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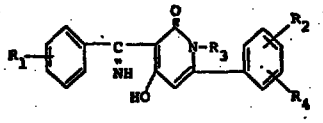
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(54) 3-(α-IMINOBENZYL)-4-HYDROXY-2(1H)-PYRIDONE DERIVATIVES

(71) We, SANDOZ LTD., of 35 Lichtstrasse, 4002 Basle, Switzerland, a Swiss Body Corporate, 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 3 - (α - iminobenzyl) - 4 - hydroxy - 2(1H) - pyridone derivatives.

More particularly, this invention provides compounds of formula I,



I

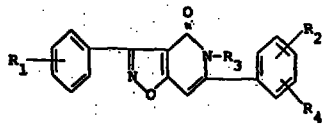
in which

R_1, R_2 and R_4, which may be the same or different, each signifies hydrogen, fluorine, chlorine, trifluoromethyl or alkyl or alkoxy of 1 to 4 carbon atoms, and

R_3 is alkyl of 1 to 4 carbon atoms,

provided that when R_1, R_2 and R_4 are each hydrogen, then R_3 is other than methyl.

The invention also provides a process for the production of compounds of formula I, comprising reducing a compound of formula II,



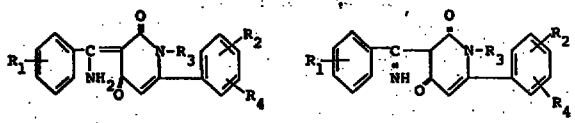
II

in which R_1, R_2, R_3 and R_4 are as defined above, in an inert organic solvent.

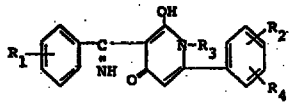
The process may be effected in conventional manner, for example by catalytic hydrogenation. Suitable catalysts include palladium on carbon, platinum oxide and Raney nickel, preferably palladium on carbon. An inert organic solvent, such as a C_{1-4} alkanol, e.g. methanol or, preferably ethanol, is suitably employed. The hydrogenation is conveniently effected at a temperature of from 10° to 50°C, preferably 20° to 30°C, and the reaction time may vary, for example from 1 to 10 hours, more usually 2 to 3 hours.

The resulting compounds of formula I may be isolated and purified using conventional techniques. Where required, free hydroxy forms of the compounds may be converted into base salt forms in conventional manner, and *vice versa*.

As will be appreciated, the compounds of formula I may exist in tautomeric forms of formulae Ia, Ib and Ic,



Ia Ib

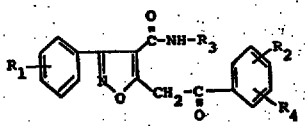


Ic

in which R_1, R_2, R_3 and R_4 are as defined above.

While reference is made above and hereinafter solely to the form of formula I, or the corresponding chemical name, it is to be understood that the invention is not intended to be limited to, or to the production or use of, any particular form of the compounds.

The compounds of formula II may be produced by cyclising a compound of formula III,



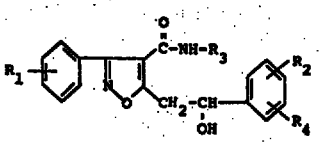
III

in which R_1, R_2, R_3 and R_4 are as defined above, in the presence of an acid and a solvent.

The cyclisation may be effected in conventional manner, for example by treatment of the compound of formula III with an acid, such as hydrochloric, *p*-toluenesulphonic, polyphosphoric or, preferably, sulphuric acid, and suitably in an inert solvent, such as an aromatic hydrocarbon, e.g. benzene or toluene. Preferably, however, an excess of the acid may be employed to provide the reaction medium. The process is suitably effected at a temperature of from 80° to 150°C, preferably at the reflux temperature of the reaction mixture, and the reaction time may, for example, vary from 12 to 36, more usually 20 to 36 hours.

The resulting compounds of formula II may be isolated and purified using conventional techniques.

The compounds of formula III may be produced by oxidising a compound of formula IV,



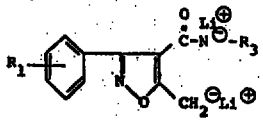
IV

in which R_1, R_2, R_3 and R_4 are as defined above.

The oxidation may be effected in conventional manner, for example with potassium permanganate or, preferably, chromium trioxide, and under aqueous acidic conditions. The preferred acids include mineral acids, such as sulphuric or hydrochloric acid and, preferably, organic acids, in particular acetic acid. The reaction temperature is conveniently from 10° to 50°C, preferably from 20° to 30°C, and the reaction time may, for example, vary from 1 to 5, more usually 1.5 to 2.5 hours.

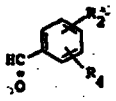
The resulting compounds of formula III may be isolated and purified using conventional techniques.

The compounds of formula IV may be produced by reacting a compound of formula V,



V

in which R_1 and R_3 are as defined above, with a compound of formula VI,



VI

in which R_2 and R_4 are as defined above, in an inert organic solvent.

The reaction is suitably effected at a temperature of from −75° to −55°C, preferably −65° to −60°C and suitable solvents include aliphatic hydrocarbons, such as pentane, hexane and heptane, and, preferably, ethers, such as diethyl ether or, in particular, tetrahydrofuran. The reaction time may, for example, vary from 1 to 5, particularly 2.5 to 3.5 hours. The compounds of formula V are desirably produced *in situ* in conventional manner from the corresponding 3 - phenyl - N - alkyl - 5-methyl - isoxazole - 4 - carboxamide by reaction with, for example, a C_{1-4} alkyl lithium, particularly *n*-butyllithium under the conditions, for example, of the subsequent step for producing compounds IV.

The resulting compounds of formula IV may be isolated and purified using conventional techniques.

The compounds of formula VI and the necessary starting materials for producing compounds of formula V are either known or may be produced in conventional manner from available materials.

The compounds of formulae III and IV are disclosed and claimed in our copending Application No. 38668/78, U.K. Specification No. (Serial No. 1 545 577).

The compounds of formula I possess pharmacological activity. In particular, they possess sleep inducing and minor tranquillising activity as indicated 1) by the hexobarbital reinduction method of Winter, J. Pharmacol. and Exp. Therap. *94* 7—11, (1948); 2) by their ability to produce docility in behaviour tests in mice given 25 to 200 mg/kg of animal body weight, i.p., of the test compound according to the 30-word adjective check sheet system basically as described by Irwin S. (Gordon Research Conference, Medicinal Chemistry, 1959) and Chen [Symposium on Sedative and Hypnotic Drugs, Williams and Wilkins, (1954)]; 3) by their ability to antagonize chlonic convulsions and death in mice given about 35 mg/kg of the test compound followed immediately by 45 to 250 mg/kg, i.p., of N-sulfamoylazepine; and 4) by scoring for loss of righting reflex according to the method of Reed-Muench ([American Journal of Hygiene *27*, 493—497, (1938)], in which mice are administered 12.5 mg/kg, i.p., of Thoridazine, immediately after which the test compound is administered at dosages of 5 to 100 mg/kg in a volume of 0.1 ml/10 g of body weight. Sixty minutes after dosing, the mice are scored for loss of righting reflex; and 5) by their ability to reduce conflicts as defined in the Geller Conflict Test [Irving Geller, Psychopharmacologia, I, 42—492 (1960)].

The compounds of formula I are therefore indicated for use as sleep inducers and minor tranquillisers. For the sleep-inducing indication, an indicated suitable daily dosage is from 35 to 1000 mg, which may be administered in divided doses of from about 8 to 500 mg, two to four times daily, but which is preferably administered as a single dose at bed-time. For the minor tranquillising activity, an indicated suitable daily dosage is from 30 to 1500 mg, suitably administered in divided dosages of from 7.5 to 750 mg, two to four times daily, or in retard form.

The compounds may be administered in free hydroxy form or in the form of pharmacologically acceptable base salts, which salt forms have the same order of activity as the free forms. Suitable salt forms include alkali metal forms, in particular lithium, sodium and potassium salt forms, and alkaline earth metal forms, in particular magnesium or calcium salt forms.

The compounds may be admixed with conventional pharmaceutically acceptable diluents and carriers, and, optionally, other excipients, and administered in such forms as hard-filled capsules and tablets.

The preferred compounds of formula I are those in which R_1 to R_4 have the following significances:—

R_1=hydrogen, chlorine, fluorine, trifluoromethyl, methyl or methoxy, particularly hydrogen or chlorine, more particularly hydrogen;

R_2=hydrogen;

R_4=hydrogen, chlorine, fluorine, trifluoromethyl, methyl, or methoxy, particularly hydrogen, chlorine, trifluoromethyl, methyl or methoxy;

R_3=methyl.

More preferred compounds are those having a combination of the above preferred significances.

The following Example 2 illustrates the invention. Example 1 is included as a description of the procedure employed in Example 2. The compound of Example 1 is disclosed and claimed in our co-pending Application No. 38667/78, U.K. Specification (Serial No. 1 545,576).

EXAMPLE 1:

3-(α-Iminobenzyl)-4-hydroxy-6-phenyl-1-methyl-2(1H)-pyridone

a) *3 - Phenyl - 5 - (β - hydroxyphenethyl) - N - methylisoxazole - 4 - carboxamide* [compound IV]

A suspension of 75 g (0.348 mole) of 3 - phenyl - 5,N - dimethyl - isoxazole-4 - carboxamide and 1 liter of tetrahydrofuran is cooled to −65°C and 478 ml of 1.6M *n*-butyllithium in hexane (0.765 mole) is added, dropwise, maintaining the temperature between −60° and −70°C. After the addition is complete, the orange suspension is stirred for 1½ hours at −60° to −70°C, and then 37.2 g (0.350 mole) of benzaldehyde in 375 ml of tetrahydrofuran is added, dropwise, maintaining the temperature between −60° and −70°C. After addition is complete, the mixture is stirred for 1½ hours at −60° to −70°C and then warmed to −30°C and quenched by the addition of saturated ammonium chloride solution. The mixture is further diluted with tetrahydrofuran and the layers are separated. The tetrahydrofuran layer is washed twice with 50% brine, and once with brine, dried over anhydrous magnesium sulphate, filtered, and evaporated *in vacuo*. The solid residue is triturated with a 50:50 mixture of ether/petroleum ether, filtered and washed with cold ether to give the heading compound, m.p. 183°—184°C.

b) *N - Methyl - 5 - phenacyl - 3 - phenylisoxazole - 4 - carboxamide* [compound III]

A suspension of 50 g (0.155 mole) of 3 - phenyl - 5 - (β - hydroxyphenethyl)-N - methyl - isoxazole - 4 - carboxamide and 800 ml of acetic acid, at room temperature, is treated, dropwise, with 18.4 g (0.185 mole) of chromium trioxide in 185 ml of water. The resulting solution is stirred for 2 hours at room temperature and a portion of the acetic acid is removed *in vacuo*. The remainder is poured onto ice water and extracted with methylene chloride. The methylene chloride layer is washed with 2N sodium hydroxide, dried over anhydrous magnesium sulphate, filtered and evaporated *in vacuo*. The solid residue is triturated with hot ether, cooled to 0°C and filtered to give the heading compound, m.p. 125°—128°C.

c) *5 - Methyl - 3,6 - diphenyl - isoxazolo[4,5-c]pyridin - 4 (5H) - one* [compound II]

A mixture of 26.1 g (0.0815 mole) of N - methyl - 5 - phenacyl - 3 - phenyl-isoxazole - 4 - carboxamide and 261 ml of 2M sulphuric acid is refluxed for 24 hours. The mixture is cooled and extracted with methylene chloride. The methylene chloride layer is washed with water and then brine, dried over anhydrous magnesium sulphate, filtered and evaporated *in vacuo*. The residue is triturated with ether and then recrystallised from ethanol to give the heading compound, m.p. 149—151.5°C.

d) *3 - (α - Iminobenzyl) - 4 - hydroxy - 6 - phenyl - 1 - methyl - 2(1H) - pyridone* [compound I]

A mixture of 16.5 g (0.0545 mole) of N - methyl - 3,6 - diphenyl - isoxazolo-[4,5-c]pyridin - 4(5H) - one, 330 ml of ethanol and 1.65 g of 10% palladium on carbon is hydrogenated at 50 p.s.i. and room temperature. The hydrogenation is ceased after 1 equivalent of hydrogen is absorbed (ca. 2.5 hours). The mixture is treated with methylene chloride and the catalyst is removed by filtration. The solvents are removed *in vacuo* to a volume of ca. 50 ml and then ether is added to precipitate solids which are removed by filtration to give the heading compound, m.p. 238°—240°C. The above compound is dissolved in methanol and treated with sodium hydroxide solution to yield after evaporation the sodium salt of 3 - (α - iminobenzyl)-4 - hydroxy - 6 - phenyl - 1 - methyl - 2(1H) - pyridone.

EXAMPLE 2:

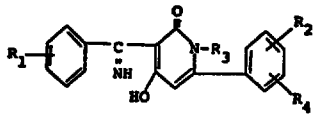
In manner analogous to Example 1, and employing appropriate starting materials in approximately equivalent amounts, the compounds of formula IV, III, II and I,

in which R_1, R_2, R_3 and R_4 have the significances indicated in the following Table, may be obtained.

Number	R_1	R_2	R_3	R_4	Melting Point °C			
					IV	III	II	I
a)	*p*-Cl	H	CH_3	H				
b)	*p*-F	H	CH_3	H	177–178	153–158	162–164	196.5–198.5
c)	*p*-CH_3	H	CH_3	H	182–183.5		154.5–155.5	236–237.5
d)	*p*-CH_3O	H	CH_3	H				
e)	*m*-CF_3	H	CH_3	H				
f)	H	H	CH_3	*p*-Cl	167–170	151–161	167–173	221–223
g)	H	H	CH_3	*p*-F				
h)	H	H	CH_3	*p*-CH_3	148–150		155–156	238–240
i)	H	H	CH_3	*p*-CH_3O	143–145	119–131	149–150	222–225
j)	H	H	CH_3	*m*-CF_3	149–151	132–143	122–126	177–178.5
k)	H	H	CH_3	*o*-CH_3	176–177	150–151.5	115.5–117	221.5–223
l)	H	3-Cl	CH_3	4-Cl				
m)	*p*-Cl	H	CH_3	*p*-Cl				

WHAT WE CLAIM IS:—

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



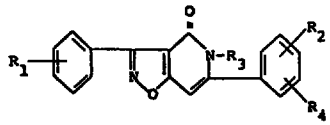
I

in which

R_1, R_2 and R_4, which may be the same or different, each signifies hydrogen, fluorine, chlorine, trifluoromethyl or alkyl or alkoxy of 1 to 4 carbon atoms, and

R_3 is alkyl of 1 to 4 carbon atoms,

provided that when R_1, R_2, and R_4 are each hydrogen, then R_3 is other than methyl characterised by reducing a compound of formula II,



II

in which R_1, R_2, R_3 and R_4 are as defined above, in an inert organic solvent.

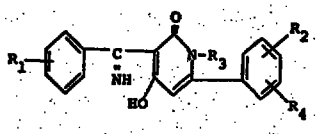
2. A process as claimed in Claim 1, substantially as herein described with reference to Example 2.

in which R_1, R_2, R_3 and R_4 have the significances indicated in the following Table, may be obtained.

Number	R_1	R_2	R_3	R_4	Melting Point °C			
					IV	III	II	I
a)	*p*-Cl	H	CH_3	H				
b)	*p*-F	H	CH_3	H	177–178	153–158	162–164	196.5–198.5
c)	*p*-CH_3	H	CH_3	H	182–183.5		154.5–155.5	236–237.5
d)	*p*-CH_3O	H	CH_3	H				
e)	*m*-CF_3	H	CH_3	H				
f)	H	H	CH_3	*p*-Cl	167–170	151–161	167–173	221–223
g)	H	H	CH_3	*p*-F				
h)	H	H	CH_3	*p*-CH_3	148–150		155–156	238–240
i)	H	H	CH_3	*p*-CH_3O	143–145	119–131	149–150	222–225
j)	H	H	CH_3	*m*-CF_3	149–151	132–143	122–126	177–178.5
k)	H	H	CH_3	*o*-CH_3	176–177	150–151.5	115.5–117	221.5–223
l)	H	3-Cl	CH_3	4-Cl				
m)	*p*-Cl	H	CH_3	*p*-Cl				

WHAT WE CLAIM IS:—

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



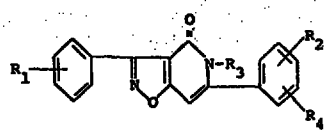
I

in which

R_1, R_2 and R_4, which may be the same or different, each signifies hydrogen, fluorine, chlorine, trifluoromethyl or alkyl or alkoxy of 1 to 4 carbon atoms, and

R_3 is alkyl of 1 to 4 carbon atoms,

provided that when R_1, R_2, and R_4 are each hydrogen, then R_3 is other than methyl characterised by reducing a compound of formula II,



II

in which R_1, R_2, R_3 and R_4 are as defined above, in an inert organic solvent.

2. A process as claimed in Claim 1, substantially as herein described with reference to Example 2.

3. A compound of formula I, stated in Claim 1, whenever produced by a process according to Claim 1 or 2.

4. A compound of formula I, stated in Claim 1.

5. A compound according to Claim 3, in which R_2 is hydrogen.

6. A compound according to Claim 4, in which R_2 is hydrogen.

7. A compound according to any one of Claims 3 to 6, in which R_1 is hydrogen, fluorine, chlorine, trifluoromethyl, methyl or methoxy.

8. A compound according to Claim 7, in which R_1 is hydrogen or chlorine.

9. A compound according to Claim 8, in which R_1 is hydrogen.

10. A compound according to any one of Claims 3 to 9, in which R_3 is methyl.

11. A compound according to any one of Claims 3 to 10, in which R_4 is hydrogen, fluorine, chlorine, trifluoromethyl, methyl or methoxy.

12. A compound according to Claim 11, in which R_4 is hydrogen, chlorine, trifluoromethyl, methyl or methoxy.

13. A compound of formula I, stated in Claim 1, in which R_2 and R_4 are each hydrogen, R_3 is methyl and R_1 is *p*-chloro.

14. A compound of formula I, stated in Claim 1, in which R_2 and R_4 are each hydrogen, R_3 is methyl and R_1 is *p*-fluoro.

15. A compound of formula I, stated in Claim 1, in which R_2 and R_4 are each hydrogen, R_3 is methyl and R_1 is *p*-methyl.

16. A compound of formula I, stated in Claim 1, in which R_2 and R_4 are each hydrogen, R_3 is methyl and R_1 is *p*-methoxy.

17. A compound of formula I, stated in Claim 1, in which R_2 and R_4 are each hydrogen, R_3 is methyl and R_1 is *m*-trifluoromethyl.

18. A compound of formula I, stated in Claim 1, in which R_1 and R_2 are each hydrogen, R_3 is methyl and R_4 is *p*-chloro.

19. A compound of formula I, stated in Claim 1, in which R_1 and R_2 are each hydrogen, R_3 is methyl and R_4 is *p*-fluoro.

20. A compound of formula I, stated in Claim 1, in which R_1 and R_2 are each hydrogen, R_3 is methyl and R_4 is *p*-methyl.

21. A compound of formula I, stated in Claim 1, in which R_1 and R_2 are each hydrogen, R_3 is methyl and R_4 is *p*-methoxy.

22. A compound of formula I, stated in Claim 1, in which R_1 and R_2 are each hydrogen, R_3 is methyl and R_4 is *m*-trifluoromethyl.

23. A compound of formula I, stated in Claim 1, in which R_1 and R_2 are each hydrogen, R_3 is methyl and R_4 is *o*-methyl.

24. A compound of formula I, stated in Claim 1, in which R_1 is hydrogen, R_3 is methyl, R_2 is 3-chloro and R_4 is 4-chloro.

25. A compound of formula I, stated in Claim 1, in which R_1 is p-chloro, R_2 is hydrogen, R_3 is methyl and R_4 is *p*-chloro.

26. A compound according to any one of Claims 3 to 25, in free hydroxy form.

27. A compound according to any one of Claims 3 to 25, in the form of a base salt.

28. A compound according to Claim 27, in the form of an alkali or alkaline earth metal salt.

29. A pharmaceutical composition comprising a compound according to any one of Claims 3 to 25, in free hydroxy form, or in the form of a pharmaceutically acceptable base salt, in association with a pharmaceutically acceptable diluent or carrier.

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