

PATENT SPECIFICATION

NO DRAWINGS

1173.308



Date of Application and filing Complete Specification: 1 Nov., 1966.
No. 5705/68.

Application made in United States of America (No. 506129) on 2 Nov., 1965.

Application made in United States of America (No. 578153) on 9 Sept., 1966.

(Divided out of No. 1173304).

Complete Specification Published: 10 Dec., 1969.

Index at acceptance: —C2 C(1E7D1, 1E7F1, 1E7H2, 1E7N5, 1E7P3, 1Q4, 1Q6C, 1Q7A, 1Q8A, 1Q9B, 1Q9F2, 1Q11J, 3A12A4A, 3A12B1, 3A12C4, 3A12C5, 213, 22Y, 220, 226, 25Y, 250, 252, 30Y, 305, 332, 351, 352, 36Y, 360, 362, 50Y, 509, 621, 671, 672, 761, 185-199-285, ML)

International Classification: —C 07 d 53/06, 57/00

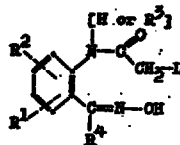
COMPLETE SPECIFICATION

The Manufacture of Benzdiaz[1,4]epine Derivatives

We, F. HOFFMANN-LA ROCHE & CO.,
AKTIENGESELLSCHAFT, a Swiss Company of
124—184 Grenzacherstrasse, Basle, Switzer-
land, 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 the manu-
facture of benzdiaz[1,4]epine derivatives.
More particularly, the invention is concerned
with a process for the manufacture of valuable
3-hydroxy-benzdiaz[1,4]epine derivatives.

The 3 - hydroxy - benzdiaz[1,4]epine de-
rivatives obtained by carrying out the process
provided by the invention are compounds of
the general formula

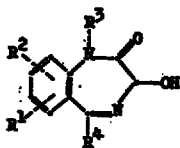


30

(II)

, wherein R¹, R², R³, R⁴ and the broken lines
have the significance given earlier and L
stands for a leading atom or group, with a
base in the presence of an inert organic sol-
vent and proceeding to the 3-hydroxy-benz-
diaz[1,4]epine derivative without isolation of
the benzoxadiaz[4,1,5]ocine of the general
formula

35

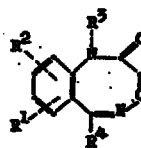


(I)

wherein R¹ and R² each represent a halogen
atom or the trifluoromethyl or nitro group,
R³ represents a lower-alkyl group and R⁴ re-
presents the phenyl group or a pyridyl or
halo-phenyl group and wherein the broken
lines denote that the substituents attached
thereby are optional.

According to the process provided by the
invention, the 3-hydroxy-benzdiaz[1,4]epine
derivatives aforesaid are manufactured by
treating an *alpha*-oxime of the general formula

[Price 4s. 6d.]



(III)

, wherein R¹, R², R³, R⁴ and the broken lines
have the significance given earlier, which is
intermediately formed.

The benzoxadiaz[4,1,5]ocines of formula
III in which R¹ (when present) is in the
8-position, R³ (when present) represents an
alkyl group containing from 1 to 4 carbon
atoms and R⁴ represents the phenyl group
or a halo-phenyl group are claimed *per se* in
the specification of our copending Application
for Letters Patent No. 3150/67 (now Serial
No. 1173305). The benzoxadiaz[4,1,5]ocines
of formula I in which R⁴ represents a pyridyl

40

45

50

group are claimed *per se* in the specification of our copending Application for Letters Patent No. 48913/66 (now Serial No. 1173304).

5 One interesting class of *alpha*oxime starting materials of formula II comprises those in which R² is absent, particularly those in which R³ is also absent and R¹ is present in the 5-position. Preferably R¹ represents a
10 halogen atom, especially a chlorine atom. When R⁴ represents a halo-phenyl group, this is preferably a 2-halo-phenyl group. A further interesting class of *alpha*oxime starting materials comprises those in which R⁴ represents a pyridyl group, particularly those in which R² and R³ are absent and in which R¹ is present in the 5-position and represents a
15 halogen atom (especially a bromine atom). With regard to the leaving group or atom L, this is preferably a chlorine, bromine or iodine atom or an arylsulphonyloxy, mesyloxy or other lower-alkylsulphonyloxy group. It will be appreciated that the term "*alpha*-oxime" is used in this specification to mean
20 that the oxime group is in the *syn*-position with respect to the amino-substituted phenyl group.

The treatment of an *alpha*oxime of formula II with a base in accordance with the process
25 provided by the invention can be carried out at room temperature or at a temperature above or below room temperature. Preferably the treatment is carried out at a temperature of from 0°C to 40°C, more preferably at a temperature of from 15°C to 30°C and most
30 preferably at room temperature. Also, while the amount of base employed is not critical, highest yields of the 3-hydroxy-benzdiaz[1,4]epine derivatives of formula I are obtained
35 when above 2 molar equivalents of the base are present for each mol of *alpha*oxime starting material of formula II. While a halogen atom or a sulphonyloxy group is preferred as the leaving atom or group in the *alpha*oximes
40 of formula II, it will, of course, be appreciated that any equivalent leaving atom or group can be present in place thereof. All that is required of the leaving atom or group is that it function efficaciously in the process
45 aforesaid; that is to say, that it acts as a suitable leaving atom or group for the purposes of the present invention.

Suitable bases which can be used in the process aforesaid include alkali-metal hydroxides (e.g. sodium hydroxide and potassium
50 hydroxide), alkali-earth-metal hydroxides (e.g. calcium hydroxide), alkali-metal alcoholates (e.g. sodium methoxide), alkali-metal hydrides (e.g. sodium hydride), alkali-metal amides (e.g. sodamide) or any other suitable
55 base. All that is required of the base to be suitable for the purposes of this invention is that it function efficaciously therein; that is to say, that the treatment therewith of an
60 *alpha*oxime of formula II results in a corres-

ponding 3-hydroxy-benzdiaz[1,4]epine derivative in accordance with the process provided by the invention. Most preferred among the many bases which will effect the desired
65 result are alkali-metal hydroxides (preferably sodium hydroxide) and alkali-metal alcoholates such as sodium methoxide.

The process provided by the invention proceeds in any suitable inert organic solvent. Suitable solvents include alkanols containing
70 from 1 to 7 carbon atoms such as methanol and ethanol, ethers such as dioxan, dimethoxy-ethane and tetrahydro-furan and any similar inert organic solvent. Water-miscible inert organic solvents are preferred.

It will be apparent from the foregoing that the 3-hydroxy-benzdiaz[1,4]epine derivatives aforesaid can be manufactured by treating
75 an *alpha*oxime of formula II with a base in the presence of any suitable inert organic solvent until a 3-hydroxy-benzdiaz[1,4]epine derivative of formula I is obtained; that is to say, without isolating an intermediately
80 formed benzoxadiaz[4,1,5]ocine of formula III.

The process provided by the present invention represents a significant advance over processes previously disclosed in the literature for the production of 3-hydroxy-benzdiaz[1,4]
85 epine derivatives of formula I, for example, treatment of a 2-haloacetamido-benzophenone *beta*oxime (the oxime group being in the *anti*-position with regard to the amino-substituted phenyl group) with alkali, reaction of the resulting 5-aryl-2,3-dihydro-1H-benzdiaz[1,4]epinone-(2) 4-oxide with an acylating agent and hydrolysis of the resulting 3-acyloxy-2,3-dihydro-1H-benzdiaz[1,4]
90 epinone-(2). The present invention provides the 3-hydroxy-benzdiaz[1,4]epine derivatives of formula I in good yields and by a simple procedure.

The following Examples illustrate the invention:

EXAMPLE 1

62 ml of 1-N sodium hydroxide solution were carefully added with stirring to a solution of 20 g (61.9 mmol) of 2-(2-chloroacetamido)-5-chloro-benzophenone *alpha*oxime (the *syn* form) in 190 ml of dioxan.
110 The resulting mixture was stirred for a further 20 hours, then filtered. The filtrate was concentrated under reduced pressure to remove dioxan and water was simultaneously added. The thus concentrated filtrate was extracted with chloroform and the chloroform
115 extract was washed with water, dried over sodium sulphate and concentrated to dryness under reduced pressure. Crystallization of the residue from a mixture of methylene chloride and hexane gave crude 7-chloro-3-hydroxy-5-phenyl-2,3-dihydro-1H-benzdiaz[1,4]
120 epinone-(2). Recrystallization from ethanol further purified the product.

EXAMPLE 2

77.4 ml of 2-N sodium hydroxide solution were carefully added with stirring over a period of 10 minutes to a solution of 25 g (77.4 mmol) of 2-(2-chloro-acetamido)-5-chloro-benzophenone *alpha*oxime (the *syn* form) in 238 ml of dioxan. The resulting mixture was allowed to stand for 22 hours and the material which crystallized was separated by filtration.

The solid obtained was washed with methanol and dried to give the sodium salt of 7-chloro-3-hydroxy-5-phenyl-2,3-dihydro-1H-benzdiaz[1,4]epinone-(2) of melting point 220°—238°C (with decomposition). The crude product was extracted with hot chloroform to leave material melting at 210°—225°C (with decomposition). Crystallization of this material from aqueous ethanol acidified to about pH 1—2 with dilute hydrochloric acid yielded 7-chloro-3-hydroxy-5-phenyl-2,3-dihydro-1H-benzdiaz[1,4]epinone-(2).

The dioxan filtrate obtained according to the first paragraph of this Example was neutralised with acetic acid and concentrated under reduced pressure to remove dioxan, while water was simultaneously added. The water-insoluble residue was partitioned with chloroform and water and the insoluble material which was formed was separated by filtration and was found to be crude 7-chloro-3-hydroxy-5-phenyl-2,3-dihydro-1H-benzdiaz[1,4]epinone-(2).

EXAMPLE 3

31 ml of 2-N sodium hydroxide solution were added with stirring to a solution of 10 g (27.2 mmol) of 2-(1-bromo-acetamido)-5-chloro-benzophenone *alpha*oxime in 95 ml of dioxan. The resulting mixture was kept at room temperature for 18 hours, then filtered. The filtrate was acidified to pH 1.6 with dilute hydrochloric acid and filtered. The filtrate was concentrated under reduced pressure, while adding water, to remove dioxan. 100 ml of chloroform were added to the aqueous residue and the resulting solid was separated by filtration to give 7-chloro-3-hydroxy-5-phenyl-2,3-dihydro-1H-benzdiaz[1,4]epinone-(2). The product was purified by recrystallization from aqueous N,N-dimethyl-formamide.

EXAMPLE 4

A solution of 5 g (20 mmol) of 2-amino-5-chloro-benzophenone *alpha*oxime in 100 ml of dioxan was cooled to 12°C and 1.6 ml (2.4 g, 21 mmol) of chloro-acetyl chloride were added dropwise thereto over a period of 40 minutes, the resulting mixture being kept slightly basic by simultaneous addition of 10% sodium hydroxide. After an additional 45 minute period, 20.3 ml of 2-N sodium hydroxide were added and stirring was con-

tinued at room temperature for 20 hours. Filtration gave a solid, melting at 196°—255°C (with decomposition), which was dissolved in 50% aqueous ethanol (pH 11.5) and acidified to pH 2.2 by addition of 3-N hydrochloric acid. The crystalline product which formed was separated by filtration to yield 7-chloro-3-hydroxy-5-phenyl-2,3-dihydro-1H-benzdiaz[1,4]epinone-(2) of melting point 195°—196°C.

EXAMPLE 5

125 ml of 2-N sodium hydroxide solution were added to a solution of 20 g (62 mmol) of 2-(2-chloro-acetamido)-5-chloro-benzophenone *alpha*oxime in 300 ml of dioxan. The resulting mixture was stirred for 15 hours, then the solid which was formed was separated by filtration to yield a sodium salt of 7-chloro-3-hydroxy-5-phenyl-2,3-dihydro-1H-benzdiaz[1,4]epinone-(2) melting at 180°—260°C [during the reaction, 8-chloro-6-phenyl-2,3-dihydro-1H-benzoxadiaz[4,1,5]ocinone-(2) was first formed].

The said sodium salt was dissolved in 350 ml of 70% ethanol, the solution was filtered to remove a small amount of insoluble material and the filtrate was acidified to pH 1.5 by the addition of 3-N hydrochloric acid. The crystalline product which was formed was separated by filtration to give 7-chloro-3-hydroxy-5-phenyl-2,3-dihydro-1H-benzdiaz[1,4]epinone-(2) melting at 191°—193.5°C. A second crop of melting point 179°—183°C formed on standing.

The dioxan solution obtained from the filtration described in the first paragraph of this Example was acidified to pH 1.6 by addition of 3-N hydrochloric acid, then concentrated under reduced pressure to remove dioxan. The residue was partitioned between chloroform and water. Filtration separated crude 7-chloro-3-hydroxy-5-phenyl-2,3-dihydro-1H-benzdiaz[1,4]epinone-(2) (melting point = 171°—176°C) which formed at the interface. The crude fractions were purified by crystallization from aqueous N,N-dimethyl-formamide to give 7-chloro-3-hydroxy-5-phenyl-2,3-dihydro-1H-benzdiaz[1,4]epinone-(2) melting at 196°—197.5°C (with decomposition).

EXAMPLE 6

In the manner described in Example 5, 2-(2-chloro-acetamide)-5-trifluoromethyl-benzophenone *alpha*oxime (melting point = 174°C—176°C) was converted into 7-trifluoromethyl-3-hydroxy-5-phenyl-2,3-dihydro-1H-benzdiaz[1,4]epinone-(2) via 8-trifluoromethyl-6-phenyl-2,3-dihydro-1H-benzoxadiaz[4,1,5]ocinone-(2) of melting point 212°—214°C after recrystallization from methanol.

EXAMPLE 7

A) *The preparation of the starting material:*

2 - (2 - *paratoluenesulphonyloxy* - acetamido - 5 - chloro - benzophenone *alpha*-oxime (melting point=159°—160°C) was prepared by reaction of 2-*paratoluenesulphonyloxy*-acetyl chloride with 2-amino-5-chloro-benzophenone *alpha*oxime.

B) *The process:*

In a manner analogous to that described in Example 5, 2-(2-*paratoluenesulphonyloxy*-acetamido) - 5 - chloro - benzophenone *alpha*-oxime was converted into 7-chloro-3-hydroxy-5-phenyl - 2,3 - dihydro - 1H - benzdiaz-[1,4]epinone - (2) *via* 8 - chloro - 6 - phenyl - 2,3 - dihydro - 1H - benzoxadiaz[4,1,5]ocinone-(2).

EXAMPLE 8

A) *The preparation of the starting material:*

2 - Amino - 5 - chloro - benzophenone *alpha*oxime was reacted with 2-mesyloxy-acetyl chloride to give 2-(2-mesyloxy-acetamido) - 5 - chloro - benzophenone *alpha*oxime of melting point 136°—138°C [after recrystallization from (methylene chloride)/hexane].

B) *The process:*

In a manner analogous to that described in Example 5, 2-(2-mesyloxy-acetamido)-5-chloro-benzophenone *alpha*oxime was converted into 7-chloro-3-hydroxy-5-phenyl-2,3-dihydro - 1H - benzdiaz[1,4]epinone-(2) *via* 8 - chloro - 6 - phenyl - 2,3 - dihydro - 1H - benzoxadiaz[4,1,5]ocinone-(2).

EXAMPLE 9

A) *The preparation of the starting material:*

From 2 - amino - benzophenone *alpha*oxime there was obtained 2-(2-chloro-acetamido)-benzophenone *alpha*oxime of melting point 136°—137°C.

B) *The process:*

The treatment of 2-(2-chloro-acetamido)-benzophenone *alpha*oxime with a base as described in Example 5 gave 3-hydroxy-5-phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epinone-(2) with 6-phenyl-2,3-dihydro-1H-benzoxadiaz[4,1,5]ocinone-(2) (melting point=236°—238°C after recrystallization from methanol) occurring as an intermediate.

EXAMPLE 10

A solution of 3 g (9 mmol) of 2-(2-chloro-acetamido) - 5 - nitro - benzophenone *alpha*oxime in 150 ml of dioxan and 18 ml sodium hydroxide was stirred at room temperature for 15 hours. 150 ml of water were then added, following which 3-N hydrochloric acid was added to bring the pH to 5. Dioxan was subsequently removed by distillation under reduced pressure and the residue was partitioned between water and methylene chloride. The organic layer was separated, dried over sodium sulphate and concentrated by distilla-

tion under reduced pressure. A solid formed and was removed by filtration [melting point=185°—190°C (with decomposition)]. The filtrate was concentrated to dryness and the residue triturated with ether. The solid obtained on filtration (melting point=247°—249°C) was recrystallized from a mixture of methylene chloride and hexane to give 8-nitro - 6 - phenyl - 2,3 - dihydro - 1H - benzoxadiaz[4,1,5]ocinone - (2) of melting point 254°—255°C. The solid of melting point 185°—190°C (with decomposition), was also triturated with ether to give 3-hydroxy - 7 - nitro - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epinone - (2) of melting point 214°—215°C (with decomposition). Recrystallization from acetonitrile did not alter the melting point.

EXAMPLE 11

A solution of 20 g (62 mmol) of 2-(2-chloro - acetamido) - 5 - chloro - benzophenone *alpha*oxime in a mixture of 400 ml of ethanol and 125 ml of 2-N sodium hydroxide was stirred at room temperature for 2 hours. The solid which separated out was removed by filtration [melting point=200°—220°C (with decomposition)]. The solid was dissolved in 300 ml of 60% aqueous ethanol (pH 11.8) and acidified to pH 1.8 with 3-N hydrochloric acid. Filtration separated 7 - chloro - 3 - hydroxy - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epinone-(2) of melting point 197°—198°C (with decomposition).

EXAMPLE 12

To a solution of 21 g (56 mmol) of 2-[2-(2-chloro - acetamido) - 5 - bromo - benzoyl] - pyridine *alpha*oxime in 700 ml of dioxan there were added 39.9 ml of 2.79-N sodium methoxide and the resulting solution was stirred at room temperature for 20 hours, then filtered to remove a small amount of gelatinous material. The filtrate was diluted with water and acidified to pH 4.1 by addition of 3-N hydrochloric acid. A light yellow solid crystallized and was separated by filtration [melting point=322°—323°C (with decomposition)]. Dioxan was removed from the filtrate by distillation under reduced pressure and the residue was partitioned between chloroform and water. The organic layer was dried over sodium sulphate and concentrated to a small volume and the residue was dissolved in ethyl acetate. The solution was filtered through a column of activated magnesium silicate (14"×0.75"). [On concentration of the ethyl acetate filtrates there crystallized 8 - bromo - 6 - [pyridyl - (2)] - 2,3 - dihydro - 1H - benzoxadiaz[4,1,5]ocinone - (2) of melting point 225°—228°C. Recrystallization from a mixture of tetrahydro-furan and hexane gave colourless rods of the product melting at 229°—231°C.] Continued

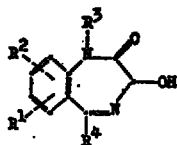
elution with ethyl acetate separated a second fraction which on concentration gave crystals. Recrystallization of the material from acetonitrile yielded a product which was separated by filtration. The acetonitrile filtrate crystallized to yield 7-bromo-3-hydroxy-5-[pyridyl - (2)] - 2,3 - dihydro - 1H - benzodiaz[1,4]epinone-(2) of melting point 198°—200°C (with decomposition). Recrystallization from a mixture of tetrahydro-furan and hexane followed by drying at 100°C gave the product in analytically pure form.

The term 'halogen' is used in this specification to mean chlorine, fluorine, bromine and iodine. When R¹ represents a halogen atom, chlorine and bromine are preferred. Further, when R⁴ represents a halo-phenyl group, the fluoro-phenyl group is preferred. The term 'lower alkyl' is used to mean both straight-chain and branched-chain alkyl groups containing up to seven carbon atoms (e.g. methyl, ethyl, propyl and isopropyl). The term 'alkylsulphonyl' means a sulphonyl group having a straight-chain or branched-chain lower-alkyl group joined thereto (e.g. mesyl). The term 'arylsulphonyl' means a sulphonyl group having preferably a phenyl, substituted-phenyl (e.g. lower alkyl-phenyl) or a naphthyl group joined thereto such as benzenesulphonyl or tosyl.

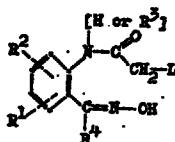
Having regard to the provisions of Section 9 of the Patents Act, 1949, attention is directed to the claims of Patents Nos. 1,022,642 and 1,022,644.

WHAT WE CLAIM IS:—

1. A process for the manufacture of compounds of the general formula



, wherein R¹ and R² each represent a halogen atom or the trifluoromethyl or nitro group, R³ represents a lower-alkyl group and R⁴ represents the phenyl group or a pyridyl or halo-phenyl group and wherein the broken lines denote that the substituents attached thereby are optional, which process comprises treating an *alpha*oxime of the general formula



, wherein R¹, R², R³, R⁴ and the broken lines have the significance given earlier in

this claim and L stands for a leaving atom or group, with a base in the presence of an inert organic solvent and proceeding to a compound of the formula first written in this claim without isolation of a benzoxadiaz[4,1,5]ocine of the general formula



, wherein R¹, R², R³, R⁴ and the broken lines have the significance given earlier in this claim, which is intermediately formed.

2. A process as set forth in claim 1, wherein an *alpha*oxime in which R³ is absent is used as the starting material.

3. A process as set forth in claim 1 or claim 2, wherein an *alpha*oxime in which R² and R³ are absent and R¹ is present in the 5-position is used as the starting material.

4. A process as set forth in claim 3, wherein an *alpha*oxime in which R¹ represents a halogen atom is used as the starting material.

5. A process as set forth in claim 4, wherein said halogen atom is a chlorine atom.

6. A process as set forth in claim 1 or claim 2, wherein an *alpha*oxime in which R⁴ represents a pyridyl group is used as the starting material.

7. A process as set forth in claim 6, wherein in said *alpha*oxime R² and R³ are absent and R¹ is present in the 5-position and represents a halogen atom.

8. A process as set forth in claim 7, wherein said halogen atom is a bromine atom.

9. A process as set forth in any one of claims 6 to 8 inclusive, wherein said pyridyl group is a pyridyl-(2) group.

10. A process as set forth in any one of claims 1 to 9 inclusive, wherein the leaving atom L stands for a chlorine, bromine or iodine atom.

11. A process as set forth in any one of claims 1 to 9 inclusive, wherein the leaving group L stands for an arylsulphonyloxy or mesyloxy group.

12. A process as set forth in any one of claims 1 to 9 inclusive, wherein the leaving group L therein stands for a lower-alkylsulphonyloxy group.

13. A process as set forth in any one of claims 1 to 12 inclusive, wherein an alkali-metal hydroxide is used as the base.

14. A process as set forth in claim 13, wherein said alkali-metal hydroxide is sodium hydroxide.

15. A process as set forth in claim 1, substantially as described with reference to Examples 1—6, 7B, 8B, 9B or 10—12.



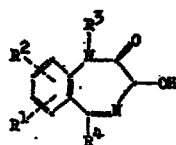
elution with ethyl acetate separated a second fraction which on concentration gave crystals. Recrystallization of the material from acetonitrile yielded a product which was separated by filtration. The acetonitrile filtrate crystallized to yield 7-bromo-3-hydroxy-5-[pyridyl - (2)] - 2,3 - dihydro - 1H - benzodiaz[1,4]epinone-(2) of melting point 198°—200°C (with decomposition). Recrystallization from a mixture of tetrahydro-furan and hexane followed by drying at 100°C gave the product in analytically pure form.

The term 'halogen' is used in this specification to mean chlorine, fluorine, bromine and iodine. When R^1 represents a halogen atom, chlorine and bromine are preferred. Further, when R^4 represents a halo-phenyl group, the fluoro-phenyl group is preferred. The term 'lower alkyl' is used to mean both straight-chain and branched-chain alkyl groups containing up to seven carbon atoms (e.g. methyl, ethyl, propyl and isopropyl). The term 'alkylsulphonyl' means a sulphonyl group having a straight-chain or branched-chain lower-alkyl group joined thereto (e.g. mesyl). The term 'arylsulphonyl' means a sulphonyl group having preferably a phenyl, substituted-phenyl (e.g. lower alkyl-phenyl) or a naphthyl group joined thereto such as benzenesulphonyl or tosyl.

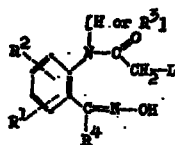
Having regard to the provisions of Section 9 of the Patents Act, 1949, attention is directed to the claims of Patents Nos. 1,022,642 and 1,022,644.

WHAT WE CLAIM IS:—

1. A process for the manufacture of compounds of the general formula

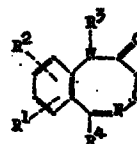


, wherein R^1 and R^2 each represent a halogen atom or the trifluoromethyl or nitro group, R^3 represents a lower-alkyl group and R^4 represents the phenyl group or a pyridyl or halo-phenyl group and wherein the broken lines denote that the substituents attached thereby are optional, which process comprises treating an α phaoxime of the general formula



, wherein R^1 , R^2 , R^3 , R^4 and the broken lines have the significance given earlier in

this claim and L stands for a leaving atom or group, with a base in the presence of an inert organic solvent and proceeding to a compound of the formula first written in this claim without isolation of a benzoxadiaz[4,1,5]ocine of the general formula



, wherein R^1 , R^2 , R^3 , R^4 and the broken lines have the significance given earlier in this claim, which is intermediately formed.

2. A process as set forth in claim 1, wherein an α phaoxime in which R^3 is absent is used as the starting material.

3. A process as set forth in claim 1 or claim 2, wherein an α phaoxime in which R^3 and R^4 are absent and R^1 is present in the 5-position is used as the starting material.

4. A process as set forth in claim 3, wherein an α phaoxime in which R^1 represents a halogen atom is used as the starting material.

5. A process as set forth in claim 4, wherein said halogen atom is a chlorine atom.

6. A process as set forth in claim 1 or claim 2, wherein an α phaoxime in which R^4 represents a pyridyl group is used as the starting material.

7. A process as set forth in claim 6, wherein in said α phaoxime R^3 and R^4 are absent and R^1 is present in the 5-position and represents a halogen atom.

8. A process as set forth in claim 7, wherein said halogen atom is a bromine atom.

9. A process as set forth in any one of claims 6 to 8 inclusive, wherein said pyridyl group is a pyridyl-(2) group.

10. A process as set forth in any one of claims 1 to 9 inclusive, wherein the leaving atom L stands for a chlorine, bromine or iodine atom.

11. A process as set forth in any one of claims 1 to 9 inclusive, wherein the leaving group L stands for an arylsulphonyloxy or mesyloxy group.

12. A process as set forth in any one of claims 1 to 9 inclusive, wherein the leaving group L therein stands for a lower-alkylsulphonyloxy group.

13. A process as set forth in any one of claims 1 to 12 inclusive, wherein an alkali-metal hydroxide is used as the base.

14. A process as set forth in claim 13, wherein said alkali-metal hydroxide is sodium hydroxide.

15. A process as set forth in claim 1, substantially as described with reference to Examples 1—6, 7B, 8B, 9B or 10—12.

16. Compounds of the formula first written
in claim 1, when manufactured by a process
as claimed in any one of the preceding claims.

W. D. WHITAKER,
Patent Agent,
For F. HOFFMANN-LA ROCHE & CO.,
Aktiengesellschaft.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1969.
Published by the Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.



W.D. Whitaker