

# PATENT SPECIFICATION

NO DRAWINGS

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Date of Application and filing Complete Specification: Sept. 9, 1966.

No. 40400/66.

Application made in United States of America (No. 487619) on Sept. 15, 1965.

Complete Specification Published: Dec. 29, 1967.

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Index at acceptance: —C2 C(1H1A1, 1H1C3, 2A3, 2A5, 2A9, 2R15)

Int. Cl.: —C 07 d 27/48

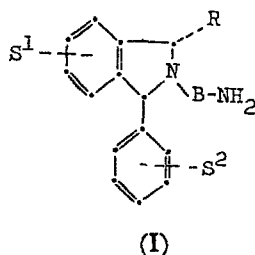
## COMPLETE SPECIFICATION

### Novel Isoindoline Derivatives and a Process for the Manufacture thereof

We, F. HOFFMAN-LA ROCHE & Co., Aktiengesellschaft, a Swiss Company of 124—184 Grenzacherstrasse, Basle, Switzerland, 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 is concerned with novel isoindoline derivatives and a process for the manufacture thereof.

The novel isoindoline derivatives provided by the invention are compounds of the general formula



wherein S<sup>1</sup> and S<sup>2</sup> each represent substitution by one or more halo, lower-alkyl, lower-alkoxy, hydroxy, sulphonyl, sulphinyl, sulphamyl, lower-alkylmercapto, lower alkyl-amino, di-(lower alkyl)-amino, acylamino and/or trifluoromethyl substituents, R represents a lower-alkyl group and B represents a straight-chain or branched-chain alkylene group containing from 2 to 12 carbon atoms in which part or all of the carbon atoms may form a 3- to 7-membered carbocyclic ring and wherein the broken lines denote that the R-group and S<sup>1</sup>- and S<sup>2</sup>-substitution is optional, and acid addition salts thereof.

The compounds of formula I hereinbefore and their pharmaceutically acceptable acid addition salts are useful as anorexigenic agents

[Price 4s. 6d.]

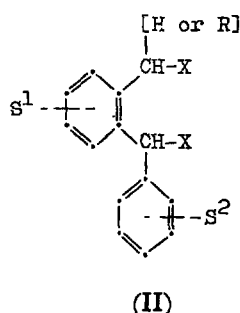
and also possess useful antidepressant properties. More particularly, they are therapeutically useful as appetite suppressants in the treatment of overweight subjects. They can be administered orally or parenterally. The preferred route of administration, however, is orally. The dosage amount and formulation can be varied depending upon the subject being treated and its individual response to said treatment and the period and interval during which administration is carried out. The novel compounds and pharmaceutically acceptable acid addition salts of this invention can be administered either alone or in the form of pharmaceutical preparations which contain them in admixture with a compatible pharmaceutical carrier. They can be formulated into a wide variety of dosage forms using either the free bases or their pharmaceutically acceptable acid addition salts. For purposes of oral administration they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, trochés, elixirs and syrups. Suitable carriers include solid diluents or fillers, liquid media and various non-toxic organic solvents such as, for example, sodium citrate, calcium carbonate, starch, gelatin, magnesium stearate, talc, polyethyleneglycols, water and glycerine.

It will be appreciated that the compounds of formula I hereinbefore may exist in the form of stereoisomers and that the invention includes both racemic mixtures as well as the separated optically active antipodes.

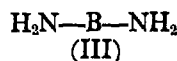
One interesting class of isoindoline derivatives provided by the invention comprises those compounds of formula I in which S<sup>1</sup> is absent, and acid addition salts thereof (particularly those compounds and salts in which B represents the ethylene group). Another interesting class of isoindoline derivatives pro-

vided by the invention comprises those compounds of formula I hereinbefore in which  $S^1$  and  $S^2$  are absent, and acid addition salts thereof. Where  $S^1$  and/or  $S^2$  is present and represent substitution comprising or including halo substitution, it is preferred that this latter substitution is chloro, bromo or fluoro substitution.

According to the process provided by the invention, the novel derivatives aforesaid are manufactured by treating a diester of the general formula

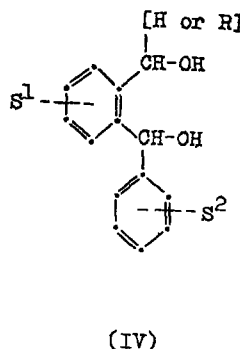


wherein  $S^1$ ,  $S^2$ , R and the broken lines have the significance given earlier and X stands for a halogen atom or a mesyloxy or tosyloxy group, with an alkylene-diamine of the general formula



wherein B has the significance given earlier, and, where required, converting the product into an acid addition salt.

The diester starting materials of formula II hereinbefore in which X stands for a halogen atom can be prepared by halogenating a corresponding diol of the general formula



wherein  $S^1$ ,  $S^2$ , R and the broken lines have the significance given earlier, in accordance with methods known *per se*; for example, by treatment with a halogenating agent such as a halo-acid, a phosphorus halide or a thionyl halide. The dioles of formula IV herein before are either known or can be readily prepared by well-known processes. Suitable dioles are, for example, 5 - chloro - 2 - hydroxymethyl -

benzhydrol, 4' - chloro - 2 - hydroxymethyl - benzhydrol, 4' - fluoro - 2 - hydroxymethyl - benzhydrol, 4' - methoxy - 2 - hydroxymethyl - benzhydrol, 2',5' - dichloro - 2 - hydroxymethyl - benzhydrol, 4,5 - dichloro - 2 - hydroxymethyl - benzhydrol, 2',4' - dichloro - 2 - hydroxymethyl - benzhydrol, 4 - methyl - 2 - hydroxymethyl - benzhydrol, 3' - trifluoromethyl - 2 - hydroxymethyl - benzhydrol, 4 - trifluoromethyl - 2 - hydroxymethyl - benzhydrol and 5 - methoxy - 2 - hydroxymethyl - benzhydrol.

One interesting class of diester starting materials of formula II comprises those in which X represents a chlorine or bromine atom. Another interesting class of diester starting materials of formula II comprises those in which  $S^1$  is absent. Yet another interesting class of diester starting materials of formula II comprises those in which  $S^1$  and  $S^2$  are absent. Where, in the diester starting materials of formula II  $S^1$  and/or  $S^2$  is present and represents substitution comprising or including halo substitution, it is preferred that this latter substitution is chloro, bromo or fluoro substitution.

Examples of alkylene-diamines of formula III hereinbefore are  $\alpha,\omega$  - diamino - alkanes such as 1,2 - diamino - ethane, 1,3 - diamino - propane, 1,4 - diamino - butane, 1,10 - diamino - decane, 1,11 - diamino - undecane and 1,12 - diamino - dodecane or amines such as 1,2 - diamino - 2 - methyl - propane, 1,3 - diamino - 2 - methyl - propane, 1,3 - diamino - butane, 2,3 - diamino - butane, 1,2 - diamino - butane, 2,5 - diamino - hexane, 1,2 - diamino - cyclohexane, 1,3 - diamino - cyclohexane and 1,4 - diamino - cyclohexane. Ethylene diamine is an especially preferred alkylene-diamine.

The treatment of a diester of formula II with an alkylene-diamine of formula III is conveniently carried out by merely adding the diester to the alkylene-diamine at room temperature. A large molar excess of alkylene-diamine is preferably used. The treatment can also be carried out at a temperature above or below room temperature, although for practical reasons it is preferred to operate at a temperature between about 0°C and 100°C. The treatment can suitably be carried out in any inert organic solvent (for example, benzene, methylene chloride, ether or tetrahydro-furan) or it can conveniently be carried out in the absence of a solvent where one or both of the starting materials are liquid under the reaction conditions employed.

One interesting embodiment of the foregoing process comprises treating a phenyl - (2 - halomethyl - phenyl) - halo - methane or a (4 - chloro - phenyl) - (2 - halomethyl - phenyl) - halo - methane with ethylene-diamine.

The compounds of formula I form acid addition salts with organic and inorganic acids

and these salts can be easily prepared by known methods. Suitable organic acids are maleic acid, fumaric acid, ascorbic acid, tartaric acid, salicylic acid and citric acid and suitable inorganic acids, are, for example, the hydrohalic acids (e.g. hydrochloric acid and hydrobromic acid), sulphuric acid, sulphamic acid and phosphoric acid.

The following Examples illustrate the invention:

#### EXAMPLE 1

The novel isoindoline derivatives of this invention were prepared according to the following general procedure: A solution of an appropriate diol of formula IV hereinbefore was dissolved in an excess of thionyl chloride. The resulting solution was kept on a steam-bath for *ca* 0.5 hour, after which time the excess of thionyl chloride was removed *in vacuo* and the residue was distilled at a pressure of 0.1 mm and at a bath-temperature ~~range~~ from about 100°C to 150°C. The colourless oil obtained was dissolved in an inert solvent (benzene, methylene chloride, ether, tetrahydrofuran, etc.) and the solution was added in small portions to a stirred excess of the requisite diamine of formula III hereinbefore. The resulting mixture was kept on a steam-bath for *ca* 0.5 hour, after which time the solvent and the excess of the diamine of formula III were removed *in vacuo*. The residue was dissolved in ether or any water-immiscible organic solvent and the solution was washed with water, dried with sodium sulphate and evaporated on a steam-bath. The residue was distilled at a pressure of 0.1 mm and at a bath temperature ranging from 100°C to 170°C to give the required isoindoline derivative of formula I hereinbefore as a colourless oil. The derivatives of formula I either crystallized on standing or were characterized in the form of their crystalline salts. In this way the following derivatives were prepared: 2 - (2 - amino - ethyl) - 1 - phenyl - isoindoline, white prisms of melting point 53°C; 2 - (2 - amino - ethyl) - 1 - phenyl - isoindoline dihydrochloride, white ~~needles~~ of melting point 215°—220°C (with decomposition); 2 - (2 - amino - ethyl) - 1 - (4 - chloro - phenyl) - isoindoline, colourless oil of boiling point *ca* 125°C (bath temperature) at 0.1 mm and 2 - (2 - amino - ethyl) - 1 - (4 - chloro - phenyl) - isoindoline monohydrochloride, white needles of melting point 218°—221°C.

#### EXAMPLE 2

10.0 g of 2 - (2 - amino - ethyl) - 1 - phenyl - isoindoline, 129.0 g of lactose, 50.0 g of corn starch and 8.0 g of a pregelatinized corn starch were blended in a suitable mixer. The mixture obtained was passed through a comminuting machine with a screen and with knives forward, returned to the mixer and moistened with water to form a thick paste. The moist mass was passed through a screen

and the resulting moist granules were dried on paper-lined trays at 43°C. The dried granules were returned to the mixer, 3 g of calcium stearate were added and the whole was mixed well. The product obtained was compressed to tablets each weighing 200 mg using standard concave punches having a diameter of 8 mm.

#### EXAMPLE 3

25.5 g of 2 - (2 - amino - ethyl) - 1 - phenyl - isoindoline, 159.5 g of lactose and 30.0 g of corn starch were mixed in a suitable mixer. The mixture was further blended by passing through a comminuting machine with a screen with knives forward. The blended powder was returned to the mixer, 5.0 g of talc were added and the resulting mixture was blended well and filled into hard gelatin capsules on a capsulating machine.

#### EXAMPLE 4

1230 g of hydrogenated castor wax and 45 g of carnauba wax were melted in a suitable size glass-lined container, mixed well and cooled to 45°C. 25 g of a fine powder of 2 - (2 - amino - ethyl) - 1 - phenyl - isoindoline were added and stirred until completely and uniformly dispersed. The resulting mixture was poured into suppository moulds to yield suppositories having an individual weight of 1.3 g. The suppositories were cooled, removed from the moulds and individually wrapped in wax paper for packaging.

#### EXAMPLE 5

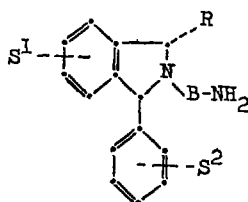
2 - (2 - amino - ethyl) - 1 - phenyl - isoindoline for parenteral injection was prepared in duplex ampoules (one containing the active material and the other containing a special diluent). 20 mg of 2 - (2 - amino - ethyl) - 1 - phenyl - isoindoline (fibre-free) were filled into an ampoule using a suitable filler. The ampoule was sealed and sterilized at 125°C for 2 hours. Immediately before use, the powder is solubilized with 2 ml of the special diluent containing 16 mg of glacial acetic acid, 3.0 mg of sodium hydroxide and 1 ml of water for injection per ml of diluent.

The special diluent mentioned in the preceding paragraph can be prepared by dissolving 16 g of glacial acetic acid in part of 10 ml of water for injection under an atmosphere of nitrogen in a suitable container, adding 3 g of sodium hydroxide to adjust the pH to approximately 3.0, diluting the resulting solution with the remaining water for injection, filtering it through a suitable candle filter, filling it into 2 ml flint ampoules (the filling should be done under an atmosphere of nitrogen), sealing the ampoules and sterilizing them at 100°C for 0.5 hour. The ampoules are subsequently inspected and those which leak or contain fibres are discarded.

It will be appreciated that the terms 'lower alkyl' and 'lower alkoxy' are used in the foregoing description and in the claims appended hereto to mean alkyl and alkoxy groups respectively which contain from one to seven carbon atoms.

**WHAT WE CLAIM IS:—**

**1. Compounds of the general formula**



- 10 wherein  $S^1$  and  $S^2$  each represent substitution by one or more halo, lower-alkyl, lower-alkoxy, hydroxy, sulphonyl, sulphinyl, sulphamyl, lower-alkylmercapto, lower alkyl-amino, di(lower alkyl)-amino, acylamino and/or trifluoromethyl substituents, R represents a lower-alkyl group and B represents a straight-chain or branched-chain alkylene group containing from 2 to 12 carbon atoms in which part or all of the carbon atoms may form a 3- to 7-membered carbocyclic ring and wherein the broken lines denote that the R-group and  $S^1$ - and  $S^2$ -substitution is optional, and acid addition salts thereof.

- 25 2. Compounds as formulated in claim 1, wherein  $S^1$  is absent, and acid addition salts thereof.

- 30 3. Compounds as set forth in claim 2, wherein B represents the ethylene group, and acid addition salts thereof.

4. Compounds as formulated in claim 1, wherein  $S^1$  and  $S^2$  are absent, and acid addition salts thereof.

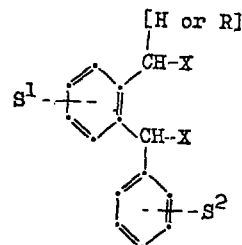
5. Compounds as set forth in claim 1, claim 2 or claim 3 insofar as  $S^1$  and/or  $S^2$  is present and represents substitution comprising or including halo substitution, wherein said halo substitution is chloro, bromo or fluoro substitution, and acid addition salts thereof.

- 40 6. 2 - (2 - amino - ethyl) - 1 - phenyl - isoindoline.

7. 2 - (2 - amino - ethyl) - 1 - (4 - chloro - phenyl) - isoindoline.

- 45 8. A pharmaceutical preparation comprising a compound as set forth in any one of the preceding claims or a pharmaceutically acceptable acid addition salt thereof in admixture with a compatible pharmaceutical carrier.

- 50 9. A process for the manufacture of the derivatives claimed in claim 1, which process comprises treating a diester of the general formula



wherein  $S^1$ ,  $S^2$ , R and the broken lines have the significance given in claim 1 and X stands for a halogen atom or a mesyloxy or tosyloxy group, with an alkylene-diamine of the general formula



wherein B has the significance given in claim 1, and, where required, converting the product into an acid addition salt.

10. A process as set forth in claim 9, wherein a diester in which  $S^1$  is absent is used as the starting material.

11. A process as set forth in claim 10, wherein said ester is treated with ethylenediamine.

12. A process as set forth in claim 9, wherein a diester in which  $S^1$  and  $S^2$  are absent is used as the starting material.

13. A process as set forth in claim 9, claim 10 or claim 11 insofar as a diester in which  $S^1$  and/or  $S^2$  is present and represents substitution comprising or including halo substitution is used as the starting material, wherein said halo substitution is chloro, bromo or fluoro substitution.

14. A process as set forth in claim 12 wherein a phenyl - (2 - halomethyl - phenyl) - halo - methane is treated with ethylenediamine.

15. A process as set forth in claim 11, wherein a (4 - chloro - phenyl) - (2 - halomethyl - phenyl) - halo - methane is treated with ethylene - diamine.

16. A process as set forth in any one of claim 9 to 15 inclusive, wherein the diester starting material is a dichloride.

17. A process for the manufacture of the derivatives claimed in claim 1 substantially as described with reference to the first of the foregoing Examples.

18. Compounds as formulated in claim 1, and acid addition salts thereof, when manufactured by the process claimed in any one of claims 9 to 17 inclusive.

W. D. WHITAKER *RB*

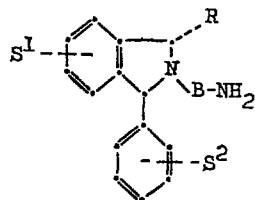
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Aktiengesellschaft.

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# WHAT WE CLAIM IS:—

## 1. Compounds of the general formula



10 wherein  $S^1$  and  $S^2$  each represent substitution by one or more halo, lower-alkyl, lower-alkoxy, hydroxy, sulphonyl, sulphinyl, sulphamyl, lower-alkylmercapto, lower alkyl-amino, di(lower alkyl)-amino, acylamino and/or trifluoromethyl substituents, R represents a lower-alkyl group and B represents a straight-chain or branched-chain alkylene group containing from 2 to 12 carbon atoms in which part or all of the carbon atoms may form a 3- to 7-membered carbocyclic ring and wherein the broken lines denote that the R-group and  $S^1$ - and  $S^2$ -substitution is optional, and acid addition salts thereof.

25 2. Compounds as formulated in claim 1, wherein  $S^1$  is absent, and acid addition salts thereof.

3. Compounds as set forth in claim 2, wherein B represents the ethylene group, and acid addition salts thereof.

30 4. Compounds as formulated in claim 1, wherein  $S^1$  and  $S^2$  are absent, and acid addition salts thereof.

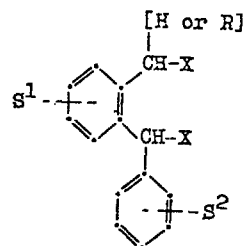
35 5. Compounds as set forth in claim 1, claim 2 or claim 3 insofar as  $S^1$  and/or  $S^2$  is present and represents substitution comprising or including halo substitution, wherein said halo substitution is chloro, bromo or fluoro substitution, and acid addition salts thereof.

40 6. 2 - (2 - amino - ethyl) - 1 - phenyl - isoindoline.

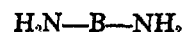
7. 2 - (2 - amino - ethyl) - 1 - (4 - chloro - phenyl) - isoindoline.

45 8. A pharmaceutical preparation comprising a compound as set forth in any one of the preceding claims or a pharmaceutically acceptable acid addition salt thereof in admixture with a compatible pharmaceutical carrier.

50 9. A process for the manufacture of the derivatives claimed in claim 1, which process comprises treating a diester of the general formula



55 wherein  $S^1$ ,  $S^2$ , R and the broken lines have the significance given in claim 1 and X stands for a halogen atom or a mesyloxy or tosyloxy group, with an alkylene-diamine of the general formula



60 wherein B has the significance given in claim 1, and, where required, converting the product into an acid addition salt.

10. A process as set forth in claim 9, wherein a diester in which  $S^1$  is absent is used as the starting material.

65 11. A process as set forth in claim 10, wherein said ester is treated with ethylenediamine.

12. A process as set forth in claim 9, wherein a diester in which  $S^1$  and  $S^2$  are absent is used as the starting material.

70 13. A process as set forth in claim 9, claim 10 or claim 11 insofar as a diester in which  $S^1$  and/or  $S^2$  is present and represents substitution comprising or including halo substitution is used as the starting material, wherein said halo substitution is chloro, bromo or fluoro substitution.

80 14. A process as set forth in claim 12 wherein a phenyl - (2 - halomethyl - phenyl) - halo - methane is treated with ethylenediamine.

85 15. A process as set forth in claim 11, wherein a (4 - chloro - phenyl) - (2 - halomethyl - phenyl) - halo - methane is treated with ethylene - diamine.

16. A process as set forth in any one of claim 9 to 15 inclusive, wherein the diester starting material is a dichloride.

90 17. A process for the manufacture of the derivatives claimed in claim 1 substantially as described with reference to the first of the foregoing Examples.

95 18. Compounds as formulated in claim 1, and acid addition salts thereof, when manufactured by the process claimed in any one of claims 9 to 17 inclusive.

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