

1188.109



PATENT SPECIFICATION

NO DRAWINGS

Inventor: RUDOLF GUSTAV GRIOT

Date of Application (No. 49342/69) and filing Complete Specification: 24 April, 1967.

Application made in United States of America (No. 568,759) on 29 July, 1966.

Application made in United States of America (No. 598,970) on 5 Dec., 1966.

(Divided out of No. 1,187,501).

Complete Specification Published: 15 April, 1970.

1188.109

Index at acceptance:—C2 C(1E7C1, 1E7E1, 1E7N5, 1E7P3)

International Classification:—C 07 d 29/12

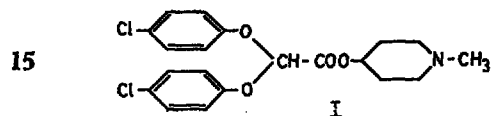
COMPLETE SPECIFICATION

Improvements in or relating to a novel Bis-(*p*-Chlorophenoxy)-Acetic Acid Ester

We, SANDOZ LTD., of Lichtstrasse 35, 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:—

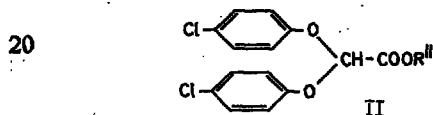
The present invention relates to a new organic compound and processes for its production.

The present invention provides the compound bis - (*p* - chlorophenoxy)acetic acid 1 - methyl - piperidyl - (4) - ester, of formula I,



The present invention further provides a process for the production of the compound of formula I, characterised in that

a) a compound of formula II,

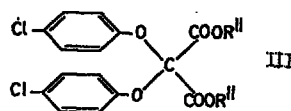


in which R'' signifies an alkyl radical having 1 to 4 carbon atoms, is reacted with a compound of formula IV,



b) a compound of formula III,

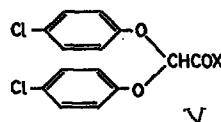
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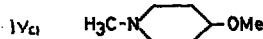
in which R'' has the above significance, is reacted with the compound of formula IV at a temperature of at least 110°C, or

c) a compound of formula V,

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in which X signifies chlorine or bromine, is reacted with the compound of formula IV or an alcoholate of formula IVa,



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in which Me signifies an alkali metal.

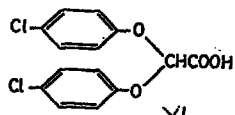
One preferred method of effecting the process variants a) and b) consists in that a compound of formula II or a compound of formula III is reacted with the compound of formula IV in an organic solvent which is inert under the reaction conditions, e.g. benzene, toluene or xylene, and in the presence of an alkali metal alcoholate, preferably sodium methoxide or sodium ethoxide, at a temperature from 80°C to 140°C, preferably however at the boiling temperature of the reaction solution. When a compound of formula III is used as starting material a temperature of at least

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110°C. necessary for partial decarboxylation, should be maintained.

- 5 The compounds of formula V used as starting materials in process c), may be prepared by treating a compound of formula VI,



with a suitable chlorinating or brominating agent.

- 10 The production of the compound of formula I in accordance with the process variant c) is preferably effected in that the compound of formula VI is treated with a suitable chlorinating agent, e.g. thionyl chloride or phosphorus pentachloride, or a brominating agent, e.g. thionyl bromide or phosphorus pentobromide, in an organic solvent which is inert under the reaction conditions, e.g. diethyl ether or tetrahydrofuran, at a temperature between 20°C and the boiling temperature of the reaction mixture. Chlorination or bromination may, however, also be effected without a solvent, when a great excess of halogenating agent is used for the halogenation reaction.

- 20 A catalytic amount of dimethyl formamide is preferably added during chlorination or bromination. The resulting compound of formula V is subsequently reacted with a compound of formula IV or IVa, preferably in an organic solvent which is inert under the reaction conditions, e.g. benzene, toluene, chloroform or diethyl ether, at a temperature from 20° to -10°C, preferably from 5° to -10°C. It is also possible to effect the reaction at a higher temperature, but in this case external cooling should be provided as the reaction is highly exothermic. When the reaction is effected with the compound of formula IV it is desirable to add an excess of the compound of formula IV or an inorganic base, e.g. an alkali metal carbonate, such as potassium carbonate, or an organic base, e.g. pyridine, in order to bind the liberated hydrogen halide. The potassium or sodium compound is preferably used as the compound of formula IVa.

- 45 The compound of formula I obtained in accordance with the above process may subsequently be isolated from the reaction mixture in manner known *per se*, by chromatography, extraction or salt formation, optionally after previous decolouration with decolourizing carbon, and may be purified, e.g. by recrystallization. The base form of the compound of formula I may be liberated in manner known *per se* from the salts which may optionally be obtained by the isolation procedure. The resulting compound of formula I may then optionally be converted into its acid addition or quaternary ammonium salts.

The compounds of formulae II and III, used as starting materials, may be obtained in that an alkali metal *p*-chloro-phenolate (obtained by treating *p*-chloro-phenol with an alkali metal hydride), preferably the sodium *p*-chloro-phenolate, is reacted with a dichloro-acetic acid alkyl ester, dibromo-acetic acid alkyl ester, dibromo-malonic acid dialkyl ester or dichloro-malonic acid dialkyl ester, in which the alkyl radical contains 1 to 4 carbon atoms, in an organic solvent which is inert under the reaction conditions, e.g. N,N-dimethyl acetamide, N,N-diethyl acetamide or dimethyl formamide, at a temperature from 20°C to 100°C. When it is desired to produce a compound of formula III the temperature should not rise above 80°C.

The compound of formula VI may be obtained in that a compound of formula II or a compound of formula III in a mixture of water and a water-miscible organic solvent, e.g. methanol or ethanol, or a cyclic ether, e.g. dioxan or tetrahydrofuran, is treated at a temperature between 20° and 100°C with a strong inorganic base, e.g. sodium hydroxide or potassium hydroxide. When an alcohol is used as solvent this must be diluted with a sufficient amount of water to prevent an esterification of the acid. The corresponding acid is liberated from its salts obtained in the above manner with a strong mineral acid, e.g. hydrochloric acid. The malonic acid derivative which may optionally be obtained is decarboxylated in manner known *per se*.

The compound of formula IV and its metal salts of formula IVa, which are also used as starting materials, are known.

The compound of formula I is a crystalline base at room temperature; by reaction with suitable organic or inorganic acids it may be converted into a pharmaceutically acceptable acid addition salt. The following acids are preferably used for this reaction: hydrochloric, hydrobromic, sulphuric, phosphoric, benzoic, acetic, maleic, *p*-toluenesulphonic or benzenesulphonic acid. The compound of formula I may also be converted into pharmaceutically acceptable quaternary ammonium salts by reacting with alkyl chlorides, iodides or bromides having 1-4 carbon atoms or with lower straight-chained dialkyl sulphates.

The compound of formula I exhibits pharmacodynamic properties, and possesses hypocholesteremic and hypolipemic effects in animals. It is indicated for use as a hypocholesteremic/hypolipemic agent. An indicated daily dose is 0.25 to 2 g, preferably administered 2 to 4 times a day in doses of 62.5 mg to 1 g or in sustained release form.

The compound may be used, for example, for oral administration in the form of a tablet having the following composition: 1-3% of binding material (e.g. tragacanth), 3-10% of starch, 2-10% of talcum, 0.25-1% of magnesium stearate, the corresponding amount of

active material and filling material, e.g. lactose, to make up to 100%, all %'s being by weight.

The compound may be used in the form of its pharmaceutically acceptable acid addition or quaternary ammonium salts which have the same order of activity as the compound in the form of a free base.

The invention also provides pharmaceutical compositions comprising a pharmaceutically effective amount of the compound of formula I or a pharmaceutically acceptable acid addition or quaternary ammonium salt thereof in admixture with a pharmaceutically acceptable inert diluent or carrier.

Compounds of formula III are claimed in our application No. 684/67 (Serial No. 1177841).

The expression "in manner known *per se*" as used herein designates methods in use or described in the literature on the subject, for other compounds.

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

EXAMPLE 1:

Bis-(*p*-chlorophenoxy)acetic acid 1-methyl-piperidyl-(4) ester

A mixture of 14.4 g (0.151 mole) of 1-methyl-4-hydroxypiperidine in 70 ml of toluene is cooled to about -5° in an ice-salt bath. To the cooled mixture is then added dropwise with stirring a solution of 25 g (0.076 mole) of bis-(*p*-chlorophenoxy)-acetyl chloride in 50 ml of toluene, while maintaining the temperature of the reaction mixture from -5° to 0° with external cooling. After the addition is completed, the mixture is stirred for an additional 10 minutes and then 50 ml of ice-water and 75 ml of a saturated aqueous sodium bicarbonate solution are added and the phases separated. The organic phase is then washed 3 times with 100 ml (each) of water, then dried over magnesium sulphate and evaporated. The residue thus obtained is recrystallized from ethanol, using some charcoal to remove coloured by-products, to obtain bis-(*p*-chlorophenoxy)acetic acid 1-methyl-piperidyl-(4) ester, m.p. $92-93.6^{\circ}$.

Fumarate: The fumarate is obtained in that the free base is neutralized with fumaric acid in methanol and the resulting product is subsequently recrystallized from methanol at a temperature of -15° . m.p. $100-112^{\circ}$ (with decomposition).

Hydrochloride: The hydrochloride is obtained in that the free base is treated with a solution of hydrogen chloride in ethanol and the resulting product is subsequently recrystallized from ethanol. m.p. $158-159^{\circ}$.

Methiodide: The methiodide is obtained in that the free base is treated with an excess of methyl iodide and the resulting product is subsequently recrystallized from ethanol. m.p. $166-167^{\circ}$.

Methobromide: The methobromide is obtained in that a solution of the free base in methylene chloride is treated at 0° with an excess of gaseous methyl bromide and the resulting product is subsequently recrystallized from ethanol. m.p. $195-197^{\circ}\text{C}$.

EXAMPLE 2:

Bis-(*p*-chlorophenoxy)acetic acid 1-methyl-piperidyl-(4) ester

1 g of sodium methoxide is added while stirring to a mixture of 65 g (0.157 mole) of bis-(*p*-chlorophenoxy)malonic acid diethyl ester, 36 g (0.314 mole) of 1-methyl-4-hydroxy-piperidine and 300 ml of toluene. The resulting mixture is distilled at atmospheric pressure until the temperature of the distillation mixture reaches 120° and cooling is then effected to 50° . After the addition of 300 ml of benzene the flask residue is cooled to 20° and dilution is effected with 300 ml of water. The organic phase is separated and the aqueous phase extracted with 300 ml of benzene. The organic phases are subsequently combined, washed twice, each time with 300 ml of water and evaporation is subsequently effected in a rotary evaporator in a vacuum (100 mm of Hg). The resulting residue is recrystallized from 200 ml of isopropanol and the resulting crystalline material is filtered off at 5° . After washing with 100 ml of isopropanol and 500 ml of petroleum ether bis-(*p*-chlorophenoxy)acetic acid 1-methyl-piperidyl-(4) ester, having a m.p. of $93-95^{\circ}$, is obtained.

EXAMPLE 3:

Description of a composition suitable for tablet manufacture

Bis-(<i>p</i> -chlorophenoxy)acetic acid 1-methyl-piperidyl-(4) ester	50 g	
tragacanth	2 g	
lactose	39.5 g	
maize starch	5 g	
talcum	5 g	
magnesium stearate	3 g	
alcohol SD 30	} the necessary amounts	110
distilled water		

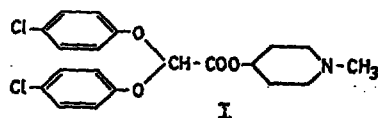
The weight of the tablets produced depends on the dose of active compound to be administered.

Alcohol SD 30 is described in, e.g., "Alcohols, Solvents and other Chemicals", Publisher Industries Inc. (1949), page 47.

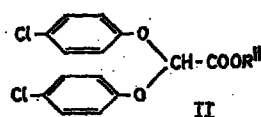


WHAT WE CLAIM IS:—

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



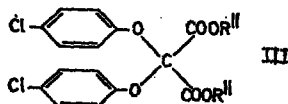
5 characterised in that
a) a compound of formula II,



10 in which R'' signifies an alkyl radical having 1 to 4 carbon atoms,
is reacted with a compound of formula IV.

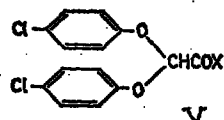


b) a compound of formula III,

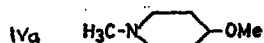


15 in which R'' has the above significance,
is reacted with the compound of formula IV
stated above at a temperature of: at least 110°C, or

c) a compound of formula V,



20 in which X signifies chlorine or bromine,
is reacted with the compound of formula IV
stated above or an alcoholate of formula IVa,



in which Me signifies an alkali metal.

25 2. A process according to Claim 1, in which
the reaction of the compound of formula II

with the compound of formula IV is effected
in an inert organic solvent in the presence of
an alkali metal alcoholate at a temperature
80° to 140°C.

3. A process according to Claim 1, in which
the reaction of the compound of formula III
with the compound of formula IV is effected
in an inert organic solvent in the presence of
an alkali metal alcoholate at a temperature
from 110° to 140°C.

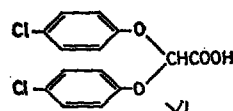
4. A process according to Claim 1, in which
the compound of formula V is reacted with the
compound of formula IV or IVa in an inert
organic solvent at a temperature from 20° to
-10°C.

5. A process according to Claim 1, in which
the compound of formula II or III is produced
by reacting an alkali metal *p*-chlorophenolate
with a dichloro- or dibromo-acetic acid alkyl
ester or a dichloro- or dibromo-malonic acid
dialkyl ester, in which the alkyl radical con-
tains from 1 to 4 carbon atoms inclusive, in
an inert organic solvent.

6. A process according to Claim 5, in which,
when a compound of formula II is being pre-
pared, the reaction is effected at a temperature
from 20° to 100°C.

7. A process according to Claim 5, in which,
when a compound of formula III is being pre-
pared, the reaction is effected at a temperature
from 20° to 80°C.

8. A process according to Claim 1, in which
the compound of formula V is produced in
that the compound of formula VI,



is treated with a chlorinating or brominating
agent in an inert organic solvent at a tem-
perature between 20°C and the boiling tem-
perature of the reaction mixture.

9. A process according to Claim 8, in which
the chlorinating agent is thionyl chloride or
phosphorus pentachloride.

10. A process according to Claim 8, in
which the brominating agent is thionyl
bromide or phosphorus pentabromide.

11. A process for the production of the
compound of formula I, stated in Claim 1,
and its acid addition and quaternary ammo-
nium salts, substantially as herein described
with reference to Example 1 or 2.

12. The compound of formula I, stated in
Claim 1.

13. The compound of formula I, whenever
prepared by a process according to any of
Claims 1 to 11.

14. Pharmaceutically acceptable acid addi-
tion or quaternary ammonium salts of the



compound of formula I according to Claim 12 or 13.

5 15. Fumarate, hydrochloride, methiodide or methobromide salt of the compound of formula I.

10 16. Pharmaceutical compositions comprising a pharmaceutically effective amount of the compound of formula I or a pharmaceutically acceptable acid addition or quaternary ammonium salt thereof in admixture with a pharmaceutically acceptable diluent or carrier.

17. A composition according to Claim 16 in unit dosage form, in which said compound

is present in an amount of from 0.25 to 2 g, or in sustained release form, in which said compound is present in an amount of from 62.5 mg to 1 g. 15

18. Pharmaceutical compositions substantially as herein described with reference to Example 3. 20

B. A. YORKE & CO.,
Chartered Patent Agents,
23, Great Castle Street,
London, W.1N 8 AE
Agents for the Applicants.