tetrahydrofuran (100 ml.). The mixture was heated under reflux for 7 hours, cooled and 5 N sodium hydroxide (16 ml.) cautiously added. The inorganic material was filtered off and the tetrahydrofuran removed to leave 5 - aminomethyl - 5 - (*m* - methoxyphenyl) - octan - 1 - ol as a viscous oil which was distilled at 132—138°C/0.005 mm. to give 3.2 g. of a colourless glass.

This compound could also be prepared by similar reduction of ethyl 5 - cyano - 5 - *m*-methoxyphenyloctanoate.

(d) The 5 - aminomethyl - 5 - (*m* - methoxyphenyl)octan-1-ol (4.14 g.) was dissolved in dry chloroform (20 ml.) cooled to 0°C and saturated with gaseous hydrogen chloride. Thionyl chloride (3.8 g.) was added dropwise keeping the temperature at 0—5°C. The reaction mixture was allowed to warm to room temperature then heated under reflux for 2 hours. The chloroform was removed under reduced pressure, leaving an oil which was added to water (50 ml.) and the material insoluble in water extracted with ether and discarded. The aqueous layer was basified with sodium bicarbonate solution and extracted with ether. After drying over magnesium sulphate, the ether was removed to leave 3.85 g. of a dark oil which was dissolved in propan-2-ol (100 ml.), anhydrous potassium carbonate (4.0 g.) added and the mixture heated under reflux for 6 hours. Removal of the potassium carbonate and evaporation of the propan-2-ol gave an oil which was distilled affording 1.8 g. of 3 - (*m* - methoxyphenyl) - 3 - propylhexahydro-1H-azepine as a colourless mobile oil b.p. 118—120°C/0.001 mm.

(e) The above hexahydro-1H-azepine (2.77 g.) was hydrogenated at 45 p.s.i. in the presence of formaldehyde (40% aqueous, 2 ml.), 10% palladium on charcoal (2.0 g.) and absolute ethanol (100 ml.). The theoretical quantity of hydrogen was absorbed in 20 min. Filtration of the catalyst and evaporation of the solvent left a colourless mobile oil which was treated with oxalic acid (1.3 g.) in acetone. Colourless needles of 3 - (*m* - methoxyphenyl) - 1 - methyl - 3 - propyl - hexahydro-1H-azepine oxalate, 2.32 g., m.p. 124—126°C, were obtained. (Found C, 64.8; H, 8.3; N, 4.0, $C_{19}H_{29}NO_5$ requires C, 64.9; H, 8.3; N, 4.0%)

EXAMPLE 2

3 - (m - Hydroxyphenyl) - 1 - methyl - 3 - propylhexahydro-1H-azepine

The oxalate of Example 1 (3.28 g.) was heated under reflux with 48 to 50% hydrobromic acid (30 ml.) for 3 hours. The hydrogen bromide was removed under reduced pressure and the residual oil dried by repeatedly re-evaporating with propan-2-ol (100 ml.). The oil was crystallised from acetone ether to yield 2.28 g. of fine white needles. Recrystallisation from propan-2-ol/ether gave the hydrobromide of the title compound as colourless, hygroscopic needles m.p. 118—126°C. (Found: C, 58.35; H, 8.15; H, 4.35. $C_{16}H_{26}BrNO$ requires C, 58.6; H, 8.0; N, 4.3%).

The hydrobromide could be converted to the free base by treatment with aqueous sodium carbonate solution and recrystallising from light petroleum (b.p. 100—120°C), m.p. 119—121°C. (Found: C, 77.8; H, 10.1; N, 5.3. $C_{16}H_{25}NO$ requires C, 77.9; H, 10.2; N, 5.7%).

EXAMPLE 3

3 - (m - Methoxyphenyl) - 3 - propylhexahydro-1H-azepine

(a) 2-(*m*-Methoxyphenyl)pentanenitrile (75.6 g., 0.4 mole) in dry ether (200 ml.) was added to a stirred suspension of sodium amide (from

9.4 g. sodium) in liquid ammonia (400 ml.) The mixture was stirred for 30 mins then ethyl 4-iodobutyrate (99.25 g., 0.4 mole) in dry ether (200 ml.) was added dropwise. The mixture was stirred at the temperature of refluxing liquid ammonia for 5 hours. Ammonium chloride (10 g.) was added and the mixture allowed to warm to room temperature. Water (300 ml.) was added, the organic layer separated, washed with water, 2N sulphuric acid and water. After drying over magnesium sulphate and removing the ether, the product was distilled yielding 77.6 g. of ethyl 5-cyano-5 - (*m* - methoxyphenyl)octanoate, b.p. 156—175°C at 0.02 mm, n^{23}_D 1.5020.

Ethyl 5 - cyano - 5 - (*m* - methoxyphenol)-octanoate may also be prepared by hydrolysis of 5 - cyano - 5 - (*m* - methoxyphenyl)-octanenitrile with sulphuric acid: ethyl alcohol mixture (1 : 10, v/v) for 30 hours.

(b) Ethyl 5 - cyano - 5 - (*m* - methoxyphenyl)octanoate (32.0 g.) was hydrogenated at an initial pressure of 1200 p.s.i. and final temperature of 140°C in cyclohexane (400 ml) with nickel catalyst (*ca.* 8 g.) for 18 hours. Removal of the catalyst and evaporation of the cyclohexane left a colourless viscous oil which was crystallised from ethyl acetate affording 18.3 g. of colourless needles of 6 - (*m* - methoxyphenyl) - 6 - propylhexahydro - 2H - azepin - 2 - one m.p. 109—110°C.

When reduction was carried out at a lower temperature the product consisted mainly of ethyl 5 - aminomethyl - 5 - (*m* - methoxy - phenyl)-octanoate. Cyclisation of this compound could be achieved by heating under reflux for 18 hours in decalin or by heating under reflux with a solution of sodium ethoxide in absolute ethanol.

(c) 3 - (*m* - Methoxyphenyl) - 3 - propylhexahydro - 2H - azepin - 2 - one (12 g.) in dry tetrahydrofuran (200 ml.) was added dropwise to a stirred suspension of lithium aluminium hydride (12 g.) in ether (200 ml.) and the mixture was then stirred and heated under reflux for 7 hours. The reaction mixture was decomposed by the addition of water (12 ml.), 2N sodium hydroxide (24 ml.) followed by water (12 ml.). The inorganic material which precipitated was filtered off, the solvents were removed and the colourless oil remaining was distilled furnishing 9.8 g. of 3 - (*m* - methoxyphenyl) - 3 - propylhexahydro - 1H - azepine b.p. 123—4°C/0.15 mm.

(d) This compound could be methylated as in Example 1(e) to give the same product as in that Example, or could be reacted with allyl bromide to give 1 - allyl - 3 - (*m* - methoxyphenyl) - 3 - propylhexahydro - 1H - azepine.

EXAMPLE 4

3 - (m - Methoxyphenyl) - 1 - 3 - dimethyl-hexhydro-1H-azepine

(a) 2-(*m*-Methoxyphenyl)propionitrile (25.2 g.) was reacted with sodium amide (from 3.6 g. of sodium) in liquid ammonia (300 ml.) and ethyl 4-iodobutyrate (38.5 g.) following the method of Example 3(a). After similar working up, the product was distilled affording 22.5 g. of ethyl 5 - cyano - 5 - (*m* - methoxyphenyl)hexanoate, b.p. 132—142°C/0.003 mm.

(b) This compound (15.2 g.) was hydrogenated at an initial pressure of 1000 p.s.i. and final temperature of 140° in the presence of nickel catalyst (*ca.* 6 g.) in cyclohexane (250 ml.) for 20 hours. The catalyst was removed by filtration, the cyclohexane removed to afford 14.1 g. of a viscous oil which was heated under reflux in dekalin in a nitrogen atmosphere for 20 hours. The decalin was removed under reduced pressure and the residue crystallised from ethyl acetate to give colourless needles of 6 - (*m* - methoxyphenyl)-6 - methyl - hexahyro - 2H - azepin - 2 - one, 5.3 g., m.p. 114—115°C.

A further 2.7 g. of crystalline material could be obtained by distillation of the mother liquors, followed by recrystallisation from ethyl acetate.

(c) The hexahydro - 2H - azepin - 2 - one (11.7 g.) in dry tetrahydrofuran was added to a suspension of lithium aluminium hydride (12 g.) in ether (200 ml.). The procedure described in Example 3(c) was followed and the product obtained was distilled yielding 8.9 g. of 3 - (*m* - methoxyphenyl) - 3 - methyl-hexahydroazepine, b.p. 118—125°C/0.5 mm.

(d) 3 - (*m* - Methoxyphenyl) - 3 - methyl-hexahydro-1H-azepine (8.75 g.) was reacted with formaldehyde (40% aq., 4 ml) in the presence of 10% palladium on charcoal (1.5 g.) in ethanol (100 ml.) in the presence of hydrogen at 40 atm. pressure following the procedure described in Example 1(e) to give 3 - (*m* - methoxyphenyl) - 1,3 - dimethyl - hexahydro-1H-azepine, as a colourless oil, 7.7 g., b.p. 106—7°C/0.4 mm., n_D^{23} 1.5339, (Found: C, 76.8; H. 9.8; N, 5.9. $C_{15}H_{23}NO$ requires C, 77.2; H, 9.9; N, 6.0%)

The hydrochloride of m.p. 154—5°C could be prepared by treatment with propan-2-ol and a solution of hydrogen chloride in ether. (Found: C, 66.7; H, 8.9; N, 5.0. $C_{15}H_{23}NO.HCl$ requires C, 66.7; H, 8.9; N, 5.2%)

EXAMPLE 5

3 - (m - Hydroxyphenyl) - 1,3 - dimethyl-hexahydro-1H-azepine

The product of Example 4 (5.1 g.) was heated under reflux with 48—50% hydrobromic acid (50 ml.) for 3 hours. The hydrogen bromide was removed under reduced pressure and the residual oil dried by repeatedly evaporating from propan-2-ol. The title compound crystallised as the hydrobromide in colourless needles from propan-2-ol/ether, 6.0 g., 174—5°C. (Found: C, 55.8; H, 7.2; N, 4.4; $C_{14}H_{21}NO.HBr$ requires C, 56.0; H, 7.4; N, 4.6%).

EXAMPLE 6

3 - (m - Acetoxyphenyl) - 1,3 - dimethylhexahydro-1H-azepine

The product of Example 5 (2.0 g.) was heated under reflux with acetic anhydride (6 ml.) and pyridine (3 ml.) for 3 hours. The reaction mixture was evaporated to a brown oil which was dissolved in water and basified with sodium bicarbonate solution. The basic material was extracted with ether, dried over magnesium sulphate and evaporated to a colourless oil. The oil was dissolved in propan-2-ol and treated with a solution of hydrogen chloride in dry ether to give the hydrochloride of the title compound. Yield 1.7 g., m.p. 164—5°C (Found: C, 64.3; H, 8.2; N, 4.6. $C_{18}H_{24}NO_2Cl$ requires C, 64.55; H, 8.1; N, 4.7%)

EXAMPLE 7

By replacing the allyl bromide used in Example 3(d) with the reactants listed below, the following compounds can be prepared.

Reactant	*Product*
Propyl chloride	3 - (*m* - methoxyphenyl) - 1,3 - dipropylhexahydro-1H-azepine.
Prop-2-ynyl bromide	3 - (*m* - methoxyphenyl) - 3 - propyl - 1 - (prop - 2 - ynyl) - hexahydro - 1H - azepine
Cyclopropylmethylchloride	1 - Cyclopropylmethyl - 3 - (*m* - methoxyphenyl) - 3 - propylhexahydro - 1H - azepine.
Phenacyl bromide	3 - (*m* - methoxyphenyl) - 1 - phenacyl - 3-propylhexahydro-1H-azepine.
Phenethyl chloride	3 - (*m* - methoxyphenyl) - 1 - phenethyl - 3-propylhexahydro-1H-azepine.
p-Nitrophenethyl-chloride	1 - (*p* - nitrophenethyl - 3 - (*m* - methoxyphenyl) - 3 - propyl - hexahydro - 1H - azepine which can be reduced to the corresponding *p*-amino compound
β-Benzoylethyl chloride	1 - (*β* - benzoylethyl) - 3 - (*m* - methoxyphenyl) - 3 - propylhexahydro - 1H - azepine
3 - Methyl - but - 2 - enyl chloride	3 - (*m* - methoxyphenyl) - 1 - (3 - methylbut-2 - enyl) - 3 - propylhexahydro - 1H - azepine.

EXAMPLE 8

3 - (m - Acetoxyphenyl) - 1 - methyl - 3 - propylhexahydro-1H-azepine

The procedure of Example 6 was followed, but using 3 - (*m* - hydroxyphenyl) - 1 - methyl - 3 - propylhexahydro - 1H - azepine (1.5 g.) as starting material to give the title compound (1.36 g.) after basification with sodium carbonate, b.p. (0.01 mm.) 176—8°C. (Found: C, 74.8; H, 9.5; N, 4.8. $C_{18}H_{27}NO_2$ requires C, 74.7; H, 9.4; N, 4.8%).

EXAMPLE 9

4 - (m - Methoxyphenyl) - 1 - methyl - 4 - propylhexahydro-1H-azepine

4 - Ethylcarbonyl - 4 - (*m* - methoxyphenyl) - 1 - methylhexahydro - 1H - azepine hydrochloride (17.1 g.) was added to a stirred solution of hydrazine hydrate (184 ml. of 99% solution) and hydrazine hydrochloride (46.2 g.) in diethylene glycol (750 ml.). The reaction mixture was maintained at 120—130°C for 3 hours then potassium hydroxide pellets (85%, 80 g.) were added portionwise. When the addition was completed, water and hydrazine were slowly distilled from the reaction mixture until the internal temperature had reached 220°C. This temperature was maintained for 3 hours. The reaction mixture was cooled, poured into water (1 litre) and extracted with ether. After drying over magnesium sulphate and removing the solvent, 6.8 g. of basic oil were obtained. When treated with 1 mole of fumaric acid in acetone/ether a total of 5 g. of 4 - (*m* - methoxyphenyl) - 1-methyl - 4 - propylhexahydro - 1H - azepine fumarate were obtained, m.p. 153—5°C. (Found: C, 66.9; H, 8.1; N, 3.9. $C_{21}H_{23}NO_5$ requires C, 66.8; H, 8.3; N, 3.7%).

EXAMPLE 10

4 - (m - Hydroxyphenyl) - 1 - methyl - 4 - propylhexahydro-1H-azepine

The fumarate of Example 9 (5.5 g.) was heated under reflux with 48—50% hydrobromic acid for 3 hours. The excess acid was removed by evaporation under reduced pressure and dried by re-evaporation with several

portions of butan-2-one. On redissolving the residual oil in butan-2-one, 4.5 g. of crystals of the hydrobromide of the title compound were obtained, m.p. 157—9°C. Recrystallisation from acetone/propan-2-ol raised the m.p. to 159—161°C. (Found: C, 58.3; H, 8.4; N, 4.2; Br. 24.2. $C_{16}H_{26}BrNO$ requires C, 58.6; H, 8.0; N, 4.3; Br. 24.4%).

EXAMPLE 11

4 - (m - Acetoxyphenyl) - 1 - methyl - 4 - propylhexahydro-1H-azepine

The product of Example 10 (984 mg.) was heated at 110°C with pyridine (2 ml.) and acetic anhydride (4 ml.) for 3 hours. The reaction mixture was concentrated at reduced pressure, poured into water, basified with sodium carbonate and extracted into ether. The product was distilled to yield the title compound of b.p. 140—150°C at 10^{-4}mm. (Found: C, 74.8; H, 9.4; N, 4.8; $C_{18}H_{27}NO_2$ requires C, 74.7; H, 9.4; N, 4.8%).

EXAMPLE 12

The procedure of Example 9 can be followed, but replacing the starting material by one of the compounds specified below (which were prepared as described herein) to give the following products.

Starting material	*Product*
4 - (*m* - Methoxyphenyl) - 1 - methyl - 4-propylcarbonylhexahydro-1H-azepine	4 - *n* - Butyl - 4 - (*m* - methoxyphenyl) - 1-methylhexahydro-1H-azepine
4 - (*m* - Methoxyphenyl) - 1 - methyl - 4-*n* - pentylcarbonylhexahydro - 1H - azepine	4 - Hexyl - 4 - (*m* - methoxyphenyl) - 1-methylhexahydro-1H-azepine
4 - Formyl - 4 - (*m* - methoxyphenyl) - 1-methylhexahydro-1H-azepine	4 - (*m* - Methoxyphenyl) - 1,4 - dimethyl-hexahydro-1H-azepine
4 - Ethylcarbonyl - 4 - (*m* - isopropoxy-phenyl) - 1 - methylhexahydro - 1H - azepine	4 - (*m* - Isopropoxyphenyl) - 1 - methyl - 4-propylhexahydro-1H-azepine
4 - Ethylcarbonyl - 4 - (*m* - *n* - butoxy-phenyl) - 1 - methylhexahydro - 1H - azepine	4 - (*m* - *n* - Butoxyphenyl) - 1 - methyl - 4-propylhexahydro-1H-azepine

EXAMPLE 13

The product of Example 9 can be demethylated by reaction with cyanogen bromide and the 4 - (*m* - methoxyphenyl)-4 - propyl - hexahydro - 1H - azepine formed can be reacted with one of the halides listed below to give the products indicated.

Reactant	*Product*
Propyl chloride	4 - (*m* - Methoxyphenyl) - 1,4 - dipropyl hexahydro-1H-azepine
Prop-2-ynyl bromide	4 - (*m* - Methoxyphenyl - 4 - propyl - 1-prop-2-ynyl)hexahydro-1H-azepine
Cyclopropylmethyl chloride	1 - Cyclopropylmethyl - 4 - (*m* - methoxy-phenyl) - 4 - propylhexahydro-1H-azepine
Phenacyl bromide	4 - (*m* - Methoxyphenyl) - 1 - phenacyl - 4-propylhexahydro-1H-azepine
Phenethyl chloride	4 - (*m* - Methoxyphenyl) - 1 - phenethyl - 4-propylhexahydro-1H-azepine
p-Nitrophenethyl chloride	4 - (*m* - Methoxyphenyl) - 1 - (*p* - nitrophen-ethyl) - 4 - propylhexahydro - 1H - azepine, which can be reduced to the corresponding *p*-amino compound
β-Benzoylethyl chloride	1 - (β - Benzoylethyl) - 4 - *m* - methoxy-phenyl) - 4 - propylhexahydro - 1H - azepine

Reactant	*Product*
3 - Methylbut - 2 - enyl chloride	4 - (*m* - Methoxyphenyl) - 1 - (3 - methylbut - 2 - enyl) - 4 - propylhexahydro - 1H-azepine
Allyl bromide	1 - Allyl - 4 - (*m* - methoxyphenyl) 4-propyl - hexahydro - 1H - azepine
n-Hexyl chloride	1 - (*n* - Hexyl) - 4 - (*m* - methoxyphenyl)-4 - propylhexahydro - 1H - azepine.

EXAMPLE 14

3 - (m - Methoxyphenyl) - 1,3 - dimethylhexahydro-1H-azepine

(a) 2 - (*m* - Methoxyphenyl)propionitrile (64 g.) was added to a stirred suspension of sodium amide (18 g.) in dry toluene (160 ml.) at 60°C. On completion of the addition, dry tetrahydrofuran (20 ml.) was added and the mixture stirred at 80°C for 1 hour. This mixture was then added dropwise to a solution of 1 - bromo - 4 - chlorobutane (72 g.) in dry toluene (200 ml.) at 5—10°C under nitrogen over a period of 2 hours, the mixture was allowed to warm up to room temperature and stirred overnight. The reaction mixture was poured into water and the toluene layer separated. The organic layer was washed successively with 2N hydrochloric acid and water. After drying over magnesium sulphate, and evaporating the solvent, 6 - chloro - 2-(*m* - methoxyphenyl) - 2 - methyl - hexanenitrile was obtained on careful distillation as a colourless oil (43.4 g.), b.p. 152—154° at 0.8 mm. (Found: C, 67.0; H, 7.3; N, 5.7. $C_{14}H_{18}ClNO$ requires C, 66.8; H, 7.2; N, 6.0%).

(b) The chloronitrile of part (a) (3.13 g.) in dry toluene (100 ml.) was added to methylmagnesium iodide (0.0285 mole) in ether (20 ml.) under a steam of nitrogen. On completion of the addition the ether was distilled from the reaction mixture until the internal temperature was 90°C and then heated at this temperature for 24 hours. After cooling, the reaction mixture was poured onto a mixture of ice and ammonium chloride, the aqueous layer was separated and extracted with benzene. The combined organic layers were dried over magnesium sulphate and evaporated under reduced pressure at 40°C leaving a viscous oil. The oil was repeatedly extracted with boiling ether leaving a yellow gum which deposited pale yellow rhombs from propan-2-ol of 3 - (*m* - methoxyphenyl) - 2,3 - dimethyl - 4,5,6,7, - tetrahydro - 3H - azepine hydroiodide (1.0 g.), m.p. 164—168°C. The compound could be recrystallised for analysis from propan-2-ol. (Found, C, 50.35; H, 6.2; N, 3.8 $C_{15}H_{21}NO.HI$ requires C, 50.2; H, 6.0; N, 3.8%).

(c) The tetrahydroazepine hydroiodide (6.1 g.) was added portionwise to a refluxing solution of aluminium lithium hydride (1.5 g.) in ether (200 ml.). On completion of the addition, dry tetrahydrofuran (100 ml.) was added and the mixture heated under reflux for 4 hours. After cooling to room temperature the reaction mixture was decomposed by the addition of water (1.5 ml.), and 2N sodium hydroxide (3 ml.). Filtration and evaporation afforded an oil which was distilled yielding 3.1 g. of the title compound as a colourless oil, b.p. 128—130°C at 0.5 mm. (Found: C, 77.15; H, 9.9; N, 5.8. $C_{15}H_{23}NO$ requires C, 77.2; H, 9.9; N, 6.0%).

The above oil was dissolved in propan-2-ol and treated with a solution of hydrogen chloride in dry ether to give colourless needles of the hydrochloride, m.p. 166—167°C. (Found: C, 66.8; H, 8.8; N, 5.0. $C_{15}H_{23}NO.HCl$ requires C, 66.7; H, 9.0; N, 5.2%).

EXAMPLE 15

1,2,3 - Trimethyl - 3 - (m - methoxyphenyl)-hexahydro-1H-azepine

The azepine of Example 14(c) (3.0 g.) in absolute ethanol (100 ml.) containing 40% aq. formaldehyde (2 ml.) was hydrogenated at an initial pressure of 48 p.s.i. After the theoretical quantity of hydrogen had been absorbed the catalyst was filtered off leaving the product as an oil (2.21 g.), b.p. 104—110°C. at 0.01 mm. (Found: C, 78.0; H, 10.2; N, 5.4. $C_{16}H_{25}NO$ requires C, 77.9; H, 10.2; N, 5.7:).

The above oil was converted to the hydrobromide in propan-2-ol with 50% aqueous hydrogen bromide. The product was recrystallised from propan-2-ol and had m.p. 232—235°C. Found: C, 58.5; H, 8.0; N, 4.2. $C_{16}H_{25}NO.HBr$ requires C, 58.4; H, 8.0; N, 4.3%).

EXAMPLE 16

3 - (m - Hydroxyphenyl) - 1,2,3 - trimethylhexahydro-1H-azepine

The azepine of Example 15 (2.1 g.) was heated under reflux with 50% hydrobromic acid for 2 hours. On cooling, colourless chunky rhombs of the hydrobromide (2.06 g.) were obtained, m.p. 234—6°C. The product could be obtained as either needles m.p. 230—231°C, or rhombs m.p. 234—40°C, clear 250°C, on recrystallisation from methanol. These two crystal forms were shown to be identical by interconversion, I.R.

spectrum and anlysis. (Found: C, 57.3; H, 7.8; N, 4.2 $C_{15}H_{23}NO$. HBr requires C, 57.3; H, 8.0; N, 4.6%).

EXAMPLE 17

3 - Butyl - 3 - (m - methoxyphenyl) - 1 - methylhexahydro-1H-azepine

(a) Ethyl 5 - cyano - 5 - (*m* - methoxyphenyl)-nonanoate was prepared following the method of Example 3(a), using sodium amide (from sodium 5.36 g.) in liquid ammonia (400 ml.), 2 - (*m* - methoxyphenyl) - hexanitrile (45 g.) and ethyl 4-iodobutyrate (53.4 g.). The product was obtained as a colourless oil (48.7 g.), b.p. 150—166°C at 0.01 mm.

(b) The product of Example 17(a) (30.0 g.) was hydrogenated in the presence of Raney nickel (*ca* 6g.) and cyclohexane (400 ml.) following the procedure of Example 3(b). The product was recrystallised from ethyl acetate affording 15.12 g. of 6 - butyl - 6 - (*m*-methoxyphenyl)hexahydro - 2H - azepine - 2-one, m.p. 108—9°C.

(c) The product of Example 17(b) (12.2 g.) in dry tetrahydrofuran (200 ml.) was reduced with aluminium lithium hydride (12 g.) in dry ether (200 ml.) by the method of Example 3(c). The product was distilled, b.p. 130—140°C at 0.25 mm., affording 7.14 g. of 3 - butyl - 3 - (*m* - methoxyphenyl) hexahydro-1H-azepine as a colourless mobile oil.

(d) The secondary base obtained in Example 17(c) (7.14 g.) was reductively methylated as described in Example 1(e). The title compound, obtained as a crude oil from the reaction mixture, was converted to its oxalate (5.01 g.), m.p. 147—50°C. (Found: C, 65.5; H, 8.6; N, 3.75. $C_{18}H_{29}NO.C_2H_2O_4$ requires C, 65.6; H, 8.6; N, 3.8%).

EXAMPLE 18

3 - Butyl - 3 - (m - hydroxyphenyl) - 1 - methylhexahydro-1H-azepine

The oxalate of Example 17(d) (4.1 g.) was heated under reflux with 50% hydrobromic acid (40 ml.) for 2 hours. The product was isolated following the procedure described in Example 2 and converted to the free base. Recrystallisation from light petroleum (b.p. 80—100°C) afforded the title compound (1.7 g.), m.p. 116—118°C. (Found: C, 78.0; H, 10.5; N, 5.25. $C_{17}H_{27}NO$ requires C, 78.1; H, 10.4; N, 5.4%).

EXAMPLE 19

3 - Ethyl - 3 - (m - methoxyphenyl)hexahydro - 1H-azepine

(a) Ethyl 5 - cyano - 5 - (*m* - methoxyphenyl)heptanoate was prepared following the method of Example 3(a), using sodium amide (from sodium 3.74 g.) in liquid ammonia (150 ml.), and 2 - (*m* - methoxyphenyl)-butyronitrile (26.3 g.). The product was distilled b.p. 148—155°C/0.01 mm. yielding 27.1 g. of a colourless liquid.

(b) The product of Example 19(a) (20.5 g.) in cyclohexane (200 ml.) was hydrogenated in the presence of Raney nickel (*ca.* 6 g.) following the procedure described in Example 3(b). The product after distillation was recrystallised from ethyl acetate affording 10.0 g. of 6-ethyl-6 - (*m* - methoxyphenyl) - hexahydro - 2H - azepin - 2 - one, m.p. 87—88°C.

(c) The azepinone of Example 19(b) (9.1 g.) in dry tetrahydrofuran (50 ml.) and ether (50 ml.) was added dropwise to a stirred suspension of aluminium lithium hydride (7.5 g.) in dry ether (50 ml.). After heating under reflux for 3 hours the reaction mixture was worked up following the procedure described in Example 3(c) and distilled yielding 7.66 g. of the title compound as a colourless oil, b.p. 108—110°C/0.01 mm.

EXAMPLE 20

3 - Ethyl - 3 - (m - hydroxyphenyl)hexahydro-1H-azepine

The product of Example 19(c) (2.2 g.) was heated under reflux with 50% hydrobromic acid for 1.5 hours. The reaction mixture was evaporated to dryness and re-evaporated with three portions of propan-2-ol. The oil obtained was disolved in propan-2-ol and diluted with ether. The title compound (2.5 g.) was obtained as its hydrobromide, m.p. 183—5°C. (Found: C, 55.9; H, 7.43; N, 4.35. $C_{11}H_{21}NO.HBr$ requires C, 56.0; H, 7.4; N, 4.7%).

EXAMPLE 21

3 - Ethyl - 3 - (m - hydroxyphenyl) - 1 - methylhexahydro-1H-azepine

(a) The azepine of Example 19(c) (5.13 g.) was reductively methylated by the method of Example 1(e). The crude oil obtained was converted to the hydrobromide (4.9 g.), m.p. 142—3°C. Recrystallisation from propan - 2 - ol raised the m.p. of the 3 - ethyl - 3 - (*m* - methoxyphenyl)-1 - methylhexahydro - 1H - azepine hydrobromide obtained to 143—4°C. (Found: C, 58.8; H, 8.2; N, 4.0. $C_{15}H_{23}NO.HBr$ requires C, 58.6; H, 8.0; N, 4.3%).

(b) The methoxy compound of Example 21(a) (2.85 g.) was heated under reflux with 80% hydrobromic acid (15 ml.) for 2 hours and worked up following the procedure as described for Example 5. The title compound was obtained as its hydrobromide (2.47 g.), m.p. 221—2°C. (Found: C, 57.4; H, 7.8; N, 4.3. $C_{15}H_{23}NO.HBr$ requires C, 57.4; H, 7.7; N, 4.5%).

EXAMPLE 22

3 - (m - Hydroxyphenyl) - 3 - propylhexahydro-1H-azepine

The product of Example 3(c) (6.1 g.) was heated under reflux with 50% hydrobromic acid (40 ml.) for 2.5 hours. The product was worked up as described in Example 21(b) above to yield the hydrobromide of the title compound (5.88 g.), m.p. 74—8°C as a hygroscopic solid. (Found: C, 57.4; H, 7.8; N, 4.5. $C_{15}H_{23}NO.HBr$ requires C, 57.4; H, 7.7; N, 4.5%).

EXAMPLE 23

1 - Carbethoxy - 3 - (m - hydroxyphenyl)-3 - propyl - hexahydro - 1H - azepine

Ethyl chloroformate (1 ml.) in chloroform (10 ml.) was added to a cooled solution of the product obtained in Example 22 (3.14 g.) in chloroform (10 ml.) and triethylamine (2.03 g.). On completion of the addition the reaction was stirred at room temperature for 2 hours. Ether was added to precipitate the triethylamine hydrochloride/hydrobromide, and the filtrate washed with water. Evaporation afforded a glass which was distilled, b.p. 210—220°C (bath temperature) at 0.005 mm. giving 1.54 g. of viscous oil. (Found: C, 70.2; H, 8.9; N, 4.3. $C_{18}H_{27}NO_3$ requires C, 70.8; H, 8.9; N, 4.6%).

EXAMPLE 24

1 - Allyl - 3 - (m - hydroxyphenyl) - 3 - propylhexahydro-1H-azepine

A mixture of the product of Example 22 (4.3 g.), 3 - bromoprop - 1 - ene (1.655 g.) and potassium carbonate (anhydrous, 8.1 g.) in butan-2-one (100 ml.) was heated under reflux while stirring for 16 hours. The reaction mixture was cooled and the solid material removed by filtration. Removal of the solvent afforded an oil which was dissolved in acid and extracted with ether; these ether extracts were discarded. The acid layer was basified with concentrated ammonia solution and extracted with ether. After drying, the ether was removed to yield a viscous oil which gave a crystalline toluene-*p*-sulphonate salt (2.5 g.), m.p. 126—7°C. (Found: C, 67.5; H, 8.0; N, 3.0. $C_{18}N_{27}NO$. $C_7H_8O_3S$ requires C, 67.4; H, 8.0; N, 3.0%).

EXAMPLE 25

3 - (m - Hydroxyphenyl) - 3 - methylhexahydro-1H-azepine

The product of Example 4(c) (12.64 g.) in 50% aqueous hydrobromic acid (120 ml.) was heated under reflux for 1 hour. The acid was removed by evaporation under reduced pressure and the product dried by azeotroping with propan-2-ol. The product (15.6 g.) crystallised as its hydrobromide, a white solid, from propan-2-ol, m.p. 203—4°C. (Found: C, 54.3; H, 6.8; N, 4.75. $C_{13}H_{19}NO.HBr$ requires C, 54.55; H, 7.0; N, 4.5%).

EXAMPLE 26

1 - Allyl - 3 - (m - hydroxyphenyl) - 3 - methyl-hexahydro-1H-azepine

The product of Example 25 (2.86 g.) was heated under reflux, while stirring, with a mixture of potassium carbonate (anhydrous, 2.8 g.), 3 - bromoprop - 1 - ene (1.21 g.) and butan-2-one (100 ml.) for 20 hours. The solid was removed by filtration and the filtrate evaporated to a viscous oil. The oil was dissolved in ether and the basic material isolated in the usual fashion. Distillation afforded a viscous oil (1.62 g.) b.p. (0.001 mm.) 160—165°C. (Found: C, 78.4; H, 9.5; N, 5.65. $C_{16}H_{23}NO$ requires C, 78.3; H, 9.45; N, 5.7%).

EXAMPLE 27

3 - (m - Hydroxyphenyl) - 2,3 - dimethyl - hexahydro-1H-azepine

The azepine of Example 14(c) (4.6 g.) was heated under reflux with 50% aqueous hydrobromic acid (10 ml.) for 2 hours. The solvent was removed under reduced pressure and the orange oil repeatedly evaporated with propan-2-ol. The product crystallised from propan-2-ol/ether as a colourless hydrobromide (3.55 g.) m.p. 163—165°C. (Found: C, 55.9; H, 7.4; N, 4.7. $C_{14}H_{21}NO.HBr$ requires C, 5.60; H, 7.4; N, 4.7%).

EXAMPLE 28

1 - Allyl - 2,3 - dimethyl - 3 - (m - hydroxyphenyl)hexahydro-1H-azepine

2,3 - Dimethyl - 3 - (*m* - hydroxyphenyl)-hexahydro-1H-azepine hydrobromide (1.5 g.) was heated under reflux with anhydrous potassium carbonate (2.8 g.) and 1 - bromo - 2-propane (0.61 g.) in propan-2-one (75 ml.) for 16 hours. The reaction mixture was cooled, filtered and evaporated to an oil which was dissolved in propan-2-ol and acidified with 50% aqueous hydrogen bromide. Repeated evaporation with small quantities of propan-2-ol removed the last traces of water and the product was crystallised from propan-2-ol (800 mg.), m.p. 212—214°C. (Found: C, 60.0; H, 7.95; N, 4.0. $C_{17}H_{25}NO.HBr$ requires C, 59.9; H, 7.7; N, 4.1%).

EXAMPLE 29

3 - (m - Acetoxyphenyl) - 3 - ethylhexahydro-1H-azepine

The azepine hydrobromide of Example 20 (1.5 g.) was heated in a sealed tube with a mixture of hydrogen bromide in glacial acetic acid (5 ml.) and acetyl bromide (3 ml.) for 2 hours at 100°C. The tube was cooled and the reaction mixture evaporated to dryness at room temperature and reduced pressure. Propan-2-ol (25 ml.) was added and also evaporated off at room temperature. The residue was recrystallised from propan-2-one/ether affording 1.36 g. of off-white needles, m.p. 120—125°C. The product was recrystallised from propan-2-one/ether to give 725 mg. of the title compound, m.p. 125—30°C (does not clear). (Found: C, 56.1; H, 7.1; N, 4.0. $C_{16}H_{23}NO_2HBr$ requires C, 56.15; H, 7.1; N, 4.1%).

EXAMPLE 30

3 - (m - Acetoxyphenyl) - 1 - acetyl - 3 - ethylhexahydro-1H-azepine

The azepine hydrobromide of Example 20 was heated under reflux for 3 hours with acetylbromide (5 ml.) and hydrogen bromide in acetic acid (45%, 10 ml.). The acetic acid and acetyl bromide were removed under

reduced pressure and the last traces removed by co-distillation with toluene. The residue was distilled affording a pale yellow glass (0.47 g.), b.p. at 0.5 mm. 170—180°C. (Found: C. 71.25; H, 8.4; N, 4.6. $C_{18}H_{25}NO_3$ requires C, 71.25; H, 8.31; N, 4.6%).

EXAMPLE 31

3 - (m - Hydroxyphenyl) - 3 - iso - propyl - hexahydro-1H-azepine

(a) 2 - (*m* - Methoxyphenyl) - 3 - methylbutyronitrile (37.8 g.) was added dropwise to a suspension of sodium amide (from sodium 4.6 g.) in liquid ammonia (200 ml.). On completion of the addition, the reaction mixture was stirred at −30°C for 0.5 hour then ethyl 4-iodobutyrate (50.8 g.) in ether (150 ml.) was added dropwise. The reaction mixture was stirred for 3 hours and left overnight. The reaction mixture was worked up as described in Example 3(a). The product was distilled affording 28.6 g. of ethyl 5-cyano - 5 - *m* - methoxyphenyl - 6 - methylheptanoate, b.p. 146—148°C/0.01 mm.

(b) The above ester (24.8 g.) was hydrogenated in cyclohexane (250 ml.) in the presence of nickel catalyst (*ca.* 6.0 g.) as described in Example 4(b). Removal of the solvent afforded 4.69 g. of white crystals, m.p. 146—148°C. Recrystallisation from ethyl acetate afforded colourless needles of 6-(m-methoxyphenyl) - 6 - isopropylhexahydro - 2H - azepin-2-one, m.p. 148—150°C. (Found: C, 73.7; H, 9.0; N, 5.2. $C_{16}H_{23}NO_2$ requires C, 73.35; H, 8.9; N, 5.4%).

(c) The above azepinone (6.8 g.) in tetrahydrofuran (150 ml.) was reduced with lithium aluminium hydride (5.0 g.) as described in Example 3(c). The product was distilled affording 6.1 g. of colourless oil, b.p. 110—112°C/0.01 mm. The obtained 3-(*m*-methoxyphenyl) - 3 - iso - propylhexahydro - 1H-azepine could be converted to a hydrobromide and recrystallised from propan - 2 - one - ether, m.p. 170—171°C. (Found: C, 58.65; H, 8.0; N, 4.3. $C_{16}H_{25}NO.HBr$ requires C, 58.6; H, 8.0; N, 4.3%).

(d) The azepine of part (c) (2.5 g.) as the free base was heated under reflux with 50% aqueous hydrobromic acid (10 ml.) for 1 hour. The solvent was removed under reduced pressure and the last traces of water were removed by azeotroping with propan-2-ol. The title compound as its hydrobromide was obtained as colourless needles, 2.08 g., m.p. 95—98°C from propan-2-ol/ether. (Found: C, 57.4; H, 8.1; N, 4.0. $C_{15}H_{23}NO.HBr$ requires C, 57.3; H, 7.7; N, 4.5%).

EXAMPLE 32

3 - (m - Hydroxyphenyl) - 1 - methyl - 3 - iso - propylhexahydro - 1H - azepine

(a) 3 - (*m* - Methoxyphenyl) - 3 - *iso* - propylhexahydro-1H-azepine (3.0 g.) was reacted with 40% aqueous formaldehyde (3 ml.) in the presence of 10% palladium charcoal (2.0 g.) in ethanol (80 ml.) in a Parr hydrogenator as described in Example 1(e). After workup, the product (3.0 g.) was used crude for the next experiment.

(b) The product from the above reaction (3.0 g.) was heated under reflux with 50% aqueous hydrogen bromide for 1 hour. the solvent was removed under reduced pressure and the product dissolved in water and converted to the free base. After extraction with benzene, drying, removing the solvent, the title compound was obtained as a fumarate (3.0 g.), m.p. 180—182°C. (Found: C, 66.0; H, 8.3; N, 3.8. $C_{16}H_{23}NO$. $C_4H_4O_4$ requires C, 66.1; H, 8.0; N, 3.85).

EXAMPLE 33

3 - Butyl - 3 - (m - hydroxyphenyl)hexahydro-1H-azepine

The azepine of Example 17(c) (1.61 g.) was heated under reflux with 50% aqueous hydrobromic acid (5 ml.) for 1.5 hours. The solvent was evaporated to an oil under reduced pressure and the product dried by repeatedly evaporating with portions of propan-2-ol. The hydrobromide of the title compound was obtained as off-white hygroscopic needles, (1.64 g.), m.p. 88—94°C. (Found: 58.35; H, 8.2; N, 4.0. $C_{16}H_{25}NO.HBr$ requires C, 58.7; H, 8.0; N, 4.3%).

EXAMPLE 34

1 - Allyl - 3 - ethyl - 3 - (m - hydroxyphenyl)hexahydro-1H-azepine

A mixture of 3 - ethyl - 3 - (*m* - hydroxyphenyl)hexahydro-1H-azepine hydrobromide (3.0 g.), allyl bromide (1.2 g.) and potassium carbonate (3.0 g.) in acetone (40 ml.) was heated under reflux for 16 hours. The excess of acetone was removed under reduced pressure, acetic anhydride (1 ml.) added, warmed for 1 hour at 100°C and then basified with sodium carbonate solution. The precipitated oil was extracted into ether which in turn was extracted with dilute hydrochloric acid. The acid extract was then basified and again extracted with ether. The organic extract was dried ($MgSO_4$) and evaporated *in vacuo* to give 2.6 g. of the crude allyl derivative.

The residue was dissolved in the minimum amount of *iso*-propanol and then 50% hydrobromic acid added until the solution was slightly acid. The precipitated brown oil was crystallised from a mixture of acetone and ether, and then recrystallised from a mixture of ethanol and ether to give 1.55 g. of the title compound as its hydrobromide, m.p. 141—142°C. (Found: C, 60.1; H, 7.7; N, 3.9. $C_{17}H_{25}NO.HBr$ requires C, 60.15; H, 7.7; N, 4.1%).

EXAMPLE 35

3 - Ethyl - 1 - formyl - 3 - (m - hydroxyphenyl)hexahydro-1H-azepine

A mixture of 3 - ethyl - 3 - (*m* - hydroxyphenyl)hexahydro-1H-azepine (1.5 g.) and 95% formic acid (10 ml.) was heated at 160°C

for 16 hours. Evaporation of the excess of formic acid *in vacuo* gave an oily residue which was dissolved in benzene, washed with water, dilute sodium carbonate solution and water, dried ($MgSO_4$) and evaporated to give 1.2 g. of the crude product. Fractional distillation then gave 0.5 g. of the product, b.p. 240—250°C/0.001 mm. (Found: C, 72.4; H, 8.65; N, 5.6. $C_{15}H_{21}NO_2$ requires C, 72.8; H, 8.5; N, 5.7%).

EXAMPLE 36

1 - Carbethoxy - 3 - ethyl - 3 - (m - hydroxyphenyl)hexahydro-1H-azepine

To a stirred and ice-cooled solution of 3-ethyl - 3 - (*m* - hydroxyphenyl)hexahydro-1H-azepine hydrobromide (4.0 g.) in chloroform (20 ml.) was added a solution of triethylamine (2.66 g.) in chloroform (10 ml.) followed by dropwise addition of a solution of ethyl chloroformate (1.44 g.) in chloroform (10 ml.). The resulting mixture after stirring for 2 hours at ice-temperature was allowed to stand a further 16 hours at room temperature. Ether was added to precipitate the mixture of triethylamine hydrochloride and triethylamine hydrobromide which was then filtered off. The filtrate was washed with water, dried ($MgSO_4$). evaporated under reduced pressure and the residual red oil fractionally distilled to give 2.1 g. of the title compound, b.p. 172—180°C/0.001 mm. (Found: C, 70.3; H, 8.8; N, 4.9. $C_{17}H_{24}NO_3$ requires C, 70.35; H, 8.3; N, 4.8%).

EXAMPLE 37

3 - Ethyl - 3 - (m - methoxyphenyl)hexahydro-1H-azepine

A solution of 6 - ethyl - 6 - (*m* - methoxyphenyl)hexahydro - 2H - azepin - 2 - one (12.3 g.) in sodium dried benzene (30 ml.) was added dropwise to a benzene solution (56 ml.) of sodium dihydro-bis(2-methoxyethoxy) aluminate (40.34 g.). The mixture was then heated under reflux for 5 hours and the complex then decomposed by addition of 2N sodium hydroxide solution. The organic layer was separated and then extracted with dilute hydrochloric acid. The acidic extract was basified by addition of 0.880 ammonia soltuion and extracted with ether, which after drying ($MgSO_4$) was evaporated under reduced pressure to give 7.0 g. of the title compound. This compound was also prepared by lithium aluminium hydride reduction of the same 2H - azepin - 2 - one, details of which are given in Example 19.

EXAMPLE 38

4 - (m - Hydroxyphenyl) - 4 - propylhexahydro-1H-azepine

(a) 1 - Methyl - 4 - (*m* - methoxyphenyl)-4 - propylhexahydro - 1H - azepine (2.82 g.) in dry methylene chloride (15 ml.) was treated dropwise at 5°C with phenylchloroformate (1.63 g.). The reaction mixture was left at room temperature for 4 hours then washed with 2*N* sodium hydroxide solution and 2*N* sulphuric acid. After drying over magnesium sulphate the solvent was removed leaving 3.8 g. of a colourless oil.

(b) The crude oil obtained above (1.3 g.) was heated under reflux with 50% aqueous hydrogen bromide (10 ml.) for 1.5 hours. The solvent was removed under reduced pressure, the residual oil was dissolved in water, made alkaline and extracted with ether. The product was distilled in a bulb-tube affording 304 mg. of a colourless glass, b.p. 180—200° at 0.003 mm. (Found: C, 76.9; H, 9.8, N, 5.8. $C_{15}H_{23}NO$ requires C, 77.2; H, 9.9; N, 6.0%).

EXAMPLE 39

6 - Ethyl - 6 - (m - methoxyphenyl)hexahydro - 2H - azepin - 2 - one

(a) A mixture of ethyl 5 - cyano - 5 - (*m*-methoxyphenyl)heptanoate (16.0 g.), concentrated sulphuric acid (11.9 ml.) and palladium on charcoal catalyst (2.0 g.) in methanol (125 ml.) was hydrogenated at room temperature and 50 lbs./sq. inch pressure in a Parr hydrogenator. The catalyst was filtered off, washed with methanol, and the filtrate and washings combined and evaporated *in vacuo*. The residue was basified with 0.880 ammonia solution, extracted with ether, dried ($MgSO_4$) and evaporated to give 15.2 g. of ethyl 5-aminomethyl - 5 - (*m* - methoxyphenyl)heptanoate.

(b) The above amino-ester was heated under reflux in toluene (200 ml.) for 24 hours, the liberated ethanol-toluene azeotrope removed by distillation up a suitable column. The excess of toluene was evaporated *in vacuo* and the residue crystallised from a mixture of ethyl acetate and petroleum ether (b.p. 60—80°C) to give 8.05 g. of the title compound, m.p. 87—89°C.

This compound has also been prepared by a one step reduction and cyclisation at high temperature, without isolating the intermediate aminomethyl ester of part (a) of this Example. Details for the one step process are given in Example 19(b).

EXAMPLE 40

3 - (m - Methoxyphenyl) - 3 - ethyl - hexahydroazepine (by catalytic reduction)

(a) 2-(*m*-Methoxyphenyl)butyronitrile (70 g.) was added dropwise to a stirred suspension of sodium amide (18 g.) in dry toluene (160 ml.) at 70°C. On completion of the addition the mixture was stirred at 80°C for 1 hour. Anhydrous tetrahydrofuran (20 ml.) was added to make the solution homogeneous, cooled and added slowly over a period of 2 hours to a stirred solution of 1-bromo-4-chlorobutane (72 g.) in toluene (200 ml.) at 10—15°C. The reaction mixture was allowed to warm up to room temperature then left overnight. Water (100 ml.) was added, the organic layer separated and washed with dilute acid, dried over magnesium sulphate and distilled affording 69.5 g. of 1 - chloro - 5-

cyano - 5 - (*m* - methoxyphenyl)heptane as a colourless oil b.p. (0.005 mm.) 150—151°C. (b) The chloronitrile of part (a) above (13.2 g.) was hydrogenated at an initial pressure of 50 p.s.i. in the presence of methanol (100ml.) containing concentrated sulphuric acid (75 ml.) and palladium-on-charcoal (10%, 3 g.) Uptake of hydrogen ceased when 1 mole of hydrogen had been absorbed. The catalyst was filtered off and replaced with a fresh portion (3 g.) and more concentrated sulphuric acid (5 ml.). A further mole of hydrogen was absorbed. After the catalyst had been removed and the methanol evaporated under reduced pressure, the product was dissolved in water, made basic with concentrated ammonia solution and extracted with ether and dried. Evaporation yielded 14 g. of 5 - aminomethyl - 1 - chloro - 5 - (*m*-methoxyphenyl)heptane as an oil. The product was disolved in 2*N* hydrochloric acid and added dropwise to 1*N* sodium hydroxide solution (4 L.) at 50°C. The temperature was raised over 2 hours to 100°C and the mixture heated at 100° for 3 hours. The reaction mixture was cooled, concentrated to 1 L. and extracted with ether. The basic material was isolated by an acid-base extraction of the ether solution and distilled affording 3.7 g. of colourless oil, b.p. (0.05 mm.) 112—120°C. The hydrobromide was obtained in the usual way and was identical to that of Example 19(c).

EXAMPLE 41

3 - (m - Benzyloxyphenyl) - 3 - ethyl - hexahydro-1H-azepine

The phenol (1 equivalent) of Example 20 in dry dimethyl formamide was added to a suspension of sodium hydride (1 equivalent of a 50% dispersion in oil) in the same solvent. When evolution of hydrogen had ceased, benzylchloride (1 equivalent) was added to the stirred solution keeping the temperature between 5—10°C by cooling. On completion of the addition the product was obtained by pouring into water, extracting with benzene and either distilling the product or converting to the required salt.

EXAMPLE 42

3 - Ethyl - 3 - (*m* - hydroxyphenyl)-hexahydro-1H-azepine	30 mg.
Lactose	120 mg.
Magnesium stearate	5 mg.

Capsules of the above were made up by thoroughly mixing together batches of the above ingredients and filling hard gelatine capsules (155 mg.) with the mixture.

EXAMPLE 43

3 - Ethyl - 3 - (*m* - hydroxyphenyl)-hexahydro-1H-azepine	30 mg.
Lactose	100 mg.
Avicel (Registered Trade Mark	30 mg.
Dried Maize Starch	40 mg.
Magnesium stearate	5 mg.

Tablets of the above composition were made by milling the active ingredient to 40 mesh (British Standard), sieving through a 40 mesh (British Standard) sieve, mixing the milled material with the other components and compressing to form tablets.

As above indicated, the new compounds of this invention display analgesic activity as shown by standard tests in laboratory animals. Many show analgesic activity comparable to that of codeine phosphate, and appear to be non-addicting and free of certain undesirable side-effects frequently encountered in analgesics, such as tendency to cause convulsions and/or constipation.

The following tables summarise some of the pharmacological testing we have had conducted. Compounds were screened as to analgesic activity by a modification of the Rat Tail Flick of D'Amour and Smith, J. Pharm. *72*:74, 1941. Test material was administered subcutaneously at a dosage level of 25 mg./kg. and analgesia in the animals was determined as a percentage of the total possible analgesia that could appear in the experimental period.

TABLE 1

Test Material	Percentage of Total Possible Analgesia				
	20—30	30—40	40—50	50—60	>60
Codeine Phosphate					X
Product of Example 1(e)	X				
Product of Example 2 (HBr salt)					X
Product of Example 2 (base)					X
Product of Example 5	X				
Product of Example 6		X			
Product of Example 8					X
Product of Example 10				X	
Product of Example 11					X
Product of Example 15	X				
Product of Example 16	X				
Product of Example 18					
Product of Example 20					X
Product of Example 21(a)			X		
Product of Example 21(b)			X		
Product of Example 22					X
Product of Example 23		X			
Product of Example 24					X
Product of Example 25				X	
Product of Example 26			X		
Product of Example 27			X		
Product of Example 28	X				
Product of Example 29					X
Product of Example 31				X	
Product of Example 33		X			
Product of Example 34					X
Product of Example 38	X				

Table II compares the median analgesic dose (AD_{50}), the median convulsant dose (CD_{50}) and the median lethal dose (LD_{50}) of certain compounds of this invention with the corresponding values for codeine phosphate and d-propoxyphene hydrochloride. In these tests, the test materials were administered intraperitoneally in mice.

TABLE II

Test Material	AD_{50}	CD_{50}	LD_{50}	$\frac{CD_{50}}{AD_{50}}$	$\frac{LD_{50}}{AD_{50}}$
Codeine Phosphate	25.5	112	127	4.39	4.98
d-Propoxyphene hydrochloride	45.5	120	190	2.64	4.18
Product of Example 2	25.5	28	95	1.10	3.73
Product of Example 8	22.8	53	150	2.32	6.58
Product of Example 10	24.3	100	105	4.12	4.32
Product of Example 20	15.92	*	61.25	*	3.85
Product of Example 22	37	*	140	*	3.78
Product of Example 24	40.1	50.4	127.3	1.26	3.18
Product of Example 29	14.0	*	70	*	5.0
Product of Example 34	12.0	70.0	70.0	5.8	5.8

* No sign of convulsant properties.

A somewhat similar comparison of the analgesic and toxic properties of these compounds on the basis of oral administration to mice is shown in Table III.

TABLE III

Test Material	AD_{50}	CD_{50}	LD_{50}	$\frac{CD_{50}}{AD_{50}}$	$\frac{CD_{50}}{AD_{50}}$
Codeine Phosphate	54	410	410	7.59	7.59
d-Propoxyphene hydrochloride	125	—	285	2.28	2.28
Product of Example 2	88	220	560	2.50	6.36
Product of Example 8	65	240	530	3.69	8.15
Product of Example 10	125	540	540	4.32	4.32
Product of Example 20	31.11	*	142.9	*	4.59
Product of Example 22	68	*	600	*	8.82
Product of Example 24	160.3	254.6	>360	1.59	>2.24

* No sign of convulsant properties.

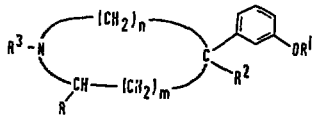
It will be evident from the foregoing tables that compounds of this invention show very strong analgesic properties, and that in several, at least, the analgesic effect is attained at a dosage much lower than the lethal or convulsive doses.

It has been found that the compounds of Examples 5, 6, 16, 26, 27, 28 and 34 also exhibit morphine antagonism activity; this is a strong indication that such compounds will prove to be non-addicting.

It has long been known that many analgesics, e.g. codeine, have a constipating effect, and this is ordinarily rather undesirable. We have conducted tests of a number of compounds of this invention by two methods to appraise this effect. Reduction in the number of faeces voided by individual rats after dosing with the compounds of the invention was taken as a measure of constipating action. An alternative method employed has been determination of the rate of travel of an inert coloured substance (charcoal) along the small intestine following dosage with test compound. In all such tests we have conducted, the new compounds of this invention appear to be less constipating than codeine.

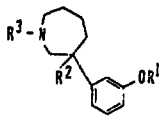
WHAT WE CLAIM IS:—

1. A compound of the general formula



and the acid addition and quanternary ammonium salts thereof, in which R^1 is a hydrogen atom, a loyer alkyl radical, a benzyl radical or a lower alkanoyl radical, R^2 is a lower alkyl radical, R^3 is a hydrogen atom, a lower alkyl, lower alkenyl, lower alkylnyl, cyclopropylmethyl, lower alkanoyl, lower alkoxycarbonyl, formyl, phenacyl or phenethyl group both of which may be substituted in the benzene ring or a β-benzoylethyl radical which may be substituted in the benzene ring, n is 3 or 4, m is 0 or 1 with the proviso that n+m is always equal to 4, R is a hydrogen atom or a lower alkyl radical when m is 0, or a hydrogen atom only when m is 1, and the term "lower" means that the radical contains up to 6, preferably up to 4 carbon atoms.

2. A compound of the general formula



and the acid addition and quaternary ammonium salts thereof, in which R^1 is a hydrogen atom, a lower alkyl radical, a benzyl radical or a lower alkanoyl radical, R^2 is a lower alkyl radical, R^3 is a hydrogen atom, a lower alkyl, lower alkenyl, lower alkynyl, cyclopropylmethyl, lower alkanoyl, phenacyl or phenethyl group both of which may be substituted in the benzene ring or a β-benzoylethyl radical which may be substituted in the benzene ring, and the term "lower" means that the radical contains up to 6 preferably up to 4 carbon atoms.

3. A compound according to Claim 2, in which R^1 is a hydrogen atom or a lower alkanoyl radical, R^2 is a lower alkyl radical and R^3 is a hydrogen atom or a lower alkenyl radical.

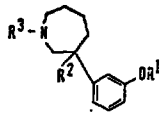
4. A compound according to Claim 2 in which R^1 is a methyl radical.

5. A compound according to Claim 2 or Claim 3, in which R^1 is an acetyl radical.

6. A compound according to any one of Claims 2, 3, 4 or 5, in which R^2 is an ethyl or *n*-propyl radical.

7. A compound according to any one of Claims 2 to 6, in which R^3 is an alyl radical.

8. A compound of the general formula



and the acid addition and quaternary ammonium salts thereof, in which R^1 is a hydrogen atom, a lower alkyl radical or a lower alkanoyl radical, R^2 is a lower alkyl radical and R^3 is a hydrogen atom, or a lower alkyl, lower alkenyl, lower alkynyl, cyclopropylmethyl, lower alkanoyl or phenacyl or phenethyl group both of which may be substituted in the benzene ring, or a β-benzoylethyl group which may be substituted in the benzene ring, and the term "lower" means that the radical contains up to 6, preferably up to 4 carbon atoms.

9. A compound according to Claim 8, in which R^1 is a hydrogen atom or a lower alkanoyl radical, R^2 is a lower alkyl radical and R^3 is a lower alkyl radical.

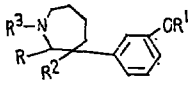
10. A compound according to Claim 8, in which R^1 is a methyl radical.

11. A compound according to Claim 8 or Claim 9, in which R^1 is an acetyl radical.

12. A compound according to any one of Claims 8 to 11, in which R^2 is an ethyl or *n*-propyl radical.

13. A compound according to any one of Claims 8 to 12 in which R^3 is a methyl radical.

14. A compound of the general formula



and the acid addition and quaternary ammonium salts thereof, in which R is a hydrogen atom or a lower alkyl radical, R^1 is a hydrogen atom, a lower alkyl radical, a benzyl radical or a lower alkanoyl radical, R^2 is a lower alkyl radical, R^3 is a hydrogen atom, a lower alkyl, lower alkenyl, lower alkynyl,

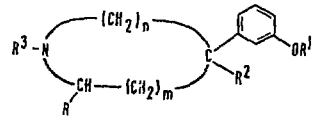
It will be evident from the foregoing tables that compounds of this invention show very strong analgesic properties, and that in several, at least, the analgesic effect is attained at a dosage much lower than the lethal or convulsive doses.

It has been found that the compounds of Examples 5, 6, 16, 26, 27, 28 and 34 also exhibit morphine antagonism activity; this is a strong indication that such compounds will prove to be non-addicting.

It has long been known that many analgesics, e.g. codeine, have a constipating effect, and this is ordinarily rather undesirable. We have conducted tests of a number of compounds of this invention by two methods to appraise this effect. Reduction in the number of faeces voided by individual rats after dosing with the compounds of the invention was taken as a measure of constipating action. An alternative method employed has been determination of the rate of travel of an inert coloured substance (charcoal) along the small intestine following dosage with test compound. In all such tests we have conducted, the new compounds of this invention appear to be less constipating than codeine.

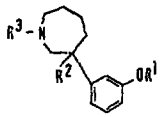
WHAT WE CLAIM IS:—

1. A compound of the general formula



and the acid addition and quanternary ammonium salts thereof, in which R^1 is a hydrogen atom, a loyer alkyl radical, a benzyl radical or a lower alkanoyl radical, R^2 is a lower alkyl radical, R^3 is a hydrogen atom, a lower alkyl, lower alkenyl, lower alkylnyl, cyclopropylmethyl, lower alkanoyl, lower alkoxycarbonyl, formyl, phenacyl or phenethyl group both of which may be substituted in the benzene ring or a β-benzoylethyl radical which may be substituted in the benzene ring, n is 3 or 4, m is 0 or 1 with the proviso that n+m is always equal to 4, R is a hydrogen atom or a lower alkyl radical when m is 0, or a hydrogen atom only when m is 1, and the term "lower" means that the radical contains up to 6, preferably up to 4 carbon atoms.

2. A compound of the general formula



and the acid addition and quaternary ammonium salts thereof, in which R^1 is a hydrogen atom, a lower alkyl radical, a benzyl radical or a lower alkanoyl radical, R^2 is a lower alkyl radical, R^3 is a hydrogen atom, a lower alkyl, lower alkenyl, lower alkynyl, cyclopropylmethyl, lower alkanoyl, phenacyl or phenethyl group both of which may be substituted in the benzene ring or a β-benzoylethyl radical which may be substituted in the benzene ring, and the term "lower" means that the radical contains up to 6 preferably up to 4 carbon atoms.

3. A compound according to Claim 2, in which R^1 is a hydrogen atom or a lower alkanoyl radical, R^2 is a lower alkyl radical and R^3 is a hydrogen atom or a lower alkenyl radical.

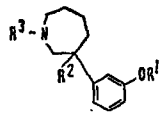
4. A compound according to Claim 2 in which R^1 is a methyl radical.

5. A compound according to Claim 2 or Claim 3, in which R^1 is an acetyl radical.

6. A compound according to any one of Claims 2, 3, 4 or 5, in which R^2 is an ethyl or *n*-propyl radical.

7. A compound according to any one of Claims 2 to 6, in which R^3 is an alyl radical.

8. A compound of the general formula



and the acid addition and quaternary ammonium salts thereof, in which R^1 is a hydrogen atom, a lower alkyl radical or a lower alkanoyl radical, R^2 is a lower alkyl radical and R^3 is a hydrogen atom, or a lower alkyl, lower alkenyl, lower alkynyl, cyclopropylmethyl, lower alkanoyl or phenacyl or phenethyl group both of which may be substituted in the benzene ring, or a β-benzoylethyl group which may be substituted in the benzene ring, and the term "lower" means that the radical contains up to 6, preferably up to 4 carbon atoms.

9. A compound according to Claim 8, in which R^1 is a hydrogen atom or a lower alkanoyl radical, R^2 is a lower alkyl radical and R^3 is a lower alkyl radical.

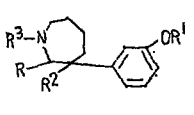
10. A compound according to Claim 8, in which R^1 is a methyl radical.

11. A compound according to Claim 8 or Claim 9, in which R^1 is an acetyl radical.

12. A compound according to any one of Claims 8 to 11, in which R^2 is an ethyl or *n*-propyl radical.

13. A compound according to any one of Claims 8 to 12 in which R^3 is a methyl radical.

14. A compound of the general formula



and the acid addition and quaternary ammonium salts thereof, in which R is a hydrogen atom or a lower alkyl radical, R^1 is a hydrogen atom, a lower alkyl radical, a benzyl radical or a lower alkanoyl radical, R^2 is a lower alkyl radical, R^3 is a hydrogen atom, a lower alkyl, lower alkenyl, lower alkynyl,

cyclopropylmethyl, lower alkanoyl, lower alkoxycarbonyl, phenacyl or phenethyl group both of which may be substituted in the benzene ring a β-benzoylethyl radical which may be substituted in the benzene ring, and the term "lower" means that the radical contains up to 6, preferably up to 4 carbon atoms.

15. A compound according to Claim 14, in which R^1 is a hydrogen atom, R and R^2 are alkyl radicals and R^3 is a hydrogen atom.

16. A compound according to Claim 14 or Claim 15, in which R is a methyl radical.

17. A compound according to Claim 14 or Claim 16, in which R^1 is methyl.

18. A compound according to any one of Claims 14 to 17, in which R^2 is a methyl radical.

19. A compound according to any one of Claims 14, 16, 17 or 18, in which R^3 is a methyl or allyl radical.

20. 1 - Allyl - 3 - ethyl - 3 - (*m* - hydroxyphenyl)hexahydro-1H-azepine.

21. 3 - (*m* - Acetoxyphenyl) - 3 - ethylhexahydro-1H-azepine.

22. 3 - Ethyl - 3 - (*m* - hydroxyphenyl)-hexahydro-1H-azepine.

23. 1 - Allyl - 3 - (*m* - hydroxyphenyl)-3 - propylhexahydro - 1H - azepine.

24. 3 - (*m* - Hydroxyphenyl) - 3 - propylhexahydro-1H-azepine.

25. 3 - (*m* - Acetoxyphenyl) - 1 - methyl-3 - propylhexahydro - 1H - azepine.

26. 3 - (*m* - Hydroxyphenyl) - 1 - methyl-3 - propylhexahydro - 1H - azepine.

27. 4 - (*m* - Acetoxyphenyl) - 1 - methyl-4 - propylhexahydro - 1H - azepine.

28. 3 - (*m* - Methoxyphenyl) - 1 - methyl-3 - propylhexahydro - 1H - azepine.

29. 3 - (*m* - Methoxyphenyl) - 3 - propylhexahydro-1H-azepine.

30. 1 - Allyl - 3 - (*m* - methoxyphenyl)-3 - propylhexahydro - 1H - azepine.

31. 3 - (*m* - Methoxyphenyl) - 1,3 - dimethylhexahydro-1H-azepine.

32. 3 - (*m* - Hydroxyphenyl) - 1,3 - dimethylhexahydro-1H-azepine.

33. 3 - (*m* - Acetoxyphenyl) - 1,3 - dimethylhexahydro-1H-azepine.

34. 3 - Butyl - 3 - (*m* - methoxyphenyl)-1-methylhexahydro-1H-azepine.

35. 3 - Butyl - 3 - (*m* - hydroxyphenyl)-1 - methylhexahydro - 1H - azepine.

36. 3 - (*m* - Hydroxyphenyl) - 3 - methylhexahydro-1H-azepine.

37. 3 - Ethyl - 3 - (*m* - methoxyphenyl)-1 - methylhexahydro - 1H - azepine.

38. 3 - Ethyl - 3 - (*m* - hydroxyphenyl)-1 - methylhexahydro - 1H - azepine.

39. 1 - Allyl - 3 - (*m* - hydroxyphenyl)-3 - methylhexahydro - 1H - azepine.

40. 3 - Butyl - 3 - (*m* - hydroxyphenyl)-hexahydro-1H-azepine.

41. 3 - Ethyl - 3 - (*m* - methoxyphenyl)-hexahydro-1H-azepine.

42. 3 - (*m* - Acetoxyphenyl) - 1 - acetyl-3 - ethylhexahydro - 1H - azepine.

43. 3 - (*m* - Hydroxyphenyl) - 3 - *iso*-propylhexahydro-1H-azepine.

44. 3 - (*m* - Hydroxyphenyl) - 1 - methyl-3 - *iso* - propylhexahydro - 1H - azepine.

45. 4 - (*m* - Methoxyphenyl) - 1 - methyl-4 - propylhexahydro - 1H - azepine.

46. 4 - (*m* - Hydroxyphenyl) - 1 - methyl-4 - propylhexahydro - 1H - azepine.

47. 4 - (*m* - Hydroxyphenyl) - 4 - propylhexahydro-1H-azepine.

48. 3 - (*m* - Hydroxyphenyl) - 1,2,3-trimethylhexahydro-1H-azepine.

49. 1,2,3 - Trimethyl - 3 - (*m* - methoxyphenyl) - hexahydro - 1H - azepine.

50. 3 - (*m* - Methoxyphenyl - 2,3 - dimethylhexahydro-1H-azepine.

51. 3 - (*m* - Hydroxyphenyl) - 2,3 - dimethylhexahydro-1H-azepine.

52. 1 - Allyl - 2,3 - dimethyl - 3 - (*m*-hydroxyphenyl)hexahydro-1H-azepine.

53. 1 - Carbethoxy - 3 - (*m* - hydroxyphenyl) - 3 - propylhexahydro - 1H - azepine.

54. 1 - Carbethoxy - 3 - ethyl - 3 - (*m*-hydroxyphenyl)hexahydro-1H-azepine.

55. A compound according to any one of Claims 20 to 26, 28 to 41, 43 and 44 when in the form of its pharmaceutically acceptable acid addition or quaternary ammonium salt.

56. A compound according to any one of Claims 27 and 45 to 47 when in the form of its pharmaceutically acceptable acid addition or quaternary ammonium salt.

57. A compound according to any one of Claims 48 to 52 when in the form of its pharmaceutically acceptable acid addition or quaternary ammonium salt.

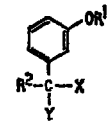
58. A compound according to Claim 14 substantially as described herein and shown with reference to any one of examples 14 to 26.

59. A compound according to Claim 8 substantially as described herein and shown with reference to any one of examples 9 to 13.

60. A compound according to Claim 2 substantially as described herein and shown with reference to any one of examples 1 to 8.

61. A compound according to Claim 1 substantially as described herein and shown with reference to any one of examples 27 to 41.

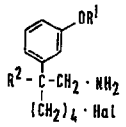
62. A process for the preparation of a compound as claimed in any one of Claims 1 to 14, 20 to 47 and 53 to 55 in which a precursor of the general formula



wherein R^1 and R^2 have the meanings defined

in Claim 1, X is $-CH_2.NH_2$ when Y is $-(CH_2)_4.Hal$, $-(CH_2)_4.OH$ or $-(CH_2)_3.COOAlk$, or X is —CN when Y is $-(CH_2)_3.COOAlk$, or X is —COOAlk when Y is $-(CH_2)_4.NH_2$ or $-(CH_2)_3.CN$; Hal is a halogen atom and Alk is lower alkyl radical) is cyclised by a method of the kind in actual use or described in the literature on the subject, followed if necessary by reduction.

63. A process according to Claim 62 for the preparation of a compound according to any one of Claims 2, 4 or 6 wherein R^1 is a lower alkyl or benzyl radical, R^2 is a lower alkyl radical and R^3 is a hydrogen atom, in which the precursor is a compound having the general formula



in which R^1 is a lower alkyl or benzyl radical, R^2 is a lower alkyl radical and Hal is a halogen atom.

64. A process according to Claim 63 in which the precursor is cyclised by heating in a solvent with or without the presence of a base.

65. A process according to Claim 63 or 64 in which the precursor is prepared by reducing the corresponding halo-nitrile of formula

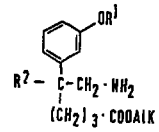


in which R^1 and R^2 are lower alkyl radicals and Hal is a halogen atom.

66. A process according to Claim 63 or 64 in which the precursor is prepared by halogenating an aminohydroxy compound of formula

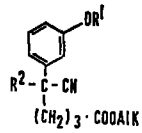


67. A process according to Claim 62 for the preparation of a compound according to any one of Claims 2, 4, 6 and 7 wherein R^1 is a lower alkyl radical, R^2 is a lower alkyl radical and R^3 is a hydrogen atom, lower akyl, lower alkenyl, lower alkynyl, cyclopropymethyl or phenethyl group which may be substituted in the benzene ring, in which the precursor has the formula



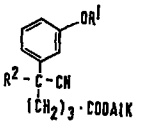
wherein R^1 and R^2 are as defined above and Alk is a lower alkyl radical, and is cyclised to a 6,6 - disubstituted hexahydro - 2H - azepin-2-one which is reduced with a hydride transfer agent, if desired with preliminary "alkylation" (as hereinbefore defined with the proviso that the group R^3 introduced is other than phenacyl or β-benzoylethyl both of which may be substituted in the benzene ring), of the cyclised product.

68. A process according to Claim 67 in which the precursor is prepared by catalytic reduction at a temperature up to 80°C. of the corresponding nitrile of formula



wherein R^1 is a lower alkyl radical, R^2 is a lower alkyl radical and Alk is a lower alkyl radical.

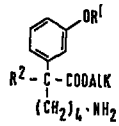
69. A process according to Claim 62 for the preparation of a compound according to Claims 2, 4, 6 and 7 wherein R^1 is a lower alkyl radical, R^2 is a lower alkyl radical and R^3 is a hydrogen atom, lower alkyl, lower alkenyl, lower alkynyl, cyclopropylmethyl or phenethyl group which may be substituted in benzene ring, in which the precursor is a compound of formula



(wherein R^1 and R^2 have the meanings defined above and Alk is a lower alkyl radical), which precursor is cyclised by catalytic hydrogenation at a temperature above 100°C to form a 6,6-disubstituted hexahydro-2H-azepin-2-one which is subsequently reduced with a hydride transfer reagent, if desired with preliminary "alkylation" (as herein before defined with the proviso that the group R^3 introduced is other than phenacyl or β-benzoylethyl both of which may be substituted in the benzene ring), of the cyclised product.

70. A process according to Claim 62, for the preparation of a compound according to any one of Claims 2, 4, 6 and 7 wherein R^1 is a lower alkyl radical, R^2 is a lower alkyl radical and R^3 is a hydrogen atom, lower alkyl, lower alkenyl, lower alkynyl, cyclopropylmethyl or phenethyl group which may

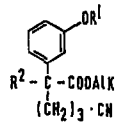
be substituted in the benzene ring, in which the precursor is a compound of formula



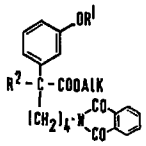
(wherein R^1 and R^2 have the meanings defined above and Alk is a lower alkyl radical), which precursor is cyclised to a 3,3-disubstituted hexahydro - 2H - azepin - 2 - one and subsequently reduced with a hydride transfer reagent, if desired with preliminary "alkylation" (as hereinbefore defined with the proviso that the group R^3 introduced is other than phenacyl or β-benzoylethyl both of which may be substituted in the benzene ring), of the cyclised product.

71. A proces according to Claim 70 in which R^1 in the compound produced by the reduction reaction is a lower alkyl radical and that the lower alkyl radical is removed by standard methods to give the compound wherein R^1 is a hydrogen atom.

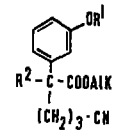
72. A process according to Claim 70 in which the precursor is prepared by catalytic hydrogenation at a temperature of up to 80°C of a compound of formula



73. A process according to Claim 70 in which the precursor is prepared by removing the phthaloyl protecting group of a compound of formula



74. A process according to Claim 62 for the preparation of a compound according to any one of Claims 2, 4, 6 and 7 wherein R^1 is a lower alkyl radical, R^2 is a lower alkyl radical and R^3 is a hydrogen atom, lower alkyl, lower alkenyl, lower alkynyl, cyclopropylmethyl or phenethyl group which may be substituted in the benzene ring, in which the precursor has the formula



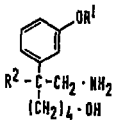
(wherein R^1 and R^2 have the meanings defined above and Alk is a lower alkyl radical), which precursor is cyclised by catalytic hydrogenation at a temperature of about 100°C. to form a 3,3-disubstituted hexahydro-2H-azepin-2-one which is then reduced with a hydride transfer reagent, if desired with preliminary "alkylation" (as hereinbefore defined with the proviso that the group R^3 introduced is other than phenacyl or β-benzoylethyl both of which may be substituted in the benzene ring), of the cyclised product.

75. A process according to any one of Claims 67, 68, 69, 70 or 74 in which R^3 in the compound produced by the reduction with the hydride transfer agent is a hydrogen atom, and that this compound is "alkylated" (as hereinbefore defined) or acylated at the nitrogen atom.

76. A process according to any one of Claims 67, 68, 69 or 74 in which R^1 in the compound produced is a lower alkyl radical, and this compound is hydrolysed to give the compound wherein R^1 is a hydrogen atom.

77. A process according to Claim 76 in which a compound wherein R^1 is a hydrogen atom is acylated to give a compound in which R^1 is a lower alkanoyl radical.

78. A process according to Claim 62, for the preparation of a compound according to any one of Claims 2, 4, 6 and 7 wherein R^1 is a lower alkyl or benzyl radical, R^2 is a lower alkyl radical and R^3 is a hydrogen atom, in which the precursor is a compound of formula



wherein R^1 and R^2 have the meanings defined above.

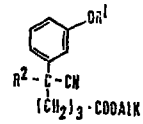
79. A process according to Claim 78 in which the precursor is halogenated by heating with an halogenating agent and then cyclised in the presence of a base.

80. A process according to Claim 78 or 79 in which R^3 in the compound produced by the cyclisation reaction is a hydrogen atom, and this compound is "alkylated" (as hereinbefore defined) or acylated at the nitrogen atom.

81. A process according to Claim 79 or 80 in which R^1 in the compound produced is a lower alkyl or benzyl radical, and the lower alkyl or benzyl radical is removed to give the compound wherein R^1 is a hydrogen atom.

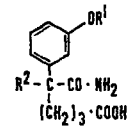
82. A process according to Claim 81 in which a compound wherin R^1 is a hydrogen atom, is acylated to introduce a group R^1 which is a lower alkanoyl radical.

83. A process according to Claim 78 in which the precursor is prepared by reducing a compound of formula



(wherein R^1 and R^2 have the meanings defined in Claim 78 and Alk is a lower alkyl radical), with a hydride transfer reagent.

84. A process according to Claim 78 in which the precursor is prepared by reducing a compound of formula

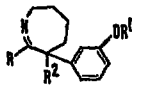


(wherein R^1 and R^2 have the meanings defined in Claim 78), with a hydride transfer reagent.

85. A process for preparing a compound as claimed in Claims 14 and 16 to 18 wherein R is a lower alkyl radical, R^1 is a lower alkyl or benzyl radical, R^2 is a lower alkyl radical and R^3 is a hydrogen atom, in which a compound of formula



wherein R^1 and R^2 have the meanings defined above and Hal is a halogen atom, is cyclised with a Grignard reagent of formula RMgI (wherein R is a lower alkyl radical) to form a tetrahydroazepine of formula



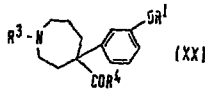
which is subsequently reduced.

86. A process according to Claim 85 in which the product of the Grignard reaction is "alkylated" (as hereinbefore defined) or acylated at the nitrogen atom.

87. A process according to Claim 85 in which R^1 in the compound produced is a lower alkyl or benzyl radical, and that the lower alkyl or benzyl radical is removed to give the compound wherein R^1 is a hydrogen atom.

88. A process according to Claim 87 in which the product, wherein R^1 is a hydrogen atom, is acylated to introduce a group R^1 which is a lower alkanoyl radical.

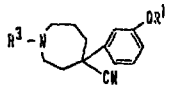
89. A process for the preparation of a compound as claimed in any of Claims 8, 10, 12 and 13 wherein R^1 and R^2 are lower alkyl radicals and R^3 is as defined in Claim 8 except for hydrogen, in which a compound of formula (XX)



(XX)

(wherein R^1 is a lower alkyl radical, R^3 is as defined in Claim 8 except for hydrogen and R^4 is a hydrogen atom or an alkyl radical containing up to 5 carbon atoms is reduced by methods known *per se*.

90. A process according to Claim 89 in which the compound of formula (XX) (wherein R^1 is a lower alkyl radical, R^4 is a hydrogen atom and R^3 is a methyl radical), is prepared by reduction of a compound of formula



(wherein R^1 and R^3 have the meanings defined defined above).

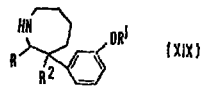
91. A process according to Claim 89 in which a compound produced by the reaction, in which R^1 is a lower alkyl radical, is hydrolysed to give a compound in which R^1 is a hydrogen atom.

92. A process according to Claim 91 in which a compound, wherein R^1 is a hydrogen atom, is acylated to introduce a group R^1 which is a lower alkanoyl radical.

93. A process according to Claim 89 in which a starting material is used wherein R^3 is methyl and the product is demethylated at the nitrogen atom by methods known *per se*, to give the corresponding compound in which R^3 is hydrogen.

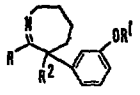
94. A process according to Claim 93 in which the product is "alkylated" (as hereinbefore defined) or acylated at the nitrogen atom.

95. A process for preparing a compound of formula



(XIX)

(wherein R is a lower alkyl radical, R^1 is a lower alkyl or benzyl radical and R^2 is a lower alkyl radical) in which a compound of formula



is reduced.

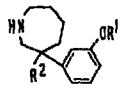
96. A process according to Claim 95, in which the reduction is effected by a hydride transfer agent.

97. A process according to Claims 95 or 96 in which the reduction product (wherein R^1 is a lower alkyl radical), is hydrolysed to give a compound in which R^1 is a hydrogen atom.

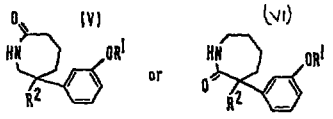
98. A process according to Claim 97 in which a compound wherein R^1 is a hydrogen atom is acylated to introduce a group R^1 which is a lower alkanoyl group.

99. A process according to Claims 95 or 96 in which the reduction product is "alkylated" (as hereinbefore defined) or acylated at the nitrogen atom.

100. A process for preparing a compound of formula



(wherein R^1 is a lower alkyl or benzyl radical and R^2 is a lower alkyl radical) in which a compound of the formula



is reduced.

101. A process according to Claim 100, in which the reducing agent is a metal hydride transfer agent.

102. A process according to Claim 100 or 101 in which the reduction product is "alkylated" (as hereinbefore defined) or acylated at the nitrogen atom.

103. A process according to Claims 100 or 101 in which the reduction product (wherein R^1 is a lower alkyl radical), is hydrolysed to give a compound in which R^1 is a hydrogen atom.

104. A process according to Claim 103 in which a compound wherein R^1 is a hydrogen atom is acylated to introduce a group R^1 which is a lower alkanoyl radical.

105. A process for preparing a compound according to Claim 1 substantially as described herein and shown with reference to any one of Examples 27 to 29, 31 to 36 and 38 to 41.

106. A process for preparing a compound according to Claim 2 substantially as described herein and shown with reference to any one of Examples 1 to 8.

107. A process for preparing a compound according to Claim 8 substantially as described herein and shown with reference to any one of Examples 9 to 13.

108. A process for preparing a compound according to Claim 14 substantially as described herein and shown with reference to any one of Examples 14 to 26.

109. A compound prepared by a process according to any one of Claims 62 to 66 and 105.

110. A compound prepared by a process according to any one of Claims 67 to 84 and 100 to 104.

111. A compound prepared by a process according to any one of Claims 89 to 94 and 107.

112. A compound prepared by a process according to any one of Claims 85 to 88, 95 to 99 and 108.

113. A pharmaceutical compositon comprising a compound according to any one of Claims 1, 61 and 109, in association with a pharmaceutically acceptable carrier.

114. A pharmaceutical composition comprising a compound according to any one of Claims 2—7, 20—26, 28—30, 31—33, 35—40, 43, 44, 60 and 110 in association with a pharmaceutically acceptable carrier.

115. A pharmaceutical composition comprising a compound according to any one of Claims 8—13, 27, 46, 47, 59 and 111 in association with a pharmaceutically acceptable carrier.

116. A pharmaceutical composition comprising a compound according to any one of Claims 14—19, 48, 49, 51—54, 58 and 112, in association with a pharmaceutically acceptable carrier.

117. A process for preparing a pharmaceutical composition in which a compound according to Claim 1 is brought into a form suitable for medical administration.

118. A process for preparing a pharmaceutical composition in which a compound according to Claim 2 is brought into a form suitable for medical administration.

119. A process for preparing a pharmaceutical composition in which a compound according to Claim 8 is brought into a form suitable for medical administration.

120. A process for preparing a pharmaceutical composition in which a compound according to Claim 14 is brought into a form suitable for medical administration.

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