PATENT SPECIFICATION (11) 1 575 509

1 575 509

(21) Application No. 33753/76 (22) Filed 13 Aug. 1976
(31) Convention Application No. 10714/75
(32) Filed 15 Aug. 1975 in
(33) Switzerland (CH)
(44) Complete Specification published 24 Sept. 1980
(51) INT CL³ C07D 209/08; A61K 31/40
(52) Index at acceptance
C2C 1343 213 220 22Y 250 251 25Y 29X 29Y 30Y 313 31Y 322 32Y 338 364 366 368 36Y 491 620 624 628 634 644 650 65X 662 668 672 682 688 802 80Y AA LQ

(72) Inventors FRANZ TROXLER and FRITZ SEEMANN

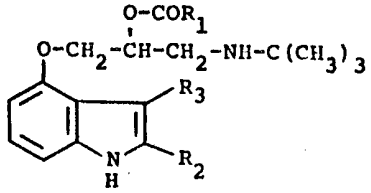
(54) ESTERS OF INDOLE-DERIVED AMINOALCOHOLS

(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:—

The present invention relates to 4 - (3-alkylaminopropoxy) - indole derivatives.

U.K. Patent Specification No. 1356310 discloses and claims a class of 3 - aminopropoxy - indole derivatives having a blocking effect on the adrenergic β-receptors.

This invention provides compounds of formula I,



I

wherein

R_1 is unsubstituted phenyl, phenyl monosubstituted in the 3- or 4-position with fluorine, chlorine or methoxy, or is 1-phenoxy(secondary)alkyl, the secondary alkyl residue of which is of 3 to 5 carbon atoms and in which the phenyl residue is unsubstituted or monosubstituted with chlorine, and

R_2 is methyl, and

R_3 is methyl or hydrogen,

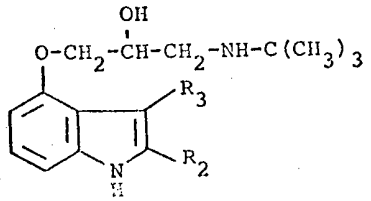
with the proviso that when R_1 is unsubstituted phenyl, R_3 is methyl.

The compounds of formula I are not specifically described in U.K. Patent Specification No. 1356310. It has now been found that they exhibit more beneficial effects than would have been expected for such compounds, e.g. exceptionally good tolerability and/or particularly high and long lasting activity having regard to the generality of the compounds specifically disclosed and claimed in U.K. Patent Specification No. 1356310.

The substituent R_1 is conveniently unsubstituted phenyl. When R_1 is 1-phenoxy-(secondary)alkyl, the phenoxy residue is preferably substituted with chlorine. Preferred such radicals include 2 - (p - chlorophenoxy)-2 - propyl.

The compounds of formula I can, by virtue of the asymmetric carbon atom in the position β to the oxygen atom, exist in the form of optically active isomers or racemates. Of the (R) and (S) enantiomorphs, those which possess the (S)-configuration at the aforementioned carbon atom are preferred.

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



II

wherein

R_2 and R_3 are as previously defined.

The process can be effected in manner analogous to known methods for the acylation of secondary alcohols, for example, by reaction with acid anhydrides or acid halides derived from acids of formula R_1COOH, wherein R_1 is as previously defined, preferably the anhydrides thereof. When the acylating agent to be used is an acid anhydride, the reaction may, for example, be effected at a temperature between 0° and 100°C, particularly in the presence of an excess of the acid anhydride. Prior to effecting the acylation, it is desirable to protonate the amino group, for example, by the addition of an acid, especially the acid R_1COOH, or to employ

the compound of formula II in the form of an acid addition salt, for example, the hydrochloride. With acid halides, the acylation may preferably be effected at room temperature or at slightly elevated temperatures.

The process of the invention does not alter the configuration of the asymmetrically substituted carbon atom. Accordingly, when racemic starting materials are employed, racemic final products of formula I are obtained, and when optically active starting materials are employed, corresponding optically active final products are obtained.

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

Free base forms of the compounds of formula I may be converted into acid addition salt forms and *vice versa* in conventional manner.

The starting compounds are either known or may be produced in accordance with known processes, or in manner analogous to known processes.

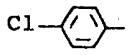
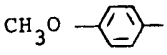
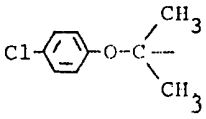
In the following non-limitative Examples, all temperatures are indicated in degrees Centigrade and are uncorrected.

EXAMPLE 1.

4-(2-Benzoyloxy-3-*tert.*butylaminopropoxy)-2,3-dimethyl-indole.

24 g of benzoic acid are dissolved, while heating, in 50 cc of hexamethylphosphoric acid triamide and 3,5 g of 1 - *tert.*-butylamino - 3 - (2,3 - dimethyl - indole - 4-yloxy) - 2 - propanol are added. After cooling, 3.0 g of benzoic acid anhydride are added and stirring is effected for 20 hours at room temperature. The resulting clear, yellow solution is poured onto ice, 0.5 litres of ether are added and stirring is effected for 2 hours. After making the liquid alkaline with concentrated ammonia, the ether phase is separated, shaken out with tartaric acid, made alkaline with caustic soda solution while cooling with ice and extracted with methylene chloride. After evaporating the solvent, the residue is crystallised with fumaric acid from methanol and acetone to produce the bis-[base] fumarate form of the title compound (M.P. 185—187°).

In manner analogous to Example 1, but employing appropriate starting materials in approximately equivalent amounts, the following compounds of formula I can be obtained.

Example	R_1	R_2	R_3	M.P.
2		CH_3	H	HMa: 167—169°
3		CH_3	H	HMa: 138—141[c]
4		CH_3	H	HMa: sinters at 85°

HMa = hydrogen malonate.

The compounds of formula I exhibit pharmacological activity. In particular, the compounds exhibit a blocking effect on the adrenergic β receptors (a β-blocking effect) as indicated in standard tests, for example, by an inhibition of the positive inotropic adrenaline effect in the spontaneously beating guinea-pig atrium and by an inhibition of the tachycardia and hyptotension induced by isoproterenol in anaesthetized cats in the infusion test.

The compounds are therefore indicated for use as β-blocking agents. Such agents are indicated for use *inter alia* in the prophylaxis and therapy of coronary diseases, especially in the treatment of Angina pectoris, in the treatment of the hyperkinetic heart syndrome and the conditions resulting from a muscular hypertrophic subvalvular aortic stenosis.

An indicated daily dose is from 1 to 200 mg, suitably from 10 to 200 mg, conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing from 0.25 to 100 mg, suitably from 2.5 to 100 mg, or in sustained release form.

Additionally, the compounds exhibit an anti-arrhythmic effect as indicated in standard tests, for example, as demonstrated in mice according to the method of Lawson, P. W., J. Pharmac. Exp. Ther. *160* (1968) 22—31, and are therefore indicated for use in the treatment of heart rhythm disorders.

An indicated daily dose is from 5 to 200 mg, conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing from 1 to 50 mg, or in sustained release form.

Furthermore, the compounds of formula I inhibit lipolysis induced by isoproterenol as indicated by standard tests. For example, *in vitro,* the inhibition of lipolysis can be observed in isolated fat cells taken from the epidermal fat tissue of rats, the cells having been isolated in accordance with the method of M. Rodbell [J. Biol. Chem. *239* (1964) 375—380].

The compounds are therefore indicated for use as inhibitors of hyperlipoidemia induced by emotional stress, and therefore for use in the treatment or prophylaxis of myocardism.

In addition, the compounds inhibit isoproterenol-induced glycogenolysis as indicated by standard tests, for example by an inhibition of glycogenolysis stimulated by isoproterenol *in vivo* in rats.

The compounds are therefore indicated for use as inhibitors of hyperglycemia induced by emotional stress and as suppressants of appetite induced by emotional stress. For these uses an indicated daily dose is from 1 to 200 mg, conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing from 0.25 to 100 mg, or in sustained release form.

The (S)-enantiomers of the compound of formula I and acid salt forms thereof are, in general, more active than the corresponding (R)-enantiomers.

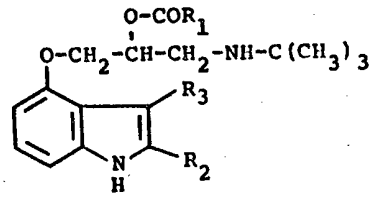
The compounds of formula I may be administered in pharmaceutically acceptable acid addition salt form. Such acid addition salt forms exhibit the same order of activity as the free base forms and are readily prepared in conventional manner. Representative acid addition salt forms include the fumarate, hydrogen fumarate and hydrogen malonate.

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 pharmaceutically acceptable diluent or carrier. Such compositions may be in the form of, for example, a solution or a capsule.

In one group of compounds, R_1 is unsubstituted phenyl, or phenyl mono-substituted with fluorine, chlorine, or methoxy.

WHAT WE CLAIM IS:—

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



I

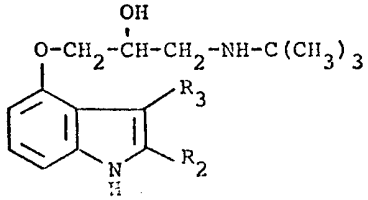
wherein

R_1 is unsubstituted phenyl, phenyl monosubstituted in the 3- or 4-position with fluorine, chlorine or methoxy, or is 1-phenoxy(secondary)alkyl, the secondary alkyl residue of which is of 3 to 5 carbon atoms and in which the phenyl residue is unsubstituted or monosubstituted with chlorine, and

R_2 is methyl, and

R_3 is hydrogen or methyl,

with the proviso that, when R_1 is unsubstituted phenyl, R_3 is methyl, comprising esterifying a compound of formula II,



II

wherein

R_2 and R_3 are as previously defined.

2. A process for the production of a compound of formula I, stated in Claim 1, substantially as hereinbefore described with reference to any one of the Examples.

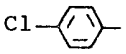
3. A compound of formula I, whenever produced by a process according to Claim 1 or 2.

4. A compound of formula I, as defined in Claim 1.

5. A compound of formula I, stated in Claim 1, wherein R, R_2 and R_3 are, respectively,

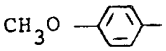
CH_3 and CH_3.

6. A compound of formula I, stated in Claim 1, wherein R_1, R_2 and R_3 are, respectively,



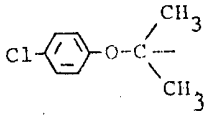
CH_3 and H.

7. A compound of formula I, stated in Claim 1, wherein R_1, R_2 and R_3 are, respectively,



CH_3 and H.

8. A compound of formula I, stated in Claim 1, wherein R_1, R_2 and R_3 are, respectively,



CH_3 and H.

9. A compound according to any one of Claims 3 to 8, in (S)-enantiomeric form.

10. A compound according to any one of Claims 3 to 8, in the form of a racemic mixture.

11. A compound according to any one of Claims 3 to 10, in free base form.

12. A compound according to any one of Claims 3 to 10, in acid addition salt form.

13. A pharmaceutical composition comprising a compound according to any one of Claims 3 to 10 in free base form or in pharmaceutically acceptable acid addition salt form in association with a pharmaceutically acceptable carrier or diluent.

B. A. YORKE & CO.,
Chartered Patent Agents,
98, The Centre, Feltham,
Middlesex, TW13 4EP.
Agents for the Applicants.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1980.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.