

PATENT SPECIFICATION

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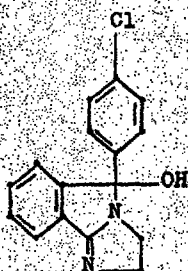
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(54) 5H-IMIDAZO (2,1-a) ISOINDOLE DERIVATIVES

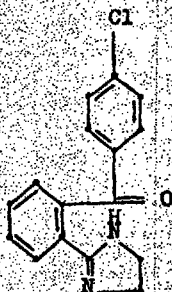
(71) We SANDOZ LTD of Lichtstrasse 35, 4000 Basle, Switzerland, a Swiss Body Corporate do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—
 This invention relates to 5-(p-chlorophenyl)-5-hydroxy-2,3-dihydro-5H-imidazo[2,1-a]isoindole of formula I,
 and in corresponding ionic forms of formula Ib and Ic,



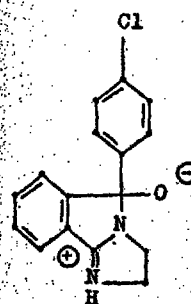
I

and acid addition salt forms thereof.

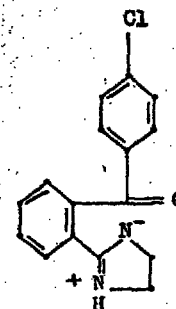
As will be appreciated by those skilled in the art, the compound of the invention also exists in the form of formula Ia,



[Price 25p]



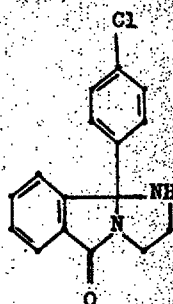
Ib



Ic

For the sake of simplicity, reference is hereafter made only to formula I or the corresponding chemical name, but it is not intended that the invention be limited to production of the compound in the particular form depicted in formula I or in the particular form defined by the corresponding chemical name.

In accordance with the invention, the compound of formula I is produced by treating the compound of formula II.



II

with lithium aluminium hydride, in an inert ether solvent, at a temperature not exceeding 45°C, and under an inert atmosphere, and contacting the reaction product, in solution, after removal of any remaining lithium aluminium hydride, with air or oxygen.

The preferred ether solvents for use in the lithium aluminium hydride treatment step are diethyl ether and tetrahydrofuran. The process temperature in this step is critical, as, at temperatures significantly in excess of 45°C, e.g. about 50°C, the desired product is not readily obtained. The step is preferably effected at a temperature of from 15° to 35°C. The inert atmosphere is suitable a nitrogen atmosphere. After a suitable period of time, e.g. from 6 hours to 8 days, any residual lithium aluminium hydride may be removed in conventional manner, for example by decomposition, suitably by addition of aqueous sodium hydroxide and, optionally, ethyl acetate. The ether solution of the reaction product may then be contacted with air or oxygen, for two to ten days. If desired, however, the oxidation may be accelerated, for example by bubbling air or oxygen into a solution of the product of the lithium aluminium hydride treatment, in a solvent, for example a C₁₋₄ alkanol such as methanol or ethanol. In this manner, appreciable yields of the desired product may be obtained within about 4 hours.

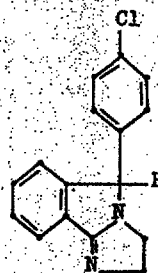
It will be appreciated that, if the product of the lithium aluminium hydride treatment is allowed to come into contact with air, for example during work-up, then some final product may initially be formed prior to the actual step of treating with air or oxygen, and indeed appreciable amounts of the final product of formula I may be formed by simply working-up the product of the lithium aluminium hydride treatment, in air. Of course, such a procedure is within the general terms of the invention.

The reaction mixture resulting from the lithium aluminium hydride treatment may generally be filtered to remove unwanted solids prior to or after the exposure to the air or oxygen. When the product of formula I crystallises to an appreciable extent before

the oxidation step, it will be appreciated that it is desirable, for improved yields of product, to filter prior to the oxidation.

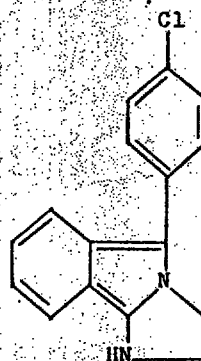
The resulting compound of formula I may be isolated and purified using conventional techniques. Where required, the free base form of the compound of formula I may be converted into pharmaceutically acceptable acid addition salt forms in conventional manner and *vice versa*.

The product of the treatment of a compound of formula II with lithium aluminium hydride is a compound of formula III,



III

which, as will be appreciated by those skilled in the art, may also exist in the form of formula IIIa,



IIIa

The compound of formula II is known or may be produced in known manner from available material (e.g. Netherlands Patent 6,501,647 published August 12th, 1965).

The compound of formula I has pharmacological activity, in particular, appetite depressant and central nervous system stimulant activity. The compound is therefore indicated for use as an anorexigenic agent and as a psychic energiser. As indicated suitable daily dosage is from about 1 mg to about 15 mg, preferably administered in divided dosages of from about 0.25 mg to about 7.5 mg, two to four times daily, in retard form.

The compound may be used, if desired mixed with conventional pharmaceutical carriers and/or other adjuvants, for oral administration in the form for example of

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tablets, elixers, suspensions or solutions, or
for parenteral administration in the form of
an injectable solution or suspension. It may,
e.g. be used in the form of a tablet having
the following composition: 1—3% of bind-
ing agent (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 100%.

10 A representative formulation is a tablet
(prepared by standard tableting techniques)

15 Compound of formula I, i.e.
5-(p-chlorophenyl)-5-
hydroxy-2,3-dihydro-5H-
imidazole[2,1-a]isoindole,
as free base

20 tragacanth
lactose
corn starch
talcum
25 magnesium stearate

Parts by
weight

10
2
79.5
5
3
0.5

30 The compound of formula I may be used
in the form of its non-toxic pharmaceutically
acceptable acid addition salts, which have the
same order of activity as the free base. Suit-
able acids for acid addition salt formation in-
clude hydrochloric, hydrobromic, sulphuric,
phosphoric, benzoic, acetic, maleic, p-toluene-
sulphonic and benzene-sulphonic acids.

Fraction	Eluant	Rf (Silica gel plate: 90 CHCl ₃ : 10 CH ₃ OH)
1	chloroform	0.90
2	chloroform	0.45
3	chloroform	0.45
4	chloroform	0.30, 0.45

75 Fractions 2 and 3 are then combined and
crystallized from methanol - methylene
chloride to obtain 5-(p-chlorophenyl)-5-
hydroxy - 2,3 - dihydro - 5H - imidazo -
[2,1-a]isoindole, m.p. 202—203°C.

Anal. Calcd. for C₁₆H₁₃ClN₂O:

C 67.0 H 5.3 Cl 12.4 N 9.8 O 5.6 %

Found:

80 C 67.5 H 5.4 Cl 12.4 N 9.8 O 5.8 %

Infrared:

KBr Pellet

Bands at 3.31, 3.39, 3.48, 3.62, 3.82, 6.06,
6.17, 6.72, 9.15 and 9.38 μ .

85 Ultraviolet Spectrum: (95% ethanol)

λ max.	E
223	21,420
269	4,930
275	4,930

The following Examples further illustrate
the invention.

EXAMPLE 1:

5-(p-Chlorophenyl)-5-hydroxy-2,3-
dihydro-5H-imidazo[2,1-a] isoindole

To a flask equipped with a stirrer, thermo-
meter, dropping funnel, condenser and gas
inlet tube, and blanketed with nitrogen, is
added 1000 ml of dry tetrahydrofuran and
10.0 g (0.263 mole) of lithium aluminium
hydride. The mixture is stirred and then a
solution of 30.0 g (0.105 mole) of 9b-(p-
chlorophenyl) - 1,2,3,9b - tetrahydro - 5H -
imidazo[2,1-a]-isoindol-5-one in 150 ml of
anhydrous tetrahydrofuran is added dropwise
such that the temperature of the reaction mix-
ture does not exceed 30°C. The resulting
mixture is stirred for an additional 6 hours at
room temperature, then cooled in an ice bath
and then treated with 100 ml of ethyl acetate,
20 ml of 2N sodium hydroxide and 30 ml
of water and contacted with air for 6 days.
The resulting mixture is filtered and the
filtrate dried by the addition of solid an-
hydrous sodium sulfate. The sodium sulfate is
then filtered off and the filtrate evaporated *in*
vacuo on a rotary evaporator. The residue is
crystallized from tetrahydrofurandithyl ether
(2:1) and then dissolved in chloroform. The
chloroform solution is then passed through a
silica gel column (250 g) and the column de-
veloped with chloroform to obtain the follow-
ing eluates:

Rf (Silica gel plate: 90 CHCl₃: 10 CH₃OH)

Mass Spectrm: Direct inlet

Parent peak M at 284. The ratio of M:
M+1: M+2 is 100.0:35.7:34.3. Other
significant peaks at 268, 256, 238, 231,
220, 190, 177, 176, 165, 155, 149, 139,
137, 130, 123, 111, 102, 83 and 81.

The preparation of the hydrochloride form
of this compound is described in Example 2.

EXAMPLE 2:

The hydrochloride salt form of 5-p-chloro-
phenyl-5-hydroxy-2,3-dihydro-5H-
imidazo[2,1-a]isoindole

5 - p - Chlorophenyl - 5 - hydroxy - 2,3 -
dihydro-5H-imidazo[2,1-a]isoindole is dis-
solved in tetrahydrofuran-methanol (1:2) and
saturated with hydrogen chloride gas. The re-
sultant solid is filtered off to give the HCl
salt of the starting material; m.p. 175—177°
C.

WHAT WE CLAIM IS:—

1. A process for the production of 5-(p-



- chlorophenyl) - 5 - hydroxy - 2,3 - dihydro - 5H-imidazo[2,1-a]isoindole or an acid addition salt form thereof, characterised by treating 9b - (p - chlorophenyl) - 1,2,3,9b - tetra - hydro-5H-imidazo[2,1-a]isoindol-5-one, with lithium aluminium hydride, in an inert ether solvent, at a temperature not exceeding 45° C, and under an inert atmosphere; and contacting the reaction product, in solution, after removal of any residual lithium aluminium hydride, with air or oxygen, and, where an acid addition salt form is required, converting the resulting product into such salt form.
2. A process according to Claim 1, in which the treatment with lithium aluminium hydride is carried out using diethyl ether or tetrahydrofuran as the inert ether solvent.
3. A process according to Claim 1 or 2, in which the treatment with lithium aluminium hydride is effected under an atmosphere of nitrogen, at a temperature of from 15° to 35°C.
4. A process according to Claim 1, 2 or 3, in which the reaction mixture resulting from the treatment with lithium aluminium hydride is treated with aqueous sodium hydroxide and ethyl acetate to remove any residual lithium aluminium hydride, and the resulting mixture is contacted with air or oxygen.
5. A process according to Claim 1, 2 or 3, in which the reaction mixture resulting from the treatment with lithium aluminium hydride is treated with aqueous sodium hydroxide and ethyl acetate to remove any residual lithium aluminium hydride, and the resulting mixture is filtered to remove unwanted solids, and the filtrate contacted with air or oxygen.
6. A process according to Claim 1, 2 or 3, in which the product resulting from the lithium aluminium hydride treatment is contacted in solution in methanol or ethanol, with air or oxygen.
7. A process according to Claim 6, in which the air or oxygen is bubbled through a solution of the product of the lithium aluminium hydride treatment, in methanol or ethanol.
8. A process for the production of 5-(p-chlorophenyl) - 5 - hydroxy - 2,3 - dihydro - 5H-imidazo isoindole or an acid addition salt form thereof, substantially as herein described with reference to any one of the Examples.
9. 5 - (p - Chlorophenyl) - 5 - hydroxy - 2,3-dihydro-5H-imidazo[2,1-a]isoindole or an acid addition salt thereof, whenever produced by a process according to any one of the preceding Claims.
10. 5 - (p - Chlorophenyl) - 5 - hydroxy - 2,3-dihydro-5H-imidazo[2,1-a]isoindole.
11. An acid addition salt form of 5-(p-chlorophenyl) - 5 - hydroxy - 2,3 - dihydro - 5H-imidazo[2,1-a]isoindole.
12. The hydrochloride form of 5-(p-chlorophenyl) - 5 - hydroxy - 2,3 - dihydro - 5H-imidazo[2,1-a]isoindole.
13. A pharmaceutical composition comprising 5 - (p - chlorophenyl) - 5 - hydroxy - 2,3 - dihydro-5H-imidazo[2,1-a]isoindole or a pharmaceutically acceptable acid addition salt form thereof, in association with a pharmaceutically acceptable carrier.
14. A pharmaceutical composition according to Claim 13, in unit dosage form, and containing from 0.25 to mg to 7.5 mg, or in unit retard form and containing from 1 mg to 15 mg of 5-(p-chlorophenyl)-2,3-dihydro-5H-imidazo[2,1-a]isoindole or a pharmaceutically acceptable acid addition salt thereof.
15. A pharmaceutical composition according to Claim 13 or 14, substantially as herein described.

for the Applicants:—
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