1 575 510

PATENT SPECIFICATION (11) 1 575 510

(21) Application No. 13931/79 (22) Filed 13 Aug. 1976
(62) Divided out of No. 1575509
(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 322 32Y 364 366 368 36Y 491 620 624 628 65X 668 672 682 688 802 80Y AA LQ

(72) Inventors FRANZ TROXLER and FRITZ SEEMANN

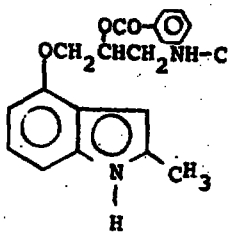
(54) AN ESTER OF AN INDOLE-DERIVED AMINOALCOHOL

(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 a 3 - aminopropoxy - 2 - methyl - indole derivative.

UK patent specification No. 1 356 310 discloses and claims a class of 3 - aminopropoxy - indole derivatives having a blocking effect on the adrenergic β receptors.

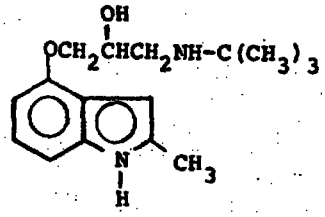
The present invention provides 4 - (2 - benzoyloxy - 3 - tert - butyl-aminopropoxy) - 2 - methyl - indole of formula I,



I

not specifically described in UK patent specification No. 1 356 310, which has now been found to have more beneficial effects than would have been expected for such a compound, i.e. exceptionally good tolerability and particularly high and long lasting activity having regard to the generality of the compounds specifically disclosed and claimed in UK patent specification No. 1 356 310.

The present invention also provides a process for the production of the compound of formula I as defined above, which comprises esterifying the compound of formula II,



II

The present process may for example be effected in conventional manner as described in the Example and in our copending application No. 33753/76 (patent specification No. 1575509) for analogous compounds.

The compound of formula II is known.

The compound of formula I can, by virtue of the asymmetric carbon atom in the position β to the oxygen atom bound to the indole nucleus, exist in the form of optically active isomers or as a racemate.

The process of the invention does not alter the configuration of the assymmetrically substituted carbon atom. Accordingly, when a racemic starting material is employed, a racemic final product of formula I is obtained, and when an optically active starting material is employed a corresponding optically active final product is obtained.

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

The free base form of the compound of formula I may be converted into acid addition salt forms and vice-versa in conventional manner.

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

EXAMPLE

4-(2-benzoyloxy-3-tert.butylaminopropoxy)-2-methyl-indole

26 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-methyl-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 1 mol of fumaric acid from methanol and acetone. M.p. of hydrogen fumarate form: 189—191°.

In analogous manner, but employing appropriate, optically active starting material in approximately equivalent amounts, the compound of formula I can be obtained in (S) form (M.P. of the hydrogen malonate 95°) and in (R) form (M.P. of the hydrogen malonate 95°).

The compound of formula I exhibits pharmacological activity. In particular, the compound exhibits 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 hypotension induced by isoproterenol in anaesthetized cats in the infusion test.

Additionally, the compound exhibits an antiarrhythmic effect as indicated in standard tests, for example, as demonstrated in mice according to the method of Lawson, J. W., *J. Pharmac. Exp. Ther. 160* (1968) 22—31.

Furthermore, the compound of formula I inhibits 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 epidymal fat tissue of rats, the cells having been isolated in accordance with the method of M. Rodbell *[J. Biol. Chem. 239* (1964) 375—380].

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

The compound is therefore indicated for use as a β-blocking agent. 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 10 mg; it may be administered in divided doses 2 to 4 times a day in unit dosage form containing from 0.25 to 5 mg, or in sustained release form.

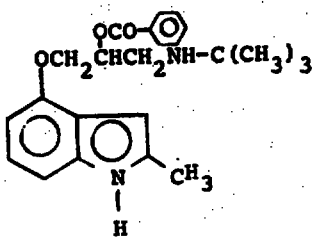
The (S)-enantiomer of the compound of formula I and acid salt forms thereof are more active than the corresponding (R)-enantiomers, and accordingly the compound is preferably in racemic or S enantiomeric form.

The compound 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 form 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 the 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.

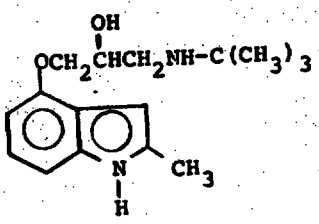
WHAT WE CLAIM IS:—

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



I

which comprises esterifying the compound of formula II,



II

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

EXAMPLE

4-(2-benzoyloxy-3-tert.butylaminopropoxy)-2-methyl-indole

26 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 - methyl - 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 1 mol of fumaric acid from methanol and acetone. M.p. of hydrogen fumarate form: 189—191°.

In analogous manner, but employing appropriate, optically active starting material in approximately equivalent amounts, the compound of formula I can be obtained in (S) form (M.P. of the hydrogen malonate 95°) and in (R) form (M.P. of the hydrogen malonate 95°).

The compound of formula I exhibits pharmacological activity. In particular, the compound exhibits 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 hypotension induced by isoproterenol in anaesthetized cats in the infusion test.

Additionally, the compound exhibits an antiarrhythmic effect as indicated in standard tests, for example, as demonstrated in mice according to the method of Lawson, J. W., *J. Pharmac. Exp. Ther. 160* (1968) 22—31.

Furthermore, the compound of formula I inhibits 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 epidymal fat tissue of rats, the cells having been isolated in accordance with the method of M. Rodbell *[J. Biol. Chem. 239* (1964) 375—380].

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

The compound is therefore indicated for use as a β-blocking agent. 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 10 mg; it may be administered in divided doses 2 to 4 times a day in unit dosage form containing from 0.25 to 5 mg, or in sustained release form.

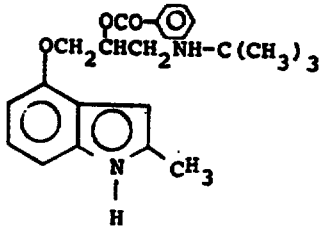
The (S)-enantiomer of the compound of formula I and acid salt forms thereof are more active than the corresponding (R)-enantiomers, and accordingly the compound is preferably in racemic or S enantiomeric form.

The compound 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 form 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 the 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.

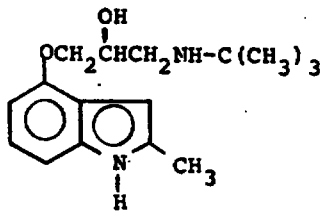
WHAT WE CLAIM IS:—

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



I

which comprises esterifying the compound of formula II,



II

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

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

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

5. The compound of claims 3 or 4, in the form of a racemate.

6. The compound of claims 3 or 4, in (S) enantiomeric form.

7. The compound of any one of claims 3 to 6, in free base form.

8. The compound of any one of claims 3 to 6, in acid addition salt form.

9. A pharmaceutical composition comprising a compound according to any one of claims 3 to 6 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.

* C L M S *