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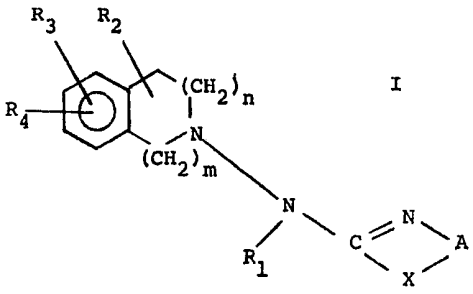
(54) N-substituted cyclic amines, their preparation and pharmaceutical compositions containing them

(57) This invention provides new compounds of formula I,



I

indicated for use as vasoconstricting agents.

In formula I:

X is an oxygen atom, a sulfur atom or a group NR_o, wherein R_o is hydrogen or alkyl of 1 to 4 carbon atoms,

A is ethylene, trimethylene or tetramethylene, when X is a group NR_o, optionally monosubstituted by alkyl of 1 to 4 carbon atoms, phenyl or phenyl mono- or independently disubstituted by alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms or halogen of atomic number of from 9 to 35,

R_1 is hydrogen, alkyl of 1 to 4 carbon atoms or alkenyl of 3 to 5 carbon atoms, wherein the double bond is other than in the position α to the nitrogen atom to which R_1 is bound,

R_2 is hydrogen or alkyl of 1 to 4 carbon atoms,

R_3 and R_4 independently are hydrogen, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, alkylthio of 1 to 4 carbon atoms or halogen of atomic number of from 9 to 35 and

either m is 0 and n is 1 or 2
or both m and n are 1

with the proviso that, when X is a group NR_o, A is unsubstituted, m is 0 and n is 1, then R_1 is other than hydrogen.

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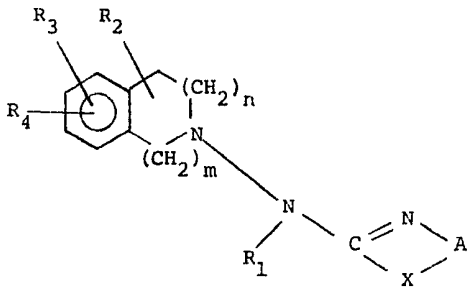
SPECIFICATION

N-substituted cyclic amines, their preparation and pharmaceutical compositions containing them

The present invention relates to N-substituted cyclic amines, their preparation and pharmaceutical compositions containing them.

In accordance with the invention, there are provided compounds of formula I,



I

wherein

X is an oxygen atom, a sulfur atom or a group NR_o, wherein R_o is hydrogen or alkyl of 1 to 4 carbon atoms,

A is ethylene, trimethylene or tetramethylene, when X is a group NR_o, optionally monosubstituted by alkyl of 1 to 4 carbon atoms, phenyl or phenyl mono- or independently disubstituted by alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms or halogen of atomic number of from 9 to 35,

R_1 is hydrogen, alkyl of 1 to 4 carbon atoms or alkenyl of 3 to 5 carbon atoms, wherein the double bond is other than in the position α to the nitrogen atom to which R_1 is bound,

R_2 is hydrogen or alkyl of 1 to 4 carbon atoms,

R_3 and R_4 independently are hydrogen, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, alkylthio of 1 to 4 carbon atoms, or halogen of atomic number of from 9 to 35 and

either m is 0 and n is 1 or 2

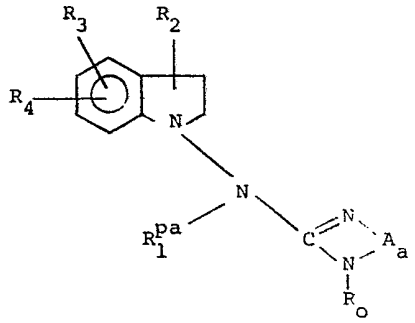
or both m and n are 1

with the proviso that, when X is a group NR_o, A is unsubstituted, m is 0 and n is 1, then R_1 is other than hydrogen.

X preferably is a sulfur atom or a group NR_o, especially a sulfur atom. A preferably is ethylene. A preferably is unsubstituted. When it is substituted, it preferably is substituted by alkyl. When it is substituted by phenyl, it preferably is substituted by unsubstituted phenyl. When phenyl is substituted, it preferably is monosubstituted. The substituent preferably is in the p-position. When phenyl is disubstituted, the substituents preferably are identical. When phenyl is disubstituted, the substituents preferably are in the m-, p-positions. When phenyl is substituted, it preferably is substituted by halogen. R_1 preferably is hydrogen. When it is other than hydrogen, it preferably is alkyl. When it is alkyl of more than 2 carbon atoms, it preferably is straight-chained. R_2 preferably is hydrogen. R_2 can be bound to any of the methylene groups present in the nitrogen-containing ring. It preferably is attached to a methylene group other than adjacent to the ring nitrogen atom. R_3 and/or R_4 preferably is hydrogen. When it is not hydrogen, it preferably is bound in a position on the phenyl ring adjacent to the fused nitrogen-containing ring. When R_3 and/or R_4 are other than hydrogen, they preferably are alkyl, alkoxy or halogen, especially alkyl or halogen. When they are both other than hydrogen, they preferably are identical. m preferably is 0. n preferably is 1.

Alkyl and/or alkoxy and/or alkylthio preferably is of 1 or 2, especially 1 carbon atom(s). Halogen preferably is chlorine or bromine, especially chlorine. Alkenyl preferably is of 3 carbon atoms.

A group of compounds of formula I is the compounds of formula Ipa



Ipa

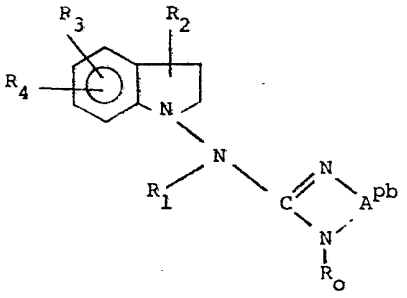
wherein

R_o, R_2, R_3, R_4 are as defined above

A_a is ethylene, trimethylene or tetramethylene and

R_1^{pa} is alkyl of 1 to 4 carbon atoms or alkenyl of 3 to 5 carbon atoms, wherein the double bond is other than in the position α to the nitrogen atom to which R_1^{pa} is bound.

Another group of compounds of formula I is the compounds of formula Ipb



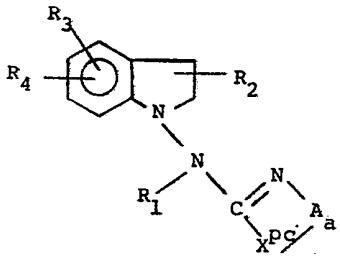
Ipb

wherein

R_o and R_1 to R_4 are as defined above and

A^{pb} is ethylene, timethylene or tetramethylene each monosubstituted by alkyl of 1 to 4 carbon atoms, phenyl or phenyl mono- or independently disubstituted by alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms or halogen of atomic number of from 9 to 35.

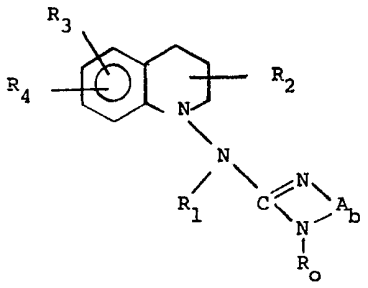
Another group of compounds of formula I is the compounds of formula Ipc



Ipc

wherein A_a and R_1 to R_4 are as defined above and X^{pc} is an oxygen or a sulfur atom.

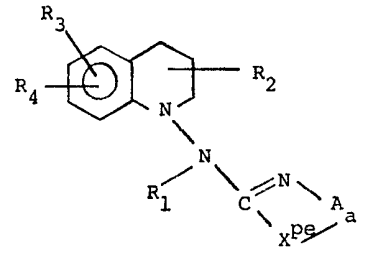
Another group of compounds of formula I is the compounds of formula Ipd



Ipd

wherein
R_o and R_1 to R_4 are as defined above and
A_b is ethylene, trimethylene or tetramethylene optionally monosubstituted by alkyl of 1 to 4 carbon atoms, phenyl or phenyl mono- or independantly disubstituted by alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms or halogen of atomic number of from 9 to 35.

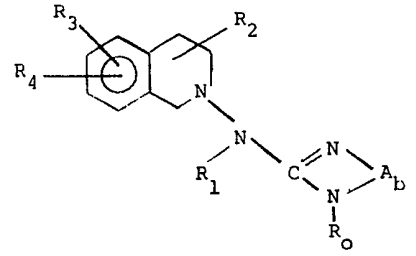
Another group of compounds of formula I is the compounds of formula Ipe



Ipe

wherein
A_a and R_1 to R_4 are as defined above and
X^{pe} is an oxygen or a sulfur atom.

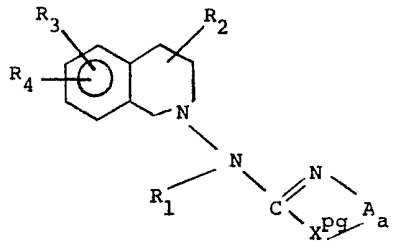
Another group of compounds of formula I is the compounds of formula Ipf



Ipf

wherein
A_b, R_o and R_1 to R_4 are as defined above.

Another group of compounds of formula I is the compounds of formula Ipg



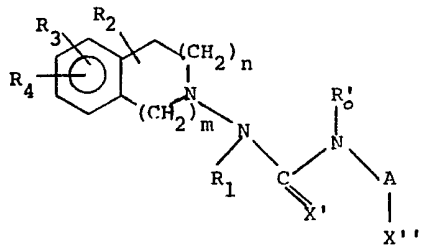
Ipg

wherein

A_a and R_1 to R_4 are as defined above and

X^{pg} is an oxygen or sulfur atom.

In accordance with the invention, a compound of formula I may be obtained by a process comprising cyclizing a corresponding compound of formula II,



II

wherein

A, R_1 to R_4, m and n are as defined above and

either

X′ is an oxygen or sulfur atom,

X″ is a leaving group and

R'_o is hydrogen

or

X′ together with a hydrogen atom is a leaving group,

X″ is a group $NR'_o{}'$ and

one of R'_o and $R'_o{}'$ is hydrogen and the other is hydrogen or alkyl of 1 to 4 carbon atoms, with the proviso that, when X″ is a group $NR'_o{}'$, A is unsubstituted, m is 0 and n is 1, then R_1 is other than hydrogen.

The process according to the invention may be effected in a manner analogous to known methods for cyclizing analogous amino derivatives.

When X′ together with a hydrogen atom is a leaving group, the reaction is preferably effected in an inert solvent such as methanol or ethanol, or, when the compound of formula VI (see below) is liquid at the reaction temperature, the reaction is conveniently effected in the absence of any additional solvent. The reaction is preferably effected in the presence of a mineral acid such as hydrochloric or hydroiodic acid. The reaction temperature may be from room temperature to about 150°C and is preferably at least 50°C, e.g. the boiling temperature of the reaction mixture.

When X′ is an oxygen atom, the reaction preferably is effected in water and when X′ is a sulfur atom, preferably in an organic solvent such as ether. The reaction temperature may be from room temperature to about 100°C, when X′ is a sulfur atom it preferably is room temperature.

When X′ together with a hydrogen atom is a leaving group, X′ is e.g. a group NR_a, wherein R_a is alkyl of 1 to 4 carbon atoms, especially methyl, or R_a is hydrogen.

When X″ is a leaving group, it is e.g. halogen or a group R_b–SO_2–O–, whrein R_b is phenyl, tolyl or lower alkyl, and especially X″ is then chlorine or bromine.

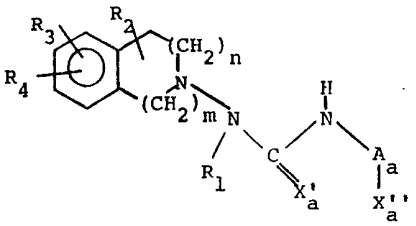
The compounds of formula I may be isolated and purified in accordance with known methods.

The compounds of formula I may be present in free base form, in the form of acid addition salts. Acid addition salt forms, for example, the hydrochloride or the hydrogen fumarate or maleate, may be produced from the free base form in known manner, and vice-versa.

The compounds of formula I may also be present in tautomeric form, i.e. with the double bond adjacent to the other nitrogen atom or to the X moiety, insofar this nitrogen atom or X moiety is not fully substituted. It is to be appreciated that such tautomeric forms also fall under the scope of formula I.

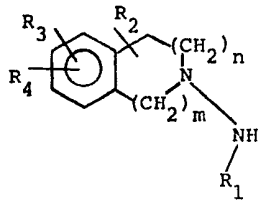
The production of the starting materials may be effected in a manner analogous to known methods.

A compound of formula IIa,



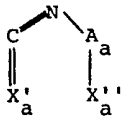
IIa

wherein R_1 to R_4, m and n are as defined above, and
X'_a is an oxygen or a sulfur atom,
X''_a is a leaving group and
A_a is as defined above, may e.g. be obtained by reacting a corresponding compound of formula III,



III

with a corresponding compound of formula IV,

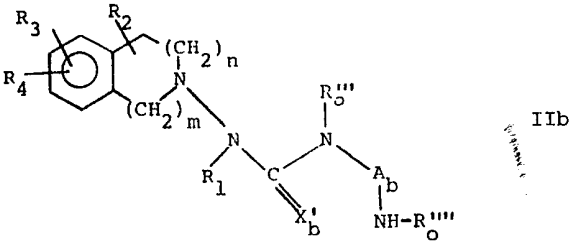


IV

preferably in a solvent such as ether, e.g. at a temperature of from about 0° to about 50°C, preferably at room temperature.

X'_a is identical to X'' when this is a leaving group. A compound of formula III wherein R_1 is other than hydrogen may be obtained by e.g. N-substituting a corresponding compound of formula III, wherein R_1 is hydrogen.

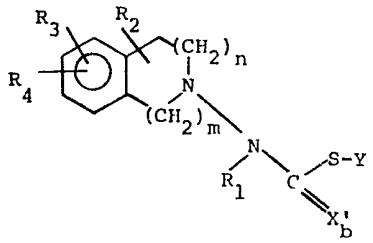
A compound of formula IIb,



IIb

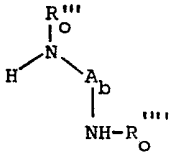
wherein
A_b, R_1 to R_4, m and n are as defined above,
X'_b together with a hydrogen atom is a leaving group and

one of R'_o'' and R'_o''' is hydrogen and the other is hydrogen or alkyl of 1 to 4 carbon atoms, with the proviso that, when A_b is unsubstituted,
m is O and
n is 1,
then R_1 is other than hydrogen, may e.g. be obtained by reacting a corresponding compound of formula V,



V

wherein the group S–Y is a leaving group, S being a sulfur atom, with a corresponding compound of formula VI,

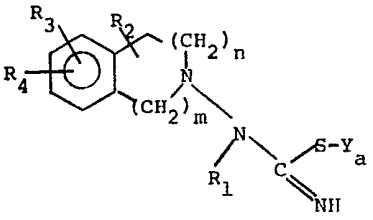


VI

The group X'_b is identical to X′ when this together with a hydrogen atom is a leaving group. Y may e.g. be alkyl of 1 to 4 carbon atoms, preferably methyl.

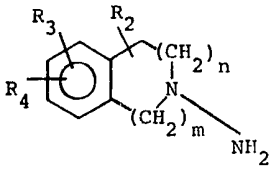
The reaction conditions for the preparation of a compound of formula IIa, particularly when X'_a is a sulfur atom, and of formula IIb may be chosen such as to be identical with the conditions for cyclization according to the invention. The compounds of formula III or V are then advantageously reacted with the compounds of formula IV or VI to give directly the correspondingly compounds of formula I, without intermediate isolation of the corresponding compounds of formula IIa or IIb.

A compound of formula Va,



Va

wherein
R_1, R_2, R_3, R_4, m and n are as defined above and
Y_a is alkyl of 1 to 4 carbon atoms,
may e.g. be obtained from a corresponding compound of formula VII,



VII

by optionally monosubstituting the primary amino moiety with an appropriate group R_1 to give a corresponding compound wherein R_1 is other than hydrogen, reacting this amine with benzoyl isothiocyanate, hydrolyzing the so obtained product to give a thiourea and S-alkylating the so-obtained thiourea.

The above-mentioned considerations on tautomerism may also apply mutatis mutandis to the starting materials described above and such tautomers are therefore also embraced by the formulae herein.

Insofar as the production of any starting material is not particularly described these compounds are known, or may be produced and purified in accordance with known processes, or in a manner analogous to processes described herein, or to known processes.

In the following Examples all temperatures are in degrees Centigrade and are uncorrected.

EXAMPLE 1: N-(4,5-Dihydrothiazol-2-yl)-2, 3-dihydro-IH-indole-1-amine

18.6 g of 2-bromoethylisothiocyanate diluted with 50 ml of ether are added dropwise under moderate cooling to a solution of 15 g of 1-amino-2,3-dihydro-IH-indole in 60 ml of either. The temperature raises from about 15° to about 21°. Stirring is maintained for 2 hours, a crystalline precipitate is formed. After decantation, the precipitate is dissolved in water, the solution is made alkaline with 10% sodium hydroxyde solution and extracted with methylene chloride. The organic phase is dried over magnesium sulfate and the solvent evaporated. The title compound is obtained (M.P. 177–178° after recrystallization from methylene chloride/petrol ether; M.P. of the hydrogen maleate 149–150°—from methanol/ethyl acetate).

EXAMPLE 2: 1-[N-(2-Imidazolin-2-yl) methylamino]-4-methylindoline

10 g of 1-(4-methylindolin-l-yl)-1,2-dimethylisothiourea hydroiodide are dissolved in 50 ml ethanol. 5–6 ml of ethylene diamine are added and the reaction mixture is heated for 10 hours under reflux. The reaction mixture is concentrated to dryness and then shaken with ethyl acetate and I N aqueous sodium hydroxide solution. The organic phase is dried over magnesium sulfate and then evaporated. The title compound is obtained (M.P. of the hydrochloride 259–260°—from methanol/ether).

The starting material is obtained as follows:

The urethane obtained by reacting 1-amino-4-methyl-indoline with chloroformic acid ethyl ester is reduced with lithium aluminium hydride in dioxan to 4-methyl-l-methylaminoindoline (M.P. of the hydrochloride 154–155°—from methanol/ether). Reaction of this product with benzoylisothiocyanate in boiling tetrahydrofuran followed by hydrolysis of the product with dilute sodium hydroxide solution for 30 minutes under reflux yields 1-(4-methylindolin-1-yl)-1-methylthiourea (M.P. 152–153°—from methanol). This thiourea is reacted with methyl iodide for 1 hour at reflux temperature. 1-(4-methylindolin-1-yl)-1,2-dimethyl-isothiourea hydroiodide (M.P. 193–195°——from methynol/ether) is obtained.

EXAMPLE 3: N-(4,5-Dihydrooxazol-2-yl)-2,3-dihydro-1H-indol-1-amine

The 1-(2-chloroethyl)-3-(2,3-dihydro-1H-indol-1-yl) urea obtained as described hereunder is suspended in 30 parts v/w of water and the mixture is heated to boiling for 30 minutes. The aqueous solution is then made alkaline with conc. aqueous ammonia solution and extracted with ethyl acetate. After drying of the organic phase over magnesium sulfate and evaporation of the solvent the title compound is obtained (M.P. of the hydrogen maleate 125–127°—from methanol/ethyl acetate).

The starting material is obtained as follows: 1.95 g of 2-chloroethylisocyanate diluted with 15 ml ether is added dropwise under stirring to a solution of 2.5 g of 1-amino-2,3-dihydro-1H-indole in 15 ml ether. Temperature rises to about 35°. Stirring is maintained for 2 hours, a precipitate is formed. After decantation and recrystallization from ether, 1-(2-chloroethyl)-3-(2,3-dihydro-1H-indol-1-yl) urea is obtained (M.P. 103–104°).

The following compounds of formula I may be obtained in analogous manner:

Example No.	Analogous to Ex. No.	R_1	R_2	R_3	R_4	m	n	A	X	M.P.	
4	2	H	H	4-Me	H	O	1	methylethylene	NH	hnl	123–124°
5	2	H	H	H	H	O	1	(3,4-dichloro phenyl)ethylene	NH	hfu	181–183°
6	2	H	H	5-Cl	H	O	1	phenylethylene	NH	hfu	209–210°
7	2	H	H	H	H	O	2	ethylene	NH	hml	140–142°
8	3	H	H	H	H	O	2	ethylene	O	b	146–147°
9	2	H	H	H	H	1	1	ethylene	NH	hml	134–135°

b = in free base form
hfu = in hydrogen fumarate form
hml = in hydrogen maleate form

The compounds of formula I possess pharmacological activity.

They possess vasoconstricting activity, as indicated by standard tests, e.g. *in vivo* in rats treated in accordance with the principles of J.S. Gillespie and T.C. Muir, *Br. J. Pharmac. Chemother.* (1967), *30*, 78–87): a pressor effect is elicited following i.v. administration of from about 0.02 to about 50 μg/kg, particularly of from about 0.02 to about 0.5 μg/kg of the compounds.

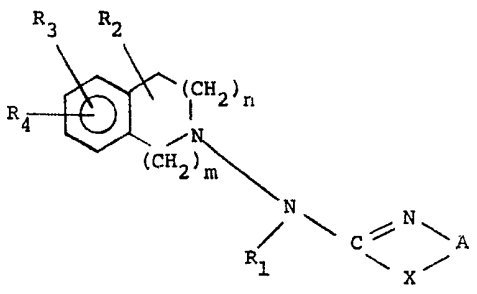
The compounds are therefore indicated for use as vasoconstricting agents, e.g. for the prophylaxis and treatment of vascular headaches such as migraine, and of orthostatic disorders such as orthostatic hypotension and its symptoms, such as vertigo. For this use an indicated daily dose is from about 0.02 to about 50 μg, conveniently given in divided doses 2 to 4 times a day in unit dosage form containing from about 0.0005 to about 0.5 mg, or in sustained release form.

The compounds of formula I may be administered in pharmaceutically acceptable acid addition salt form. Such acid addition salt forms exhibit the same order of activity as the free base forms, and are readily prepared in conventional manner. The present invention also provides a pharmaceutical composition comprising a compound of formula I, in free base form or in pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent. Such compositions may be in the form of, for example, a solution or a tablet. They can be prepared according to known methods.

The vasoconstricting activity of the compound of Example 1 is especially interesting.

CLAIMS

1. A process for the production of a compound of formula I,



I

wherein

X is an oxygen atom, a sulfur atom or a group NR_o, wherein R_o is hydrogen or alkyl of 1 to 4 carbon atoms,

A is ethylene, trimethylene or tetramethylene, when X is a group NR_o, optionally monosubstituted by alkyl of 1 to 4 carbon atoms, phenyl or phenyl mono- or independently disubstituted by alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms or halogen of atomic number of from 9 to 35,

R_1 is hydrogen, alkyl of 1 to 4 carbon atoms or alkenyl of 3 to 5 carbon atoms, wherein the double bond is other than in the position α to the nitrogen atom to which R_1 is bound,

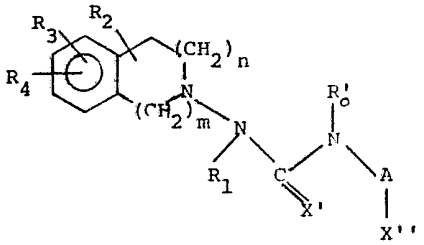
R_2 is hydrogen or alkyl of 1 to 4 carbon atoms,

R_3 and R_4 independently are hydrogen, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, alkylthio of 1 to 4 carbon atoms or halogen of atomic number of from 9 to 35 and

either m is 0 and n is 1 or 2

or both m and n are 1

with the proviso that, when X is a group NR_o, A is unsubstituted, m is 0 and n is 1, then R_1 is other than hydrogen, which comprises cyclizing corresponding a compound of formula II,



II

wherein
A, R_1 to R_4, m and n are as defined above and
either
X′ is an oxygen or sulfur atom,
X″ is a leaving group and
R_o is hydrogen
or
X′ together with a hydrogen atom is a leaving group,
X″ is a group NR_o' and
one of R_o' and R_o' is hydrogen and the other is hydrogen or alkyl of 1 to 4 carbon atoms, with the proviso that, when X″ is a group NR_o', A is unsubstituted, m is 0 and n is 1, then R_1 is other than hydrogen.

2. A process for the production of a compound as defined in claim 1, substantially as hereinbefore described with reference to any one of the Examples.

3. A compound as defined in claim 1, whenever produced by a process according to claim 1.

4. A compound as defined in claim 1.

5. A compound of claim 4, wherein X is a sulfur atom.

6. A compound of claim 4, wherein X is a group NR_o as defined in claim 1.

7. A compound of claim 4, wherein A is unsubstituted ethylene.

8. A compound of claim 4, wherein R_1 is hydrogen.

9. A compound of claim 4, wherein R_2 is hydrogen.

10. A compound of claim 4, wherein R_3 and R_4 are hydrogen.

11. A compound of claim 4, wherein R_3 is halogen and R_4 is hydrogen.

12. A compound of claim 4, wherein R_3 and R_4 are both halogen.

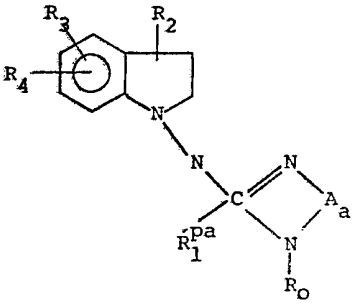
13. A compound of claim 4, wherein R_3 is alkyl and R_4 is hydrogen.

14. A compound of claim 4, wherein m is 0 and n is 1.

15. A compound of claim 4, wherein m is 0 and n is 2.

16. A compound of claim 4, wherein m and n are 1.

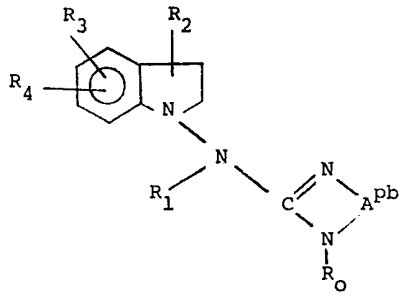
17. A compound of claim 4 of formula Ipa,



Ipa

wherein
R_o and R_2 to R_4 are as defined in claim 1,
A_a is ethylene, trimethylene or tetramethylene and
R_1^{pa} is alkyl of 1 to 4 carbon atoms or alkenyl of 3 to 5 carbon atoms, wherein the double bond is other than in the position α to the nitrogen atom to which R_1^{pa} is bound.

18. A compound of claim 4 of formula Ipb,



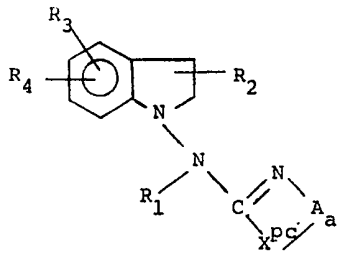
Ipb

wherein

R_o and R_1 to R_4 are as defined in claim 1 and

A^{pb} is ethylene, trimethylene or tetramethylene each mono-substituted by alkyl of 1 to 4 carbon atoms, phenyl or phenyl mono- or independently disubstituted by alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms or halogen of atomic number of from 9 to 35.

19. A compound of claim 4 of formula Ipc,



Ipc

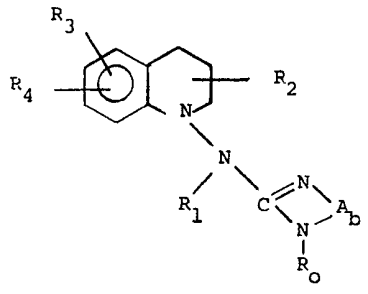
wherein

A_a is as defined in claim 17,

R_1 to R_4 are as defined in claim 1 and

X^{pc} is an oxygen or a sulfur atom.

20. A compound of claim 4 of formula Ipd,



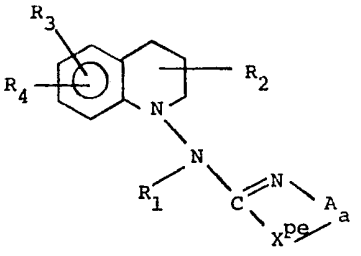
Ipd

wherein

R_o and R_1 to R_4 are as defined in claim 1 and

A_b is ethylene, trimethylene or tetramethylene optionally monosubstituted by alkyl of 1 to 4 carbon atoms, phenyl or phenyl mono- or independently disubstituted by alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms or halogen of atomic number of from 9 to 35.

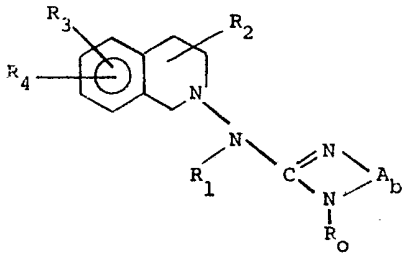
21. A compound of claim 4 of formula Ipe,



Ipe

wherein
A_a is as defined in claim 17,
R_1 to R_4 are as defined in claim 1 and
X^{pe} is an oxygen or a sulfur atom.

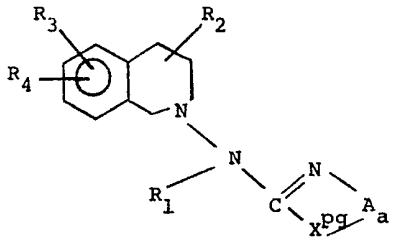
22. A compound of claim 4 of formula Ipf,



Ipf

wherein
A_b is as defined in claim 20 and
R_o and R_1 and R_4 are as defined in claim 1.

23. A compound of claim 4 of formula Ipg,



Ipg

wherein
A_a is as defined in claim 17,
R_1 to R_4 are as defined in claim 1 and
X^{pg} is an oxygen or a sulfur atom.

24. The compound of claim 4, which is N-(4,5-dihydrothiazol-2-yl)-2,3-dihydro-1H-indole-1-amine.

25. The compound of claim 4, which is 1-[N-(2-imidazolin-2-yl)-methylamino]-4-methyl-indoline.

26. A compound of claim 4, wherein R_1, R_2 and R_4 are hydrogen.

27. A compound of claim 26, wherein m is 0 and n is 1.

28. A compound of claim 26, wherein m is 0 and n is 2.

29. A compound of claim 26, wherein m and n are 1.

30. The compound of claim 27, wherein R_3, A and X are, respectively, 4-Me, methylethylene and NH.

31. The compound of claim 27, wherein R_3, A and X are, respectively, hydrogen, (3,4-dichlorophenyl)-ethylene and NH.

32. The compound of claim 27, wherein R_3, A and X are, respectively, 5-Cl, phenylethylene

and NH.

33. The compound of claim 27, wherein R_3, A and X are, respectively, hydrogen, ethylene and an oxygen atom.

34. The compound of claim 28, wherein R_3, A and X are, respectively, hydrogen, ethylene and NH.

35. The compound of claim 28, wherein R_3, A and X are, respectively, hydrogen, ethylene and an oxygen atom.

36. The compound of claim 29, wherein R_3, A and X are, respectively, hydrogen, ethylene and NH.

37. A compound according to any one of claims 3 to 36, in free base form.

38. A compound according to any one of claims 3 to 36, in acid addition salt form.

39. A pharmaceutical composition comprising a compound according to any one of claims 3 to 36 in free base form or in pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent.

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