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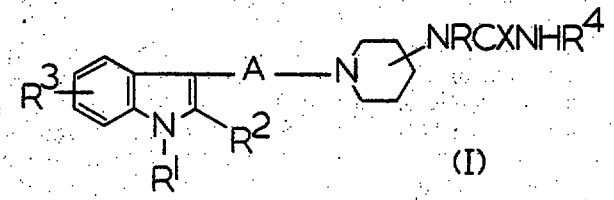
(72) Inventors JOHN LEHEUP ARCHIBALD and JOHN LAMBERT JACKSON

(54) INDOLE DERIVATIVES

(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:—

The invention relates to novel indole derivatives to processes for preparing them and to pharmaceutical compositions containing them.

The present invention provides compounds of the general formula:

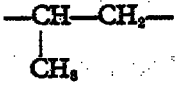


(I)

and acid addition and quaternary ammonium salts thereof, wherein R represents hydrogen or lower alkyl, R^1 represents hydrogen, lower alkyl, aryl lower alkyl or aroyl, R^2 represents hydrogen, lower alkyl, or aryl, R^3 represents hydrogen, halogen, lower alkoxy, aryl lower alkoxy, hydroxy or lower alkyl, R^4 represents hydrogen, lower alkyl, cycloalkyl of 5 to 7 carbon atoms, aryl lower alkyl, aryl (incuding heterocyclic aryl), or acyl, A represents an alkylene, mono- or dioxo- or hydroxy-alkylene radical having from 1 to 5 carbon atoms and X represents oxygen or sulphur.

The term "lower" in relation to alkyl and alkoxy radicals used herein means that the radical contains from 1 to 6 carbon atoms. Usually such radicals containing from 1 to 4 carbon atoms are preferred.

The alkylene radicals A may be straight chain or branched and when A is branched it is preferably a straight chain alkylene containing up to 4 carbon atoms in the chain and carrying one methyl substituent. A may be for example $—CH_2—$, $—CH_2CH_2—$, $—CH_2CH_2CH_2—$, $—CH_2CH_2CH_2CH_2—$,



$—CO(CH_2)_3—$ or $—CHOH(CH_2)_3—$ but is preferably $CH_2—CH_2$.

Examples of lower alkyl radicals for R, R^1, R^2, R^3 or R^4 are methyl, ethyl, *n*-propyl, iso-propyl, n-butyl and isobutyl. Examples of aryl radicals for R^2 and for the aryl portion of R^1, R^3 and R^4 radicals are phenyl and substituted phenyl.

R^4 when heteroaryl can be indolyl e.g. 3-indolyl, thienyl e.g. 2-thienyl, furyl, e.g. 2-furyl and pyridyl e.g. 2- and 3-pyridyl.

Substituted phenyl radicals which can be used for R^2 or R^1 or as the aryl portion of either of these radicals or of R^1 and R^3 include phenyl substituted by one or more substituents chosen from halogen such as chlorine, fluorine or bromine, alkoxy such as methoxy or ethoxy, alkyl such as methyl or ethyl, alkylenedioxy such as methylenedioxy and ethylenedioxy, nitro, amino, alkylamino, dialkylamino, acylamino e.g. alkanoyl amino, hydroxy, lower-alkoxycarbonyl, trihalo lower alkyl e.g. trifluoromethyl, mercapto, methylthio, methanesulphonyl, phenyl and phenyl substituted by any of the substituents mentioned in connection with the substituted phenyl radical.

The aroyl radical R^1 is preferably benzoyl or substituted benzoyl e.g. halobenzoyl.

Lower alkoxy radicals for R^3 include methoxy, ethoxy, propoxy and butoxy.

Cycloalkyl radicals for R^4 are cyclopentyl, cyclohexyl and cycloheptyl.

The acyl radical R^4 may be aroyl, e.g. benzoyl or substituted benzoyl e.g. halobenzoyl, alkanoyl e.g. acetyl or propionyl, or cycloalkanoyl e.g. cyclohexanoyl.

Preferred compounds of formula I are those in which R^1, R^2 and R^3 are hydrogen, those in which R^4 is phenyl, 2-trifluoromethylphenyl and benzoyl, those in which R is hydrogen or methyl and those in which A is $-CH_2CH_2-$.

Specific preferred compounds of the invention are:

1-phenyl-3-[1-(2-[indolyl]ethyl)piperid-4-yl]urea;
1-[1-(2-[3-indolyl]ethyl)piperid-4-yl]-3-[2-trifluoromethylphenyl]urea;
1-benzoyl-3-[1-(2-[3-indolyl]ethyl)piperid-4-yl]urea;
1-phenyl-3-[1-(2-[3-indolyl]ethylpiperid-4-yl]thiourea,
and 1-[1-(2-[3-indolyl]ethyl)piperid-4-yl]-1-methyl-3-phenyl urea

and their pharmaceutically acceptable acid addition salts.

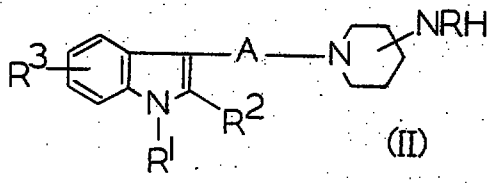
The acid addition salts of the compounds of formula I which are within the scope of the invention include those formed from inorganic and organic acids in particular pharmaceutically acceptable acid addition salts such as the sulphate, hydrochloride, hydrobromide, hydro-iodide, nitrate, phosphate, sulphonate (such as the methane sulphonate and *p*-toluene sulphonate), acetate, maleate, fumarate, tartrate and formate salts.

The quaternary ammonium salts include those formed with alkyl halides (e.g. methyl bromide or chloride) and aralkyl halides (e.g. benzyl bromide or chloride).

The compounds of formula I exhibit pharmacological activity such as action on the cardiovascular system (particularly hypotensive and/or anti-hypertensive activity).

The compounds of formula I may be prepared in a number of ways by building up the molecule from suitable starting materials in known manner. Such processes applied to the preparation of the novel compounds of formula I are included in the scope of the invention.

The preferred method for preparing compounds of formula I comprises reacting a compound of formula II



(II)

(wherein R, R^1, R^2, R^3 and A are as defined in connection with formula I) with a compound of formula IIIb

$$R^4N=C=X$$

(IIIb)

wherein R^4 is as defined in connection with formula I except hydrogen and X is oxygen or sulphur. When X is oxygen compound IIIb is an isocyanate (R^4NCO, III) and when X is sulphur compound IIIb is an isothiocyanate (R^4NCS, IIIa).

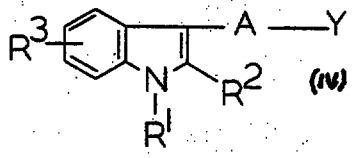
If A contains a carbonyl group this reaction should be conducted under mild conditions to avoid the possibility of reaction between the amine II (when R is hydrogen) and the carbonyl group of another molecule of amine II giving a Schiffs base.

This does not apply when the carbonyl group is adjacent to the piperidine nitrogen since it does not then behave as a ketone group. Usually the reaction to form the compound of formula I takes place at room temperature.

The starting materials of formula II wherein R is hydrogen may be prepared by methods described in our British Specification No. 1,218,570. The starting materials of formula II wherein R is lower alkyl may be prepared by alkylating corresponding compounds of formula II wherein R is hydrogen, or by methods analogous to those described in Specification No. 1,218,570.

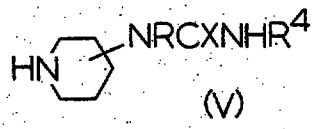
Compounds of formula I wherein R is hydrogen may be prepared by hydrolysis of the corresponding compounds of formula I where R^4 is acyl e.g. aroyl.

A second method for preparing compounds of formula I comprises reacting a compound of formula (IV)



(IV)

wherein R^1, R^2, R^3, and A are as defined in connection with formula I, and Y is a halogen atom or an equivalent replaceable atom or radical for example an organic sulphonyl radical such as a tosyl radical, with a compound of formula (V)

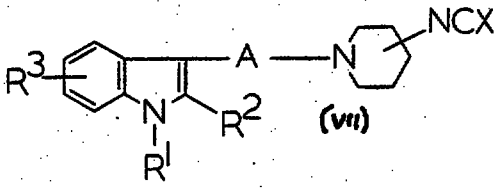


(V)

wherein R, R^4 and X are as defined in connection with formula I.

Compounds of formula IV may be prepared as described in British Specification 1,218,570. Compounds of formula (V) may be prepared by known methods.

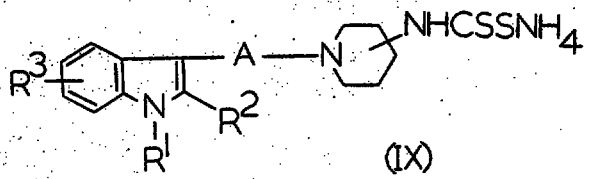
A third method of preparing the compounds of formula I comprises reacting a compound of formula



(VII)

(wherein R^1, R^2, R^3, X and A are as defined in connection with formula I) with an amine of formula R^4NH_2 (X) wherein R^4 is as defined in connection with formula I except hydrogen and acyl.

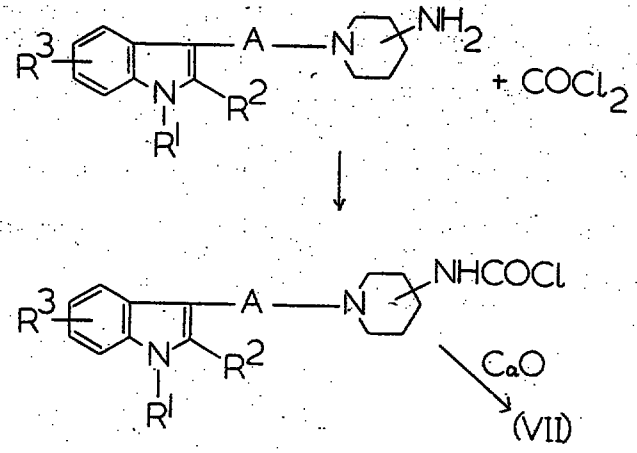
When A contains a carbonyl group care should be taken to avoid reaction between the amine (X) and the carbonyl group except when the carbonyl group is adjacent to the piperidine nitrogen. Compounds of formula (VII) (wherein neither A nor R^3 contain a hydroxy group and X is sulphur) may be prepared by reacting an amine of formula II wherein R is hydrogen either with a) thiophosgene then calcium oxide or b) carbon disulphide followed by ammonia to form a compound of formula IX



(IX)

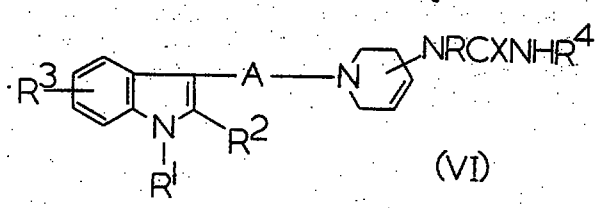
which is then treated with a heavy metal salt MB_2, wherein M is a divalent heavy metal and B_2 is two monovalent or one divalent anion. Examples of MB_2 are $CuSO_4$, $PbCO_3$, $FeSO_4$ and $Pb(NO_3)_2$.

Compounds of formula VII wherein X is oxygen and neither A nor R^3 contain a hydroxy group may be prepared by treatment of a compound of formula II, wherein R is H with phosgene followed by treatment of the product with calcium oxide according to the following reaction scheme:

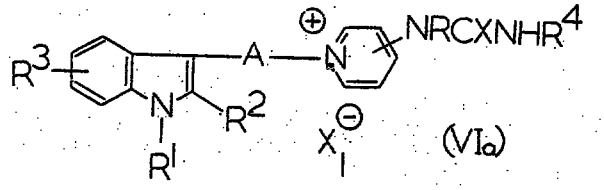


If a compound of formula I is prepared in which the chain A contains one or more carbonyl functions, then this chain may be selectively reduced e.g. with an alkali-metal borohydride, except when the carbonyl group is adjacent to the piperidine nitrogen. Thus the $COCH_2$ residue may be reduced with sodium borohydride to give the $—CH(OH)CH_2—$ residue. When X is oxygen a compound of formula I wherein A contains one or more carbonyl functions may be reduced by a hydride transfer agent (particularly lithium aluminium hydride). Thus the oxalyl residue COCO may be reduced under mild conditions to the $—CH(OH)CH_2—$ residue or under more drastic conditions to the $—CH_2CH_2—$ residue.

A further method for preparing compounds of formula I, comprises reducing a corresponding compound of formula (VI) or (VIa)



(VI)

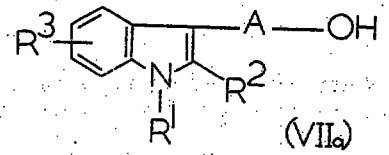


(VIa)

wherein R, R^1, R^2, R^3, R^4, and A are as defined in connection with formula I and $X_1^{\ominus}$ is an anion e.g. a halide ion.

A compound of formula (VIa) may be reduced with an alkali metal borohydride e.g. sodium borohydride to give a corresponding compound of formula (VI). Compounds of formula VIa or VI (wherein X is oxygen) may also be reduced by catalytic hydrogenation e.g. in the presence of Raney nickel or a platinum catalyst to a corresponding compound of formula I.

Another method of preparing compounds of formula I wherein X is oxygen and A is an alkylene radical comprises reacting a compound of formula (VIIa)

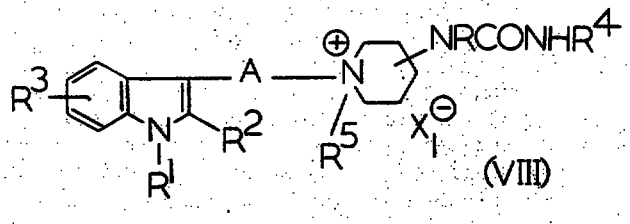


(VIIa)

wherein R^1, R^2 and R^3 are as defined in connection with formula I and A is an alkylene radical, with a compound of formula (V) as defined above wherein X is oxygen.

The reaction is preferably carried out in the presence of a catalyst, for example Raney nickel. An organic solvent, which is inert under the reaction conditions, is usually used for example xylene, toluene or benzene. Preferably the reaction is carried out by heating the reactants under reflux in a water-immiscible organic solvent, for example xylene, and removing the water formed during the reaction by azeotropic distillation. If necessary, reactive substituent groups can be blocked during a reaction and released later.

Compounds of formula (I) wherein X is oxygen may also be prepared by treating a compound of formula (VIII)



(VIII)

wherein R, R^1, R^2, R^3, R^4 and A are as defined in connection with formula I and R^5 is an aryl methyl radical and X_1^- is an anion e.g. a halide ion, under mild conditions such as to remove the group R^5. Preferably the group R^5 is removed by hydrogenolysis under standard conditions e.g. using an appropriate catalyst such as a palladium on carbon catalyst, a platinum catalyst or a nickel catalyst. In this reaction a mono or diketo lower alkylene radical A may also be reduced to a corresponding hydroxy lower alkylene radical A. If the keto compound is desired it can be obtained by oxidation of the final product.

Instead of a compound of formula (VIII) wherein R^5 is as defined above any other starting material where R^5 is an organic group which can be readily removed under mild conditions can be used.

Other conditions which may be effective to remove the group R^5 are treatment with acid e.g. with acetic acid or hydrochloric acid to remove a trityl group or treatment with alkali metal in liquid ammonia.

Examples of groups R^5 in the starting materials of formula (VIII) are arylmethyl radicals such as benzyl, diphenylmethyl, trityl or naphthylmethyl, benzyl being preferred.

A method for preparing compounds of formula (I) wherein R^4 is hydrogen and X is oxygen comprises reacting a compound of formula (II) with nitrourea ($H_2NCONH.NO_2$).

Once a compound of general formula (I) has been prepared, then if necessary one or more substituents in the molecule may be converted to another substituent within its own meanings specified in connection with formula (I).

When a compound of formula (I) is produced wherein the R^3 represents lower alkoxy or aryl-lower alkoxy hydrolysis or dealkylation to the corresponding hydroxyl compound may be brought about in known manner.

If necessary, in any of the reactions hereinbefore described, reactive substituent groups may be blocked during a reaction and released at a later stage.

The invention also includes pharmaceutical compositions containing as active ingredient an active compound of formula I as above defined. The active compound may be finely comminuted if desired. In addition to the active ingredient, the compositions also contain a non-toxic carrier. Any suitable carrier known in the art can be used to prepare the pharmaceutical compositions. In such a composition, the carrier may be a solid, liquid or mixture of a solid and a liquid. Solid form compositions include powders, tablets and capsules. A solid carrier can be one or more substances which may also act as flavouring agents, lubricants, solubilisers, suspending agents, binders, or tablet-disintegrating agents; it can also be an encapsulating material. In powders the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets the active ingredient is mxed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from 5 to 99, preferably 10—80% of the active ingredient.

Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low melting wax, and cocoa butter. The term "composition" is intended to include the formation of an active ingredient with encapsulating material as carrier to give a capsule in which the active ingredient (with or without other

carriers) is surrounded by carrier, which is thus in association with it. Similarly cachets are included.

Sterile liquid form compositions include sterile solutions, suspensions, emulsions, syrups and elixirs. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable sterile liquid carrier, such as sterile water, sterile organic solvent or a mixture of both. Preferably a liquid carrier is one suitable for parenteral injection. Where the active ingredient is sufficiently soluble it can be dissolved in normal saline as a carrier; if it is too insoluble for this it can often be dissolved in a suitable organic solvent, for instance aqueous propylene glycol or polyethylene glycol solutions. Aqueous propylene glycol containing from 10 to 75% of the glycol by weight is generally suitable. In other instances compositions can be made by dispersing the finely-divided active ingredient in aqueous starch or sodium carboxy-methyl cellulose solution, or in a suitable oil, for instance arachis oil. Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilised by intramuscular, intraperitoneal or subcutaneous injection. In many instances, a compound is orally active and can be administered orally either in liquid or solid composition form.

Preferably the pharmaceutical composition is in unit dosage form. In such form, the composition is sub-divided in unit doses containing appropriate quantities of the active ingredients; the unit dosage form can be a packaged composition, the package containing specific quantities of compositions, for example packeted powders or vials or ampoules. The unit dosage form can be a capsule, cachet or tablet itself, or it can be the appropriate number of any of these in package form. The quantity of active ingredient in a unit dose of composition may be varied or adjusted from 5 mg or less to 500 or more, according to the particular need and the activity of the active ingredient. The invention also includes the compounds in the absence of carrier where the compounds are in unit dosage form.

The following examples illustrate the invention. Temperatures are in °C.

EXAMPLE 1

1-Phenyl-3-[1-(2-[3-indolyl]ethyl)piperid-4-yl]urea

To a solution of 3-[2-(4-aminopiperidyl)ethyl]indole hydrate (1.31 g.) in warm dry benzene (125 ml.), was added phenyl isocyanate (0.63 g. 5% excess) in benzene (25 ml.).

The mixture was stirred at room temperature overnight and the title compound (1.74 g.) was filtered off. This was converted to the hydrochloride (1.39 g.) m.p. 214—219° in ethanol-HCl/ether.

$C_{22}H_{26}N_4O\,HCl\,\frac{1}{2}H_2O$ requires: C, 64.77; H, 6.92; N, 13.74
Found: C, 64.69; H, 6.91; N, 13.45%

The product exhibited very good hypotensive activity.

EXAMPLE 2

1-(4-Chlorophenyl)-3-[1-(2-[3-indolyl]ethyl)piperid-4-yl]urea

Condensation of 3-[2-(4-aminopiperidyl)ethyl]indole, hydrate (1.05 g.) and 4-chlorophenyl isocyanate (0.65 g., 5% excess) in the manner of Example (1), gave the crude title compound (1.55 g.) from which a pure hydrochloride hemi-hydrate (1.41 g, m.p. 244.4° (dec.)) was obtained by treatment with ethanolic HCl/ether.

$C_{22}H_{25}ClN_4O\,.\,HCl\,.\,\frac{1}{2}H_2O$ requires: C, 59.72; H, 6.15; N, 12.66
Found: C, 60.02; H, 6.33; N, 12.36%

The product exhibited antihypertensive activity.

EXAMPLE 3

1-[3,4-Dichlorophenyl]-3-[1-(2-[3-indolyl]ethyl]piperid-4-yl]urea

Condensation of 3-[2-(4-aminopiperidyl)ethyl]indole, hydrate (1.31 g.) and 3,4-dichlorophenyl isocyanate (0.99 g., 5% excess) in the manner of Example 1 gave the crude title compound (2.03 g.) from which a pure hydrochloride (1.70 g., m.p. 258.4°, dec.) was obtained by treatment with ethanolic HCl/ether.

$C_{22}H_{24}Cl_2N_4O\,HCl$ requires: C, 56.48; H, 5.39; N, 11.98
Found: C, 56.69; H, 5.53; N, 11.84%

The product exhibited hypotensive activity.

EXAMPLE 4

1-[1-(2-[3-Indolyl]ethyl)piperid-4-yl]-3-[4-methoxyphenyl]urea

Condensation of 3-[2-(4-Aminopiperidyl)ethyl]indole, hydrate (1.31 g.) and 4-methoxyphenyl isocyanate (0.78 g., 5% excess) in the manner of Example 1 gave the crude title product (1.86 g.) from which a pure hydrochloride, hydrate (1.96 g., 220.4°, dec.) was obtained by treatment with ethanolic HCl/ether.

$C_{23}H_{28}N_4O_2 . HCl . H_2O$ requires: C, 61.81; H, 6.99; N, 12.53
Found: C, 62.22; H, 6.84; N, 12.40%

The product exhibited hypotensive activity.

EXAMPLE 5

1-[1-(2-[3-Indolyl]ethyl)piperid-4-yl]-3-[3-tolyl]urea

Condensation of 3-[2-(4-Aminopiperidyl)ethyl]indole, hydrate (1.31 g.) and 3-tolyl isocyanate (0.70 g., 5% excess) in the manner of Example 1 gave the crude title compound (1.70 g.) from which was obtained a pure hydrochloride (1.57 g., m.p. 228.9°, dec.) by treatment with ethanolic HCl/ether.

$C_{23}H_{28}N_4O$ HCl requires: C, 66.93; H, 7.08; N, 13.57
Found: C, 67.01; H, 7.21; N, 13.66%

The product exhibited hypotensive activity.

EXAMPLE 6

1-[1-(2-[3-Indolyl]ethyl)piperid-4-yl]-3-[2,6-dimethylphenyl]urea

Using the procedure of Example 1 4-amino-1-[2-(3-indolyl)ethyl]piperidine, hydrate (1.307 g.) and 2,6-dimethylphenyl isocyanate (0.688 g., 25% excess) gave the title compound as the hydrochloride (1.110 g., 52%) m.p. 329.7° (dec).

$C_{24}H_{30}N_4O . HCl$ requires: C, 67.53; H, 7.32; N, 13.12
Found: C, 67.55; H, 7.50; N, 12.63%

The product exhibited hypotensive activity in a standard test procedure.

EXAMPLE 7

1-[1-(2-[3-Indolyl]ethyl)piperid-4-yl]-3-[2-trifluoromethylphenyl]urea

Using the procedure of Example 1 4-amino-1-[2-(3-indolyl)ethyl]piperidine, hydrate (1.307 g.) and 2-trifluoromethylphenyl isocyanate (0.982 g., 5% excess) gave the title compound as the hydrochloride (1.835 g., 82%) m.p. 233.6° (dec).

$C_{23}H_{25}N_4O . HCl$ requires: C, 59.18; H, 5.61; N, 12.00
Found: C, 59.28; H, 5.79; N, 11.66%

The product exhibited marked hypotensive activity in a standard test procedure.

EXAMPLE 8

1-Benzoyl-3-1-(2-[3-indolyl]ethyl)piperid-4-yl]urea

Using the procedure of Example 1 4-amino-1-[2-(3-indolyl)ethyl]piperidine, hydrate (1.307 g.) and benzoyl isocyanate (1.471 g.) gave the title compound as the hydrochloride (1.436 g., 63%), m.p. 248.0° (dec).

$C_{23}H_{26}N_4O_2$ HCl requires: C, 64.73; H, 6.38; N, 13.12
Found: C, 64.43; H, 6.66; N, 13.11%

The product is an intermediate for the next Example and also exhibited marked hypotensive activity and good antihypertensive activity.

EXAMPLE 9

1-[1-(2-[3-Indolyl]ethyl)piperid-4-yl]urea

1-benzoyl-3-[1-(2-[3-indolyl]ethyl)piperid-4-yl]urea hydrochloride (1.180 g.) was refluxed in 2N sodium hydroxide solution (20 ml.) for 1 hour. The reaction mixture was cooled and the title compound was filtered off, (0.678 g., 86%) m.p. 212.2° (dec).

$C_{16}H_{22}N_4O$ requires: C, 67.10; H, 7.74; N, 19.57
Found: C, 67.56; H, 7.74; N, 19.35%

The product exhibited hypotensive effects, but of short duration, at low doses in a standard test procedure. It also exhibited anti-hypertensive activity.

EXAMPLE 10

1-Phenyl-3-[1-(2-[3-indolyl]ethyl)piperid-4-yl]thiourea

4-Amino-1-[2-(3-indolyl)ethyl]piperidine hydrate (1.31 g., 0.005 mole) was dissolved in benzene (125 ml.) and phenyl isothiocyanate (0.74 g., 0.0055 mole) added dropwise with stirring. After 24 hr., the mixture was filtered to give the title compound (free base) as a white amorphous solid (1.76 g.). This was dissolved in a minimum of hot ethanol, saturated ethanol-HCl added until acid, and then the solution allowed to crystallise. Filtration afforded the title compound hydrochloride as colourless prisms (1.75 g.), m.p. 224.8°.

Analysis:

Found: C, 63.67; H, 6.74; N, 13.32
$C_{22}H_{26}N_4S$. HCl requires: C, 63.67; H, 6.56; N, 13.50%

The product exhibited hypotensive and anti-hypertensive activities.

EXAMPLE 11

1-(4-Chlorophenyl)-3-[1-(2-[3-indolyl]ethyl)piperid-4-yl]thiourea

4-Amino-1-[2-(3-indolyl)ethyl]piperidine hydrate is treated with 4-chlorophenyl isothiocyanate in the manner described in Example 10 to obtain the title compound as the hydrochloride.

EXAMPLE 12

1-[3,4-Dichlorophenyl]-3-[1-(2-[3-indolyl]ethyl]piperid-4-yl]thiourea

4-Amino-1-[2-(3-indolyl)ethyl]piperidine hydrate is treated with 3,4-dichlorophenyl isothiocyanate in the manner described in Example 10 to obtain the title compound as the hydrochloride.

EXAMPLE 13

1-[4-Methoxyphenyl]-3-[1-(2-[3-indolyl]ethyl)piperid-4-yl]thiourea

4-Amino-1-[2-(3-indolyl)ethyl]piperidine hydrate is treated with 4-methoxyphenyl isothiocyanate in the manner of Example 10 to obtain the title compound as the hydrochloride.

EXAMPLE 14

1-[3-Tolyl]-3-[1-(2-[3-indolyl]ethyl)piperid-4-yl]-thiourea

4-Amino-1-[2-(3-indolyl)ethyl]piperidine hydrate is treated with 3-tolyl isothiocyanate in the manner of Example 10 to obtain the title compound as the hydrochloride.

EXAMPLE 15

1-[2-Trifluoromethylphenyl]-3-[1-(2-[3-indolyl]ethyl]piperid-4-yl]-thiourea

4-Amino-1-[2-(3-indolyl)ethyl]piperidine hydrate is treated with 2-trifluoromethylphenyl isothiocyanate in the manner of Example 10 to give the title compound as the hydrochloride.

EXAMPLE 16

1-[1-(2-[3-Indolyl]ethyl)piperid-4-yl]-3-cyclohexyl urea

4-Amino-1-[2-(3-indolyl)ethyl]piperidine, hydrate (1.307 g, 0.005 mole) in benzene (50 ml.) was treated with cyclohexyl isocyanate (0.688 g., 0.0055 mole) and the mixture stirred for 18 hrs. Filtration afforded the title compound as colourless prisms (1.893 g.), m.p. 203.8°.

Analysis:

Found: C, 71.74; H, 9.05; N, 14.91
$C_{22}H_{32}N_4O$ requires: C, 71.70; H, 8.75; N, 15.21%

The product exhibited hypotensive activity.

EXAMPLE 17

1-[1-(2-[3-Indolyl]ethyl)piperid-4-yl]-3-(3-trifluoromethylphenyl)urea

3-[2-(4-Aminopiperidyl)ethyl]indole hydrate (1.31 g., 0.005 mole) was reacted with m-trifluoromethylphenyl isocyanate (1.03 g., 0.0055 mole) in the manner of Example 16 to give the title compound hydrochloride (0.87 g.), m.p. 200.0°.

Analysis:

Found:	C, 59.51;	H, 5.84;	N, 11.95
$C_{23}H_{25}F_3N_4O$. HCl requires:	C, 59.11;	H, 5.57;	N, 11.99%

The product exhibited hypotensive activity.

EXAMPLE 18

1-[1-(2-[3-Indolyl]ethyl)piperid-4-yl]-1-methyl-3-phenyl urea

3-[2-(4-Methylaminopiperidyl)ethyl]indole (1.28 g., 0.005 mole) and phenyl isocyanate (0.66 g., 0.0055 mole) were condensed in the manner of Example 16 to give the title compound hydrochloride (0.69 g.), m.p. 217.6°.

Analysis:

Found:	C, 65.85;	H, 7.37;	N, 13.03
$C_{23}H_{28}N_4O$. HCl . $\frac{1}{2}H_2O$ requires:	C, 66.17;	H, 7.24;	N, 13.42%

The product exhibited marked hypotensive activity.

EXAMPLE 19

1-[1-(2-[3-Indolyl]ethyl)piperid-4-yl]-1-methyl-3-phenyl thiourea

3-[2-(4-Methylaminopiperidyl)ethyl]indole (1.28 g., 0.005 mole) was stirred in dry benzene (75 ml.) and treated with phenyl isothiocyanate (0.74 g., 0.0055 mole). Stirring was continued for 24 hr. and the mixture evaporated to give the title compound, which was converted to the hydrochloride by addition of hydrogen chloride in ethanol and precipitation with ether. Yield, 0.95 g., m.p. 193.7°.

Analysis:

Found:	C, 64.05;	H, 6.99;	N, 13.11
$C_{23}H_{28}N_4S$. HCl requires:	C, 64.39;	H, 6.81;	N, 13.06%

EXAMPLE 20

1-Benzoyl-3-[1-(2-[3-indolyl]ethyl)piperid-4-yl]thiourea

To a stirred solution of ammonium thiocyanate (2.28 g.) in dry acetone (20 ml.) was added a solution of benzoyl chloride (4.22 g.) in dry acetone (20 ml.). This mixture was stirred at 45° for 5 min. then treated with a solution of 3-[2-(4-aminopiperidyl)-ethyl]indole (7.84 g.) in dry acetone (30 ml.). After refluxing for 25 min., the mixture was cooled, poured into water (250 ml.) and the liberated oil extracted into chloroform. Evaporation of the dried ($MgSO_4$) extract afforded the title compound which was crystallised from EtOH-HCl/Et_2O as the hydrochloride (1.65 g.), m.p. 212—215°.

Analysis:

Found:	C, 61.70;	H, 6.43;	N, 12.14
$C_{23}H_{26}N_4OS$. HCl . $\frac{1}{2}H_2O$ requires:	C, 61.74;	H, 6.19;	N, 12.52%

The product exhibited hypotensive activity.

EXAMPLE 21

1-[1-(2-[3-Indolyl]ethyl)piperid-4-yl]thiourea

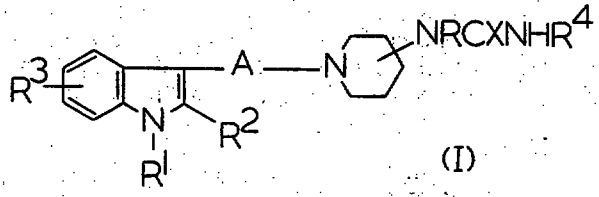
1-Benzoyl-3-[1-(2-[3-indolyl]ethyl)piperid-4-yl]-thiourea (2.21 g.) was refluxed in water (20 ml.) containing sodium hydroxide (1.0 g.) for 5 min. The mixture was cooled and filtered to afford the title compound (1.59g). Crystallisation from EtOH-HCl/ether afforded the hydrochloride (1.467 g.), m.p. 228—9°.

Analysis:

Found:	C, 56.78;	H, 7.20;	N, 16.42
$C_{16}H_{22}N_4S$. HCl requires:	C, 56.70;	H, 6.84;	N, 16.53%

WHAT WE CLAIM IS:—

1. A compound of the general formula:



(I)

and acid addition and quaternary ammonium salts thereof, wherein R represents hydrogen or lower alkyl, R^1 represents hydrogen, lower alkyl, aryl lower alkyl or aroyl, R^2 represents hydrogen, lower alkyl, or aryl, R^3 represents hydrogen, halogen, lower alkoxy, aryl lower alkoxy, hydroxy or lower alkyl, R^4 represents hydrogen, lower alkyl, cycloalkyl of 5 to 7 carbon atoms, aryl lower alkyl, aryl (including heterocyclic aryl), or acyl, A represents an alkylene, mono- or dioxo- or hydroxy-alkylene radical having from 1 to 5 carbon atoms and X represents oxygen or sulphur.

2. A compound as claimed in Claim 1, wherein A is a straight chain alkylene radical containing up to 4 carbon atoms.

3. A compound as claimed in Claim 2, wherein A is $—CH_2CH_2—$.

4. A compound as claimed in any one of Claims 1—3, wherein R^1, R^2 and R^3 are all hydrogen.

5. A compound as claimed in any one of Claims 1—4, wherein R is methyl.

6. A compound as claimed in any one of Claims 1—5, wherein R^4 represents hydrogen, lower alkyl, cycloalkyl of 5 to 7 carbon atoms, aryl, lower alkyl, aryl (including heterocyclic aryl) or aroyl.

7. A compound as claimed in Claim 6 wherein R^4 represents phenyl or substituted phenyl.

8. A compound as claimed in Claim 7, wherein R^4 represents phenyl substituted by halogen or trifluoromethyl.

9. A compound as claimed in Claim 8, wherein R^4 represents 2-trifluoromethyl phenyl.

10. A compound as claimed in Claim 6 wherein R^4 represents benzoyl.

11. A compound as claimed in Claim 6, wherein R^4 represents cyclohexyl.

12. A compound as claimed in any one of Claims 6 to 11 wherein X is sulphur.

13. A compound as claimed in any one of Claims 6 to 11 wherein X is oxygen.

14. 1-Phenyl-3-[1-(2-[3-indolyl]ethylpiperid-4-yl]urea or a pharmaceutically acceptable acid addition salt thereof.

15. 1-(4-Chlorophenyl)-3-[1-(2-[3-indolyl]ethyl)piperid-4-yl]urea or a pharmaceutically acceptable acid addition salt thereof.

16. 1-[3,4-Dichlorophenyl]-3-[1-(2-[3-indolyl]ethyl)piperid-4-yl]urea or a pharmaceutically acceptable acid addition salt thereof.

17. 1-[1-(2-[3-Indolyl]ethyl)piperid-4-yl]-3-[4-methoxyphenyl]urea or a pharmaceutically acceptable acid addition salt thereof.

18. 1-[1-(2-[3-Indolyl]ethyl)piperid-4-yl]-3-[3-tolyl]urea or a pharmaceutically acceptable acid addition salt thereof.

19. 1-[1-(2-[3-Indolyl]ethyl)piperid-4-yl]-3-[2,6-dimethylphenyl]urea or a pharmaceutically acceptable acid addition salt thereof.

20. 1-[1-(2-[3-Indolyl]ethyl)piperid-4-yl]-3-[2-trifluoromethylphenyl]urea or a pharmaceutically acceptable acid addition salt thereof.

21. 1-Benzoyl-3-[1-(2-[3-indolyl]ethyl)piperid-4-yl]urea or a pharmaceutically acceptable acid addition salt thereof.

22. 1-Phenyl-3-[1-(2-[3-indolyl]ethyl)piperid-4-yl]thiourea or a pharmaceutically acceptable acid addition salt thereof.

23. 1-[1-(2-[3-Indolyl]ethyl)piperid-4-yl]-3-cyclohexyl urea or a pharmaceutically acceptable acid addition salt thereof.

24. 1-[1-(2-[3-Indolyl]ethyl)piperid-4-yl]-1-methyl-3-phenyl urea or a pharmaceutically acceptable acid addition salt thereof.

25. 1-[1-(2-[3-Indolyl]ethyl)piperid-4-yl]-1-methyl-3-phenyl thiourea or a pharmaceutically acceptable acid addition salt thereof.

26. A compound as claimed in Claim 1, substantially as described in any one of Examples 1—5.

27. A compound as claimed in Claim 1, substantially as described in any one of Examples 6—9.

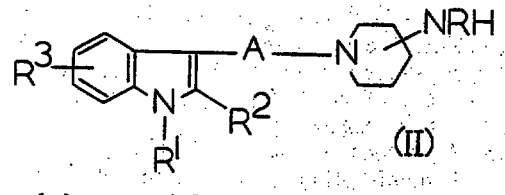
* C L M S *

28. A compound as claimed in Claim 1, substantially as described in any one of Examples 10—16.

29. A compound as claimed in Claim 1, substantially as described in any one of Examples 17—21.

30. A method for preparing a compound as claimed in Claim 1, which method comprises

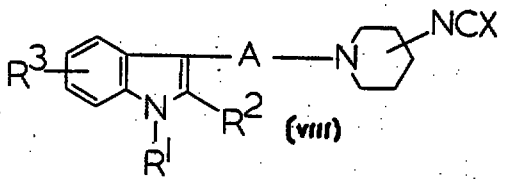
a) reacting a compound of formula II



(II)

wherein R, R^1, R^2, R^3 and A are as defined in connection with formula I with a compound of formula R^4NCX wherein R^4 is as defined in connection with formula I except hydrogen and X is oxygen or sulphur or

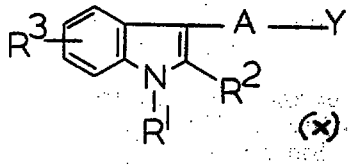
b) reacting a compound of formula (VIII)



(VIII)

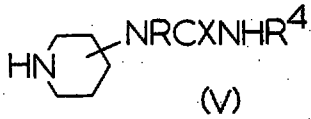
wherein R^1, R^2, R^3, A and X are as defined in connection with formula I with an amine of formula R^4NH_2 wherein R^4 is as defined in connection with formula I except hydrogen and acyl, or

c) reacting a compound of formula X



(X)

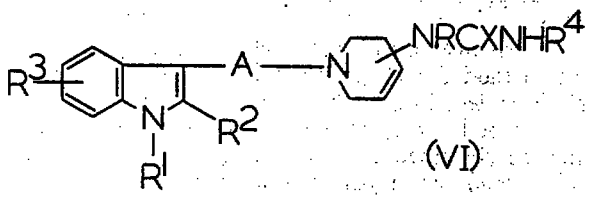
wherein R^1, R^2, R^3 and A are as defined in connection with formula I and Y is a halogen atom or an equivalent replaceable atom or radical such as an organic sulphonyl radical, with a compound of formula (V).



(V)

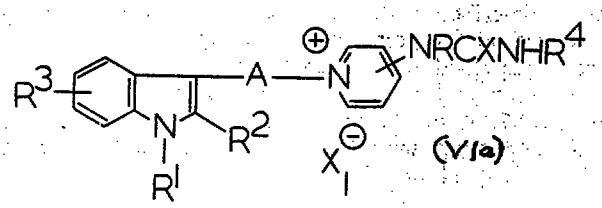
wherein R, R^4 and X are as defined in connection with formula I, or

d) reducing with alkali metal borohydride a compound of formula (VI)



(VI)

or (VIa)



(VIa)

wherein R, R^1, R^2, R^3, R^4 and A are as defined in connection with formula I and $X_1^{\ominus}$ is an anion, and if desired converting the product to an acid addition or quaternary ammonium salt.

31. A method as claimed in Claim 30, wherein X is oxygen and R^4 is as defined in Claim 6.

32. A method as claimed in Claim 30, wherein X is sulphur and R^4 is as defined in Claim 6.

33. A method as claimed in Claim 31 wherein a compound as claimed in any one of Claims 7 to 11 is prepared.

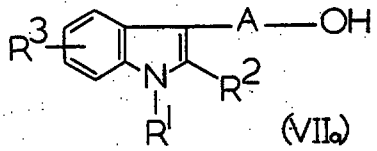
34. A method as claimed in Claim 32, wherein a compound as claimed in any one of Claims 7 to 11 is prepared.

35. A method as claimed in Claim 30, wherein a compound of formula I in which R^4 is acyl is prepared and subsequently hydrolysed to give a compound in which R^4 is hydrogen.

36. A method as claimed in Claim 35, wherein R^4 is an aroyl group.

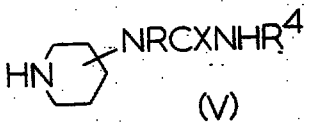
37. A modification of the method claimed in Claim 30 part (d) wherein a starting material of formula VI or VIa wherein X is oxygen is reduced by catalytic hydrogenation.

38. A method for preparing a compound as claimed in Claim 1, wherein X is oxygen which method comprises reacting a compound of formula (VIIa)



(VIIa)

wherein R^1, R^2 and R^3 are as defined in Claim 1, and A is an alkylene radical, with a compound of formula (V)

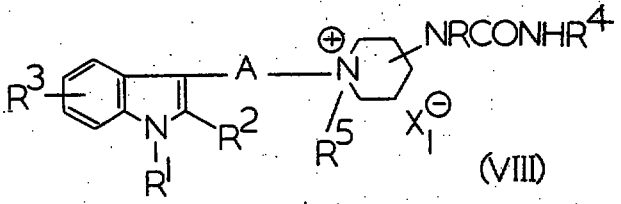


(V)

wherein X is oxygen in the presence of a Raney nickel catalyst.

39. A method as claimed in Claim 38, wherein R^4 is as defined in Claim 6.

40. A method for preparing a compound as claimed in Claim 1, wherein X is oxygen, which method comprises treating a compound of formula (VIII)



(VIII)

wherein R, R^1, R^2, R^3, R^4 and A are as defined in connection with formula I, R^5 is an aryl methyl radical and $X_1^{\ominus}$ is an anion, under mild conditions such as to remove the group R^5.

41. A method as claimed in Claim 40, wherein R^4 is as defined in Claim 6.

42. A method for preparing a compound as claimed in Claim 13, substantially as hereinbefore described with reference to any one of Examples 1 to 5.

43. A method for preparing a compound as claimed in Claim 13 substantially as hereinbefore described with reference to any one of Examples 6 to 9.

44. A method for preparing a compound as claimed in Claim 12 substantially as hereinbefore described with reference to any one of Examples 10 to 15.

45. A method for preparing a compound as claimed in Claim 6, substantially as hereinbefore described with reference to any one of Examples 17 to 21.

46. A compound whenever prepared by a method as claimed in any one of claims 30, 35, 37, 38 or 40.

47. A compound whenever prepared by a method as claimed in any one of claims 31, 33, 39, 41 or 42.

48. A compound whenever prepared by a method as claimed in Claim 32 or 43.

49. A compound whenever prepared by a method as claimed in any one of Claims 32, 34, 36, or 44.

50. A compound whenever prepared by a method as claimed in Claim 45.

51. A pharmaceutical composition comprising a compound as claimed in any one of Claims 1—5, and a pharmaceutically acceptable carrier.

52. A pharmaceutical composition as claimed in Claim 51 in unit dosage form.

53. A pharmaceutical composition as claimed in Claim 51 or Claim 52, when containing a compound as claimed in any one of Claims 6 to 12 or 28.

54. A pharmaceutical composition as claimed in Claim 51 or Claim 52, when containing a compound as claimed in any one of Claims 13 to 18 or 26.

55. A pharmaceutical composition as claimed in Claim 51 or Claim 52, when containing a compound as claimed in any one of Claims 19 to 21 or 27.

56. A pharmaceutical composition as claimed in Claim 51 or Claim 52, when containing a compound as claimed in any one of Claims 22 or 23.

57. A pharmaceutical composition as claimed in Claim 51 or Claim 52, when containing a compound as claimed in Claim 24, 25 or 29.

G. R. PORTER,
Chartered Patent Agent,
John Wyeth & Brother Limited,
Huntercombe Lane South,
Taplow,
Maidenhead,
Berkshire.

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