

1117.062



PATENT SPECIFICATION

NO DRAWINGS

1117.062

Date of Application and filing Complete Specification: 14 June, 1965.

No. 42698/67.

Application made in France (No. 978,360) on 15 June, 1964.

(Divided out of No. 1,117,061.)

Complete Specification Published: 12 June, 1968.

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Index at acceptance:—C2 C(1H2A1, 1H2A2, 1H2A9, 1H2C2, 2A2, 2A12, 2A14, 2S18)

Int. Cl.:—C 07 c 119/14

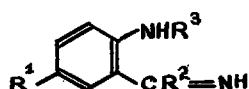
COMPLETE SPECIFICATION

Ortho-Aminoarylketimines

5 We, ETABLISSEMENTS CLIN-BYLA, a French Body Corporate, of 20 rue des Fossés Saint-Jacques, Paris, France, 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:—

10 This invention relates to ortho-aminoaryl ketimines which are valuable intermediates in the production of pharmacologically interesting benzodiazepines.

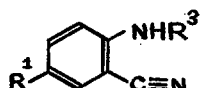
The ortho-aminoaryl ketimines have the general formula



15 in which R¹ is a hydrogen or halogen atom, a trifluoromethyl group, an alkyl group having 1 to 7 carbon atoms, an alkoxy group having 1 to 7 carbon atoms or a nitro or amino group, R² is a phenyl group which may be substituted
20 by a halogen atom, by a trifluoromethyl or nitro group or by an alkyl or alkoxy group having 1 to 7 carbon atoms or is an alkyl group having 1 to 7 carbon atoms, or a cyclo-alkyl group having 5 to 7 carbon atoms or a
25 furyl or thienyl group and R³ is a hydrogen atom or an alkyl group having 1 to 7 carbon atoms.

30 The alkyl groups have 1 to 7 carbon atoms in a straight or branched chain; for example, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, tertiary-butyl, amyl and hexyl groups.

35 In accordance with a feature of the invention the orthoaminoaryl ketimines are prepared by a process which comprises reacting an orthoaminobenzonitrile having the general formula



in which R¹ and R³ are as defined above, with an organo-magnesium compound having the general formula



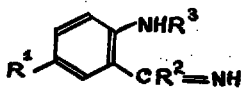
40 in which R² is as defined above and X is a halogen atom, preferably a bromine atom, and decomposing the resulting magnesium-containing compound with aqueous liquid.

45 A substantial excess of the Grignard reagent R²MgX is used, preferably 3 to 4 mols per mol of ortho-aminobenzonitrile used. The process may be carried out in anhydrous ethyl ether and the starting materials allowed to react in the boiling solvent for up to about 15 hours. After cooling, the magnesium complex is decomposed with an aqueous ammonium chloride solution and the solvent evaporated.
50 The ortho-amino aryl ketimine crystallises spontaneously in most cases and may be purified by recrystallisation from a suitable solvent, in particular from a hydrocarbon such as hexane or cyclohexane.

60 The ortho-amino aryl ketimines are thus obtained in the form of pale yellow, well defined crystalline compounds. The yield is generally high, frequently of the order of 80 to 90%. The infra red spectra of these compounds agree with the structure indicated which is, moreover, confirmed by elementary analysis. The compounds have, among others, two bands characteristic of the vibrational frequency of the N—H bond: a fine line in the region of 3480 cm⁻¹ (absent if only a
65 secondary amino group is present) and a wide band at 3270—3300 cm⁻¹ due to the N—H of the imine and to the chelated NH of the —NHR³ group; moreover, the infra red spectra show two bands in the region of 1600 cm⁻¹ (1610—1580 cm⁻¹) due to the aromatic
70 >C=C< conjugated to >C=N—.

75 The Table sets out certain imines having the general formula which may be prepared as indicated in the examples given hereinafter.

TABLE



No.	R ¹	R ²	R ³	Example
4356 CB	Cl	C ₆ H ₅	H	1
4357	Cl	C ₆ H ₅	CH ₃	2
4358	H	C ₆ H ₅	H	3
4359	Cl	C ₆ H ₁₁ (cyclohexyl)	H	4
4360	Cl	n-C ₄ H ₉	H	5
	CH ₃	C ₆ H ₅	H	6

The following examples illustrate the invention; the melting points are designated by M.pt._K or M.pt._c according to whether they are measured on a Kofler block or in a capillary tube.

EXAMPLE 1.

(2-Amino-5-chlorophenyl)-phenylmethanimine (4356 CB).

A solution of 228.7 g (1.5 mols) of 2-amino-5-chloro-benzonitrile in 1800 ml of dry ether is added slowly in the course of about 3.5 hours to a solution of phenyl magnesium bromide prepared from 109 g (4.5 gram atoms) of magnesium turnings and 848 g (5.4 mols) of bromobenzene in 3600 ml of anhydrous ether, and the mixture then heated under reflux for 15 hours.

The complex is decomposed by stirring the reaction mixture into a solution prepared from 500 g of ammonium chloride in 2000 ml of water to which 3 kg of crushed ice have been added. The resulting reaction mixture is extracted with ether three times, the ethereal extracts combined, washed with water and the ether is evaporated in vacuo at 40°C. The oily residue is taken up in 500 ml of petroleum ether and left to crystallise by cooling at -20°C. The yellowish crystals formed are dried (309 g); M.pt._K: 74°C.; yield: 92%.

EXAMPLE 2.

(2-Methylamino-5-chlorophenyl)-phenylmethanimine (4357 CB).

Using the method described in Example 1 but replacing 2-amino-5-chlorobenzonitrile by an equimolecular quantity of 2-methylamino-5-chlorobenzonitrile, compound 4357 CB is obtained in a yield of 61%: yellowish crystals; M.pt._K: 97°C. (hexane).

EXAMPLE 3.

(2-Aminophenyl)-phenylmethanimine (4358 CB).

Proceeding as in Example 1 but replacing the 2-amino-5-chloro-benzonitrile by an equimolecular quantity of 2-amino-benzonitrile, this compound is obtained in a yield of about 80% of crude product. Yellowish crystals are obtained; M.pt._c: 48°C. (diisopropyl ether).

EXAMPLE 4.

Cyclohexyl-(2-amino-5-chlorophenyl)-methanimine (4359 CB).

Proceeding as in Example 1 but replacing the bromobenzene by the equimolecular quantity of bromocyclohexane, this compound is obtained in a yield of 81%: yellowish crystals with double melting point; M.pt._K: 65°C. and then 95°C.

EXAMPLE 5.

n-Butyl-(2-amino-5-chlorophenyl)-methanimine (4360 CB)

This product is obtained by the technique employed in Example 1 but the bromobenzene is replaced by an equivalent quantity of 1-bromo-n-butane.

A brownish oil is obtained (yield: 94%). The product may be crystallised in small quantities from cold petroleum ether; M.pt._c: 27-28°C. (decomposition).

EXAMPLE 6.

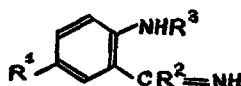
Example 1 is repeated using in place of the 2-amino-5-chlorobenzonitrile an equimolecular quantity of 2-amino-5-methylbenzonitrile.

An oily product was obtained which did not crystallise.



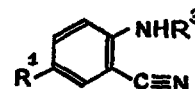
WHAT WE CLAIM IS:—

1. An ortho-aminoaryl ketimine having the general formula



- 5 in which R¹ is a hydrogen or halogen atom, a trifluoromethyl group, an alkyl group having 1 to 7 carbon atoms, an alkoxy group having 1 to 7 carbon atoms or a nitro or amino group, R² is a phenyl group which may be substituted by a halogen atom, by a trifluoromethyl or nitro group or by an alkyl or alkoxy group having 1 to 7 carbon atoms, or is an alkyl group having 1 to 7 carbon atoms, a cycloalkyl group having 5 to 7 carbon atoms, or a furyl or thienyl group and R³ is a hydrogen atom or an alkyl group having 1 to 7 carbon atoms.
- 10 2. (2 - Amino - 5 - chlorophenyl) - phenylmethane - imine.
- 20 3. (2 - Methylamino - 5 - chlorophenyl) - phenylmethane - imine.
4. (2 - Aminophenyl) - phenylmethane - imine.
5. Cyclohexyl - (2 - amino - 5 - chlorophenyl) methane - imine.
- 25 6. Butyl - (2 - amino - 5 - chlorophenyl) - methane - imine.
7. (2 - Amino - 5 - methylphenyl) - phenylmethane - imine.
- 30 8. A process for the production of an ortho-aminoaryl ketimine having the general formula

given in claim 1 which comprises reacting an ortho - aminobenzonitrile having the general formula



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in which R¹ and R³ are as defined in claim 1, with an organo-magnesium compound having the general formula



in which R² is as defined in claim 1 and X is a halogen atom, and decomposing the resulting magnesium-containing compound with aqueous liquid. 40

9. A process as claimed in claim 8 in which 3 to 4 mols of organo-magnesium compound are used per mol of ortho - aminobenzonitrile. 45

10. A process for the production of an ortho-aminoaryl ketimine according to claim 8 and substantially as hereinbefore described with reference to any of the examples. 50

11. An ortho - aminoaryl ketimine whenever produced by the process of any of claims 8—10.

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