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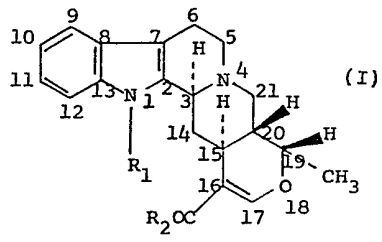
(54) **Novel oxayohimbane derivatives useful in therapy**

(57) Oxayohimbane derivatives of the formula



(I)

in which R_1 is a hydrogen, alkoxycarbonyl, alkoxycarbonylalkyl or alkylcarbonyl or a phenoxycarbonyl radical in which the phenyl radical thereof is unsubstituted or is substituted by a halogen atom or a nitro radical and R_2 is a hydroxyl or OM radical, M representing an alkali metal or alkaline earth metal, or is an alkoxy, cycloalkylalkoxy, cycloalkoxy, —NH_2, alkylamino, dialkylamino or cycloalkylamino radical, with the exception of the compounds in which simultaneously R_1 is H and R_2 is CH_3O or OH, in which definitions alkoxy and alkyl have from 1 to 4 carbon atoms, and cycloalkyl has from 3 to 6 carbon atoms, and their pharmaceutically acceptable acid addition salts, which are useful in therapy for combatting behavioural disorders and epileptic vertigo, can be prepared from raubasine by known methods.

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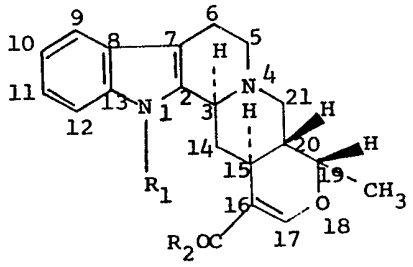
SPECIFICATION

Oxayohimbane derivatives useful in therapy and their preparation

The present invention relates to oxayohimbane derivatives useful in therapy and their preparation.

The present invention provides oxayohimbane derivatives which are compounds of general formula (I)

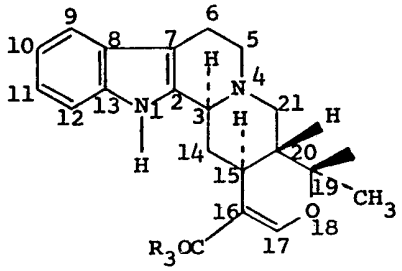


(I)

in which R_1 is a hydrogen atom, or an alkoxycarbonyl, alkoxycarbonylalkyl or alkylcarbonyl radical or a phenoxycarbonyl radical in which the phenyl radical thereof is unsubstituted or is substituted by a halogen atom or a nitro radical and R_2 is a hydroxyl or OM radical, M representing an alkali metal or alkaline earth metal, or is an alkoxy, cycloalkylalkoxy, cycloalkoxy, —NH_2, alkylamino, dialkylamino or cycloalkylamino radical, with the exception of the compounds in which simultaneously R_1 is H and R_2 is CH_3O or OH, in which definitions the R_2 alkoxy radical and the alkyl and alkoxy parts of said radicals R_1 and R_2 have from 1 to 4 carbon atoms, and the cycloalkyl part of said radicals has from 3 to 6 carbon atoms, and their pharmaceutically acceptable acid addition salts.

In the above compounds the alkyl and alkoxy radicals and parts of radicals can have a straight or branched chain, the straight chain being preferred. The preferred compounds of the invention are those in which R_1 is an alkoxycarbonyl radical or an alkoxycarbonylalkyl radical. Methoxycarbonyl is the most preferred.

The oxayohimbane derivatives can be prepared by a process which comprises (i) subjecting raubasine or its corresponding acid or a reactive derivative of such an acid, of formula:



(II)

in which R_3 is methoxy to transesterification or in which R_3 is hydroxy or a reactive radical to esterification, respectively, with an alcohol of formula R_2H (III) where R_2 is ethoxy, propoxy or butoxy, or cycloalkylalkoxy or cycloalkoxy as defined in formula (I), to produce a compound of formula (I) in which R_1 is hydrogen and R_2 is as defined in formula (III), (ii) amidifying a compound of formula (II) in which R_3 is hydroxy or a reactive radical with ammonia, an alkylamine, dialkylamine or cycloalkylamine, the alkyl and cycloalkyl radicals thereof being as defined in formula (I) to give a compound of formula (I) in which R_1 is hydrogen and R_2 is NH_2, alkylamino, dialkylamino or cycloalkylamino, respectively, or (iii) reacting a compound of formula (I) in which R_1 is hydrogen or a compound of formula (II) in which R_3 is hydroxy or methoxy with a strong base and a halide of formula R_1X, R_1 being as defined in formula (I), other than hydrogen, and X being a halogen atom, to produce a compound of formula (I) in which R_1 is other than hydrogen, and if desired forming a pharmaceutically acceptable acid addition salt of a compound of formula (I) thus prepared, or a free base of formula (I) from a said pharmaceutically acceptable salt thereof thus prepared.

Where it is necessary to carry out an esterification, transesterification or amidation to produce the desired radical R_2 and it is also necessary to produce a compound in which R_1 is other than hydrogen, the reactions can be carried out in either order (provided, of course, that reasonable reagents and conditions are chosen, e.g. to avoid hydrolysis of an ester when reacting the compound of formula (I) with a strong base in introducing the radical R_1).

The esterification reactions can be carried out by a conventional method, in particular either by direct esterification of the acid or a functional derivative preferably the acid chloride, with the alcohol R_2H (as such or as an alkali metal salt) or by transesterification of raubasine. The amides can be obtained from the corresponding acid or from one of its functional derivatives, by conventional

amidification. The compounds carrying a radical R_1 other than hydrogen can be obtained from the compounds in which R_1 is H by abstracting a proton at the 1- position N-atom (forming an anion of the compound of formula (I)) for example by reacting the starting compound, in solution in e.g. dimethylformamide, with sodium hydride, and then adding the halide R_1X (X is preferably chlorine or bromine).

The reaction can be carried out at a temperature of 0 to 20°C. The starting compounds of formula (II) are raubasine (ajmalicine) its corresponding acid, or a reactive derivative thereof effective for ester or amide formation. Raubasine can be obtained by reduction of the quanternary base serpentine, e.g. by catalytic hydrogenation or an alkyli metal borohydride, to give the tetrahydrogenated compound, raubasine, which is a methyl ester. The corresponding acid can then be obtained by saponification of raubasine.

The following Examples illustrate the invention. The analyses and the IR and NMR spectra confirm the structure of the compounds.

EXAMPLE 1

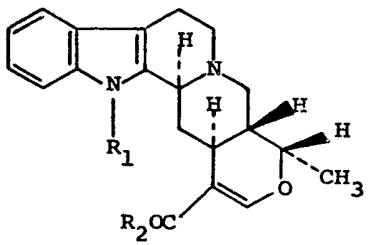
Methyl 1-ethoxycarbonylmethyl-16,17-didehydro-19α-methyl-oxayohimbane-16-carboxylate, formula I: $R_1 = CH_2COOCH_2CH_3$, $R_2 = CO_3O$, compound 6

1.8 g of sodium hydride are added, whilst stirring and under argon, to 6 g of raubasine (ajmalicine), dissolved in 100 ml of dry dimethylformamide. After 50 minutes, 3.7 ml of ethyl chloroacetate are added in the course of 10 minutes with the aid of a dropping funnel, whilst stirring, under argon and at a temperature in the region of +10°C. After 20 minutes, a precipitate is formed. 500 ml of water are then added and the precipitate is filtered off. The precipitate is dissolved in 200 ml of methylene chloride. The solution is washed with water, dried over sodium sulphate and evaporated to dryness. The title compound crystallises from methanol, m.p. = 203°C $[\alpha]_D^{25} = -116.6°$ ($c = 1$; $CHCl_3$).

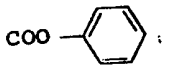
EXAMPLE 2

Oxayohimbane derivatives which have been prepared similarly are summarised in the following Table, which also includes the derivative prepared in Example 1.

TABLE



(I)

Compound	R_1	R_2	Form	Melting point (°C)	$[\alpha]_D^{25}$
1	$COCH_3$	CH_3O	HCl	276	-176.8° (c=0.2; pyridine-CH_3OH 1:1)
2	$COOCH_3$	CH_3O	HCl	228	-155.4° (c=0.3; $CHCl_3$)
3	$COOC_2H_5$	CH_3O	HCl	260	–
4	$COOC_3H_7(n)$	CH_3O	HCl	251	-155° (c=0.6; $CHCl_3$–CH_3OH 1:1)
5		CH_3O	HCl	279	-145° (c=0.2; $CHCl_3$–CH_3OH 1:1)
6	$CH_2COOC_2H_5$	CH_3O	Base	203	-116.6° (c=1; $CHCl_3$)
7	H	C_4H_9O	HCl	300	-9.5° (c=0.8; CH_3OH)
8	$COOCH_3$	C_4H_9O			
9	H	NHC_2H_5	HCl	267–8	-28.7 (c=1.7; CH_3OH)
10	$COOCH_3$	NHC_2H_5	Base	168–9	-192.7 (c=0.7; CH_3OH)
11	H	$N(CH_3)_2$			
12	$COOCH_3$	$N(CH_3)_2$			
13	$COOC_4H_9(n)$	$N(CH_3)_2$			

The above salts are converted to corresponding free bases and vice-versa, in manner known *per se*.

The oxayohimbane derivatives were subjected to pharmacological experiments.

The toxicity of the compounds was determined by intraperitoneal administration to mice. The LD 50 varies from 300 to 1,000 mg/kg.

The compounds were also subjected to the test for the anoxia caused by pressure reduction. Mice of the CDI strain were kept in an oxygen-depleted atmosphere produced by creating a partial vacuum (190 mm of mercury, corresponding to 5.25% of oxygen). The survival time of the animals was noted. This time is increased by agents which are capable of assisting the oxygenation of tissues and in particular of the brain. The compounds studied were administered intraperitoneally in several doses, 10 minutes before the experiment. The percentage increases in the survival time, relative to the values obtained for control animals, were calculated. The mean active dose (MAD), that is to say the dose which increases the survival time by 100%, was determined graphically. The MAD of the compounds of the invention varies from 10 to 60 mg/kg, when administered intraperitoneally.

These pharmacological studies show that they are active in the test for the anoxia caused in mice by pressure reduction, whilst being only slightly toxic.

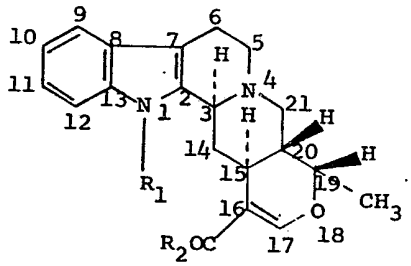
The oxayohimbane derivatives possess an anti-anoxia action, and can therefore be used in therapy (especially human therapy) for the treatment of vigilance disorders, in particular for combatting behavioural disorders which can be attributed to cerebral vascular damage and to the cerebral sclerosis encountered in geriatrics, and also for the treatment of epileptic vertigo due to cranial traumatisms, and the treatment of depression.

The said oxayohimbane derivatives can be administered as a pharmaceutical composition containing the oxayohimbane derivative defined above as active principle, in asociation with any excipient which is suitable for its administration, in particular oral or parenteral administration.

The methods of administration can be oral and parenteral. The daily posology can range from 10 to 200 mg.

CLAIMS:—

1. Oxayohimbane derivatives which are compounds of general formula (I)



(I)

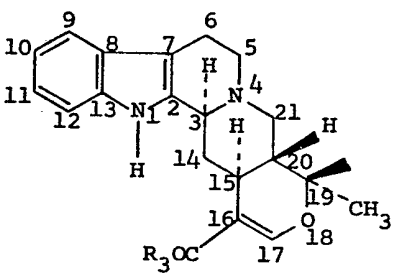
in which R_1 is a hydrogen atom, or an alkoxycarbonyl, alkoxycarbonylalkyl or alkylcarbonyl radical or a phenoxycarbonyl radical in which the phenyl radical thereof is unsubstituted or is substituted by a halogen atom or a nitro radical and R_2 is a hydroxyl or OM radical, M representing an alkali metal or alkaline earth metal, or is an alkoxy, cycloalkylalkoxy, cycloalkoxy, —NH_2, alkylamino, dialkylamino or cycloalkylamino radical, with the exception of the compounds in which simultaneously R_1 is H and R_2 is CH_3O or OH, in which definitions the R_2 alkoxy radical and the alkyl and alkoxy parts of said radicals R_1 and R_2 have from 1 to 4 carbon atoms, and the cycloalkyl part of said radicals has from 3 to 6 carbon atoms, and their pharmaceutically acceptable acid addition salts.

2. Derivatives according to Claim 1, wherein R_1 is a said alkoxycarbonyl or alkoxycarbonylalkyl radical.

3. Derivatives according to Claim 1, wherein R_1 is a hydrogen atom, a said phenoxycarbonyl radical or a said alkylcarbonyl radical.

4. As oxayohimbane derivatives according to Claim 1, methyl 1-methoxycarbonyl-16,17-didehydro-19α-methyl-16-carboxylate and its pharmaceutically acceptable acid addition salts.

5. A process for the preparation of oxayohimbane derivatives claimed in Claim 1, which process comprises (i) subjecting raubasine or its



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7. Oxayohimbane derivatives according to claim 1 when prepared by a process claimed in Claim 6.

8. A pharmaceutical composition comprising an oxayohimbane derivative claimed in any one of Claims 1 to 5 or in Claim 7, in association with a pharmaceutically acceptable excipient.

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