PATENT SPECIFICATION (11) 1 583 590

1 583 590

(21) Application No. 42276/77 (22) Filed 11 Oct. 1977
(31) Convention Application No. 12876/76
(32) Filed 12 Oct. 1976 in
(33) Switzerland (CH)
(44) Complete Specification published 28 Jan. 1981
(51) INT CL³ C07D 223/24; A61K 31/55
(52) Index at acceptance
C2C 1733 213 247 250 251 25Y 29X 29Y 30Y 313 314 316 31Y 323 326 32Y 337 339 346 351 355 366 367 368 3876 387 401 40Y 43X 486 488 490 620 625 628 62Y 635 650 658 65X 675 676 678 69Y 701 719 73Y 802 80Y AA LY MC MV NB NL NR UH

(19)

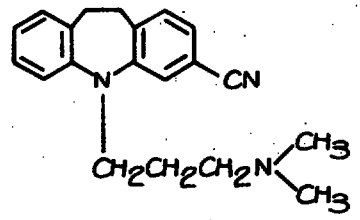


(54) TRICYCLIC COMPOUNDS

(71) We, F. HOFFMANN-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 relates to tricyclic compounds. More particularly, the invention is concerned with iminodibenzyl derivatives, a process for the manufacture thereof and pharmaceutical preparations containing same.

The iminodibenzyl derivatives provided by the present invention comprise the compound 3-cyano-N-(N,N-dimethylaminopropyl)-iminodibenzyl of the formula

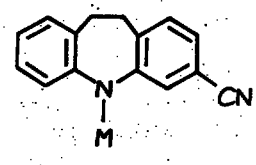


(I)

and acid addition salts thereof.

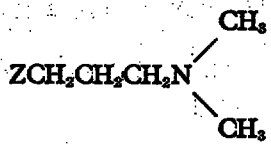
It has been found that 3-cyano-N-(N,N-dimethylaminopropyl)-iminodibenzyl of formula I and its acid addition salts, which are novel substances, are distinguished by a strong antidepressive activity which primarily manifests itself in animal experiments in an extraordinarily strong inhibition of the neuronal serotonin uptake. They can accordingly be used, for example, for the treatment of depressions of endogenous or exogenous origin. Of particular advantage is that anticholinergic side-effects, which can manifest themselves, for example, in mouth dryness, constipation, tachycardia and/or accommodation disorders, are confined to a minimum.

According to the process provided by the present invention, 3-cyano-N-(N,N-dimethylamino-propyl)-iminodibenzyl and its acid addition salts are manufactured by reacting a compound of the general formula



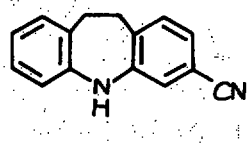
(II)

wherein M represents an alkali metal atom, with a compound of the general formula



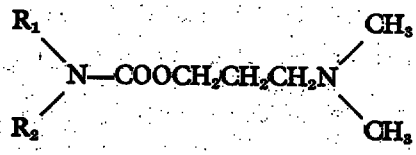
(III)

wherein Z represents a leaving atom or group,
or reacting 3-cyano-iminodibenzyl of the formula



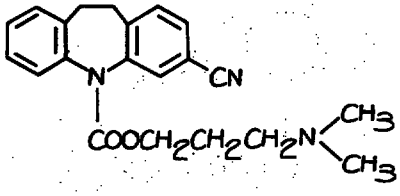
(IV)

with a compound of the general formula



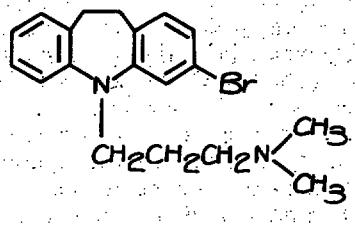
(V)

wherein R_1 and R_2 each represent a hydrogen atom or a lower alkyl group or R_1 and R_2 together with the nitrogen atom to which they are attached represent a 5-membered or 6-membered saturated heterocyclic group, or heating 3-cyano-imiodibenzyl-5-carboxylic acid (N,N-dimethylaminopropyl ester) of the formula



(VI)

or reacting 3-bromo-N-(N,N-dimethylaminopropyl)-iminodibenzyl of the formula



(VII)

with copper-I-cyanide, and, if desired, converting the base of formula I obtained into an acid addition salt.

The 3-cyano substituted starting materials of formulae II and IV can be prepared starting from iminodibenzyl. The latter is converted by heating with acetyl chloride in an inert organic solvent such as toluene into 5-acetyl-iminodibenzyl. The 5-acetyl-iminodibenzyl is transformed by means of a Friedel-Crafts reaction into 5-acetyl-3-oxalyl-iminodibenzyl. For this purpose, the 5-acetyl-iminodibenzyl is reacted with an oxalic acid mono (lower alkyl) ester chloride, preferably oxalic acid monomethyl ester chloride, in the presence of a Friedel-Crafts catalyst such as, for example, aluminium trichloride, in an inert solvent, preferably methylene chloride or carbon disulphide, especially at room temperature. The 3-oxalyl group of the resulting 5-acetyl-3-oxalyl-iminodibenzyl is esterified to some extent; for the complete hydrolysis of this ester to the α-keto acid the reaction product is subjected to an acidic or alkaline hydrolysis. It is preferred to subject the reaction product to an alkaline hydrolysis; for example, at room temperature in the presence of aqueous sodium hydroxide and methanol. The

acetyl group in the resulting 5-acetyl-3-oxalyl-iminodibenzyl is now removed by hydrolysis; for example, by treatment with an alkali metal hydroxide in water or in a monohydroxy or polyhydroxy alcohol at a temperature which should preferably be elevated (e.g. the boiling point of the mixture). The resulting 3-oxalyl-iminodibenzyl is converted by treatment with a hydroxylamine acid addition salt (e.g. hydroxylamine hydrochloride) and acetic acid into the corresponding 3-oxime acid derivative. This treatment is preferably carried out under weak alkaline, buffered conditions. For the working-up, the mixture is acidified, following which the 3-oxime acid derivative can be extracted from the aqueous phase with an inert organic solvent such as tetrahydrofuran. The organic phase is subsequently introduced dropwise into water, the 3-oxime acid derivative being converted into 3-cyano-iminodibenzyl. The temperature at which this is carried out preferably lies at about 90°—100°C.

Since 3-cyano-iminodibenzyl is only weakly basic, it is preferably converted into an alkali metal derivative of formula II prior to the reaction with a starting material of formula III. This conversion is preferably carried out by treatment with an alkali metal amide or alkali metal hydride such as, for example, sodium, potassium or lithium hydride or amide. The treatment is preferably carried out in an aprotic solvent, especially in a polar aprotic solvent such as, for example, dimethylformamide. The treatment is preferably carried out at a temperature of about 20°—100°C, especially at about 50°C.

The leaving atom or group denoted by Z in the starting materials of formula III is preferably a halogen atom or a lower alkyl- or lower aryl-substituted sulphonyloxy group. The lower alkyl or lower aryl groups present in these substituted sulphonyloxy groups contain from 1 to 4 or 6 to 10 carbon atoms, respectively, and are, in particular, methyl or phenyl or p-tolyl. The term "halogen" preferably denotes chlorine or bromine, especially chlorine.

The reaction of a compound of formula II with a compound of formula III can be carried out in an inert aprotic solvent, especially in an inert polar aprotic solvent such as, for example, dimethylformamide. The reaction is preferably carried out at a temperature between about 20°C and 100°C, especially at about 50°C.

Lower alkyl groups denoted by R_1 or R_2 in the starting materials of formula V are alkyl groups containing from 1 to 4 carbon atoms such as, for example, methyl, ethyl, isopropyl or n-butyl. Where R_1 and R_2 together with the nitrogen atom to which they are attached represent a 5-membered or 6-membered, saturatd heterocyclic group, this group can be, for example, the piperidino, the pyrrolidino or morpholino group.

The reaction of 3-cyano-iminodibenzyl of formula IV with a compound of formula V is preferably carried out in the absence of a solvent at a temperature between about 200°C and 280°C, especially at about 250°C. The reaction can be carried out under reduced pressure if desired. It is preferred to carry out the reaction in the presence of a basic catalyst such as, for example, an alkali metal salt of a weak acid (e.g. the sodium or potassium salt of acetic acid, formic acid, carbonic acid or phthalic acid).

The 3-cyano-iminodibenzyl-5-carboxylic acid (N,N-dimethylaminopropyl ester) starting material of formula VI can be prepared by the action of phosgene on 3-cyano-iminodibenzyl and subsequent reaction of the resulting 3-cyano-5-chlorocarbonyl-iminodibenzyl with dimethylaminopropanol.

The heating of 3-cyano-iminodibenzyl-5-carboxylic acid (N,N-dimethylamoniopropyl) ester of formula VI is preferably carried out at a temperature between about 150°C and about 250°C, especially under reduced pressure. The desired 3-cyano-N-(N,N-dimethylaminopropyl)-iminodibenzyl of formula I is obtained directly in this manner.

The 3-bromo-N-(N,N-dimethylaminopropyl)-iminodibenzyl starting material of formula VII can be prepared from an alkali metal salt of 3-bromo-iminodibenzyl and a compound of formula III in an analogous manner to that described earlier in connection with the reaction of a compound of formula II with a compound of formula III.

The reaction of 3-bromo-N-(N,N-dimethylaminopropyl)-iminodibenzyl of formula VII with copper-I-cyanide is preferably carried out in an aprotic polar organic solvent such as dimethylformamide at elevated temperature, preferably at a temperature between about 100°C and the boiling point of the reaction mixture. The desired 3-cyano-N-(N,N-dimethylaminopropyl)-iminodibenzyl of formula I is obtained, together with starting material and small amounts of 3-cyano-iminodibenzyl and 3-bromo-iminodibenzyl. The desired 3-cyano-N-(N,N-dimethylaminopropyl)-iminodibenzyl can be separted from the byproducts of this mixture by, for example, extraction in an organic solvent with an aqueous acid and, after alkalisation of the aqueous phase, extraction with an organic solvent, removal of the solvent and distillation of the residue.

The 3-cyano-N-(N,N-dimethylaminopropyl)-iminodibenzyl of formula I forms

salts with inorganic acids (e.g. with hydrohalic acids such as hydrochloric acid or hydrobromic acid and with other mineral acids such as sulphuric acid, phosphoric acid or nitric acid) and with organic acids (e.g. tartaric acid, citric acid, camphorsulphonic acid, methanesulphonic acid, toluenesulphonic acid, salicylic acid, ascorbic acid, maleic acid, fumaric acid, mandelic acid etc). The preferred salts are the hydrohalides, especially the hydrochloride. The acid addition salts are preferably prepared in a suitable solvent such as ethanol, acetone or acetonitrile, by treatment of the free base with the corresponding non-aqueous acid.

The 3-cyano-N-(N,N-dimethylaminopropyl)-iminodibenzyl of formula I is a crystalline solid substance which has a relatively good solubility in dimethyl sulphoxide, dimethylformamide, chlorinated hydrocarbons (e.g. chloroform and methylene chloride), alkanols (e.g. methanol and ethanol), ether and benzene. It is relatively difficultly soluble in water.

The acid addition salts of 3-cyano-N-(N,N-dimethylaminopropyl)-iminodibenzyl of formula I are crystalline solid substances. They have good solubility in dimethyl sulphoxide, dimethylformamide, alkanols (e.g. methanol and ethanol), chloroform, methylene chloride and water. They are relatively difficultly soluble in benzene, ether and n-hexane.

As mentioned earlier, the iminodibenzyl derivatives provided by the present invention are distinguished by strong antidepressive activity which can be observed, for example, on the basis of the inhibition of the serotinin uptake in the neurones of the brain of the rat. In order to demonstrate this antidepressive activity, 3-cyano-N-(N,N-dimethylaminopropyl)-iminodibenzyl (substance A) was tested against known analogues in accordance with the following experimental procedures:

Substance A:

3-Cyano-N-(N,N-dimethylaminopropyl)-iminodibenzyl hydrochloride (substance provided by the present invention).

Substance B:

N-(N,N-Dimethylaminopropyl)-iminodibenzyl hydrochloride (known substance).

Substance C:

3-Chloro-N-(N,N-dimethylaminopropyl)-iminodibenzyl hydrochloride (known substance).

1. Inhibition of the serotonin uptake in vitro

The uptake of serotonin in the synaptosomes of the forebrain of rats was tested according to J. Pharmacol. exp. Ther. *181*, 36, 1972. An inhibition of 50% (ED_{50}) could be measured at the following concentrations:

Substance	ED_{50}, mol/litre
A	1.5×10^{-9}
B	7.8×10^{-8}
C	6.4×10^{-9}

In this test substance A therefore has a 52 and 4.2 times greater activity than the two known substances B and C.

2. Inhibition of the serotonin uptake ex vivo

An analogous experimental procedure to that given under 1 was used. The test substances were, however, injected intraperitoneally; the serotonin uptake was measured after 1 hour. Untreated rats were used as the controls. The following ED_{50} values could be ascertained:

Substance	ED_{50}, mg/kg
A	0.9
B	19.0
C	2.2

In this test substance A is as active as the two known substances B and C in 21 and 2.4 times smaller doeses.

3. Inhibition of the serotonin re-uptake in vivo

The action of the so-called "membrane pump" was tested according to the method described in Biochem. Pharmacol. *20*, 707, 1971. The following ED_{50} values could be ascertained:

Substance	ED_{50}, mg/kg
A	0.7
B	12.8
C	6.5

In this test substance A is as active as the two known substances B and C in 18 or 9 times smaller doses.

The following results for the inhibition of serotonin uptake in blood platelets of the rat are given as further verification of the antidepressive activity of the iminodibenzyl derivatives provided by the present invention.

4. Inhibition of the serotonin uptake in vitro

0.5 ml of blood plasma was treated with different concentrations of test substance in 50 μl of physiological sodium chloride solution. After incubating at 37°C for 5 minutes, serotonin (C^{14}; 0.1 μM) was added and the mixture was incubated at 37°C for a further 5 minutes. The serotonin concentration was determined by means of a C^{14} measuring apparatus. A control experiment in which no test substance is used was also carried out. By varying the concentration of test substance (three different concentrations) there was determined that concentration which lead to a 50% inhibition of the serotonin uptake (ED_{50}).

Substance	ED_{50}, mmol
A	56
B	7000
C	1200

In this test substance A has a 130 or 20 times greater activity than the two known substances B and C.

5. Inhibition of the serotonin uptake in vivo

Rats were given twice daily over a period of 4 days an intrapreritoneal injection of 5.0 mg of test substance per kg. 12 hours after the last administration the rats were killed; serotonin was determined spectrofluorimetrically as described in J. Pharmacol. exp. Ther. *117*, 82 et seq, 1956, and the protein content was determined colorimetrically as described in J. Biol. Chem. 193, 265 et seq, 1951.

Substance	Number of rats	Serotonin in nmol/mg of protein	Inhibition in % of the control
Controls	24	11.25 ± 1.64	
A	12	4.09 ± 1.30	61
B	9	9.72 ± 2.12	14
C	9	10.91 ± 2.11	3

The iminodibenzyl derivatives provided by the present invention can be used as medicaments; for example, in the form of pharmaceutical preparations which contain them in association with a compatible pharmaceutical carrier material. This carrier material can be an organic or inorganic inert carrier material suitable for interal (e.g. oral) or parenteral administration such as, for example, water, gelatin, lactose, starch, magnesium stearate, talc, vegetable oils, gum arabic, polyalkyleneglycols, petroleum jelly etc. The pharmaceutical preparations can be made up in solid form (e.g. as tablets, dragées, suppositories or capsules) or in liquid form (e.g. as solutions, suspensions or emulsions). The pharmaceutical preparations may be sterilised and/or may contain adjuvants such as preserving, stabilising, wetting or emulsifying agents, salts for varying the osmotic pressure or buffers. They can also contain still other therapeutically valuable substances.

Convenient pharmaceutical dosage forms contain about 1—200 mg of 3-cyano-N-(N,N-dimethylaminopropyl)-iminodibenzyl of formula I or an acid addition salt thereof. Convenient oral dosage ranges lie at about 1 mg/kg per day to about 10 mg/kg per day. Convenient parenteral dosage ranges lie at about 0.1 mg/kg per day to about 1 mg/kg per day. It will be appreciated that the aforementioned dosage ranges can be extended upwards or downwards depending on individual requirement and the directions of the attending physician.

The following Examples illustrate the process provided by the present invention:

Example 1.

230 g (4.8 mol) of 50% sodium hydride in mineral oil, which has been washed three times with 1 litre of n-hexane, and 4.5 litres of dimethylformamide, dried over molecular sieves, are charged into a 20 litre four-necked flask provided with a stirrer, condenser, thermometer and dropping funnel and having inert gasification. To this suspension is added dropwise within ca 2 hours at room temperature a solution of 919 g (4.2 mol) of 3-cyano-iminodibenzyl in 7 litres of dimethylformamide. The mixture is stirred at 50°C for 0.5 hour, cooled down and treated dropwise at 20°—25°C within ca 1 hour with a solution of 1120 g of N,N-dimethylaminopropyl chloride in 2.5 litres of dimethylformamide. The mixture is again warmed to 50°C and stirred at this temperature for 3 hours. It is subsequently stirred at room temperature overnight. After completion of the reaction, the excess sodium hydride is decomposed by the slow dropwise addition of 2.5 litres of water while blowing nitrogen through the mixture. The mixture is subsequently poured on to 12 litres of ice-water and extracted once with 20 litres and once with 10 litres of ethyl acetate. The ethyl acetate solutions are washed once with 6 litres of water, combined and extracted once with 6 litres of 1-N hydrochloric acid and once with 8 litres of water. The acidic-aqueous phases are adjusted to pH 9 with concentrated sodium hydroxide while cooling with ice. The mixture is extracted once with 20 litres and once with 10 litres of ethyl acetate. The organic phase is washed once with 6 litres of water. The ethyl acetate solution is evaporated in vacuo

without drying. The thus-obtained residue is filtered with toluene through 6 kg of aluminium oxide (activity grade II; neutral). The thin-layer chromatographically uniform fractions are combined and evaporated. There are obtained ca 1230 g of base, this being dissolved in 10 litres of isopropanol and treated with 500 ml of 30% alkanolic hydrochloric acid until a Congo-acidic reaction is obtained. The solution is warmed to 40°—50°C for 2 hours, the hydrochloride crystallising out. The mixture is then slowly cooled down to room temperature and subsequently to 0°C. The crystallisate is filtered off, washed with 3 litres of ice-cold isopropanol and twice with 2.5 litres of absolute ether each time. The product is dried over potassium hydroxide in a drying oven for 16 hours in vacuo at 40°C. There is obtained 3-cyano-N-(N,N-dimethylaminopropyl)-iminodibenzyl hydrochloride which, for further purification, is recrystallised as follows:

1095 g of 3-cyano-N-(N,N-dimethylaminopropyl)-iminodibenzyl hydrochloride are dissolved hot in 2.6 litres of absolute ethanol and treated while stirring with 2.6 litres of absolute ether, the product crystallising out. It is left to crystallise for a further 1 hour at room temperature and for 3 hours at 0°C while stirring. The crystals are filtered off under suction, washed with 1.5 litres of ether/ethanol (1:1) and dried at 40°C in vacuo over potassium hydroxide for 16 hours. There is obtained 3-cyano-N-(N,N-dimethylaminopropyl)-iminodibenzyl hydrochloride of melting point 200°—202°C.

The 3-cyano-iminodibenzyl used as the starting material can be prepared as follows:

585 g (3 mol) of iminodibenzyl are dissolved in 2000 ml of toluene in a 6 litre four-necked flask provided with a stirrer, condenser, thermometer and dropping funnel and warmed to 80°C (internal temperature). 370 ml (408.4 g; 5.2 mol) of acetyl chloride are added dropwise at 80°C within 0.75 hour. The mixture is stirred at 80°C overnight (or for 16 hours). The mixture is subsequently cooled to room temperature using an ice-bath and the excess acetyl chloride is destroyed by the dropwise addition of 200 ml of ethanol and 1000 ml of water. The mixture is also treated with 500 ml of ether. The aqueous phase is separated and re-extracted once with 1500 ml of ether. The organic phases are individually washed three times with 1000 ml of water. The combined organic phases are treated with 50 g of carbon, dried over sodium sulphate and evaporated to dryness in vacuo. The resulting crude product is dissolved in 1000 ml of ether while stirring and the solution is stirred overnight, the product crystallising out. The crystallisate is filtered off and washed with a small amount of ice-cold ether. There are obtained 539 g of 5-acetyliminodibenzyl of melting point 95°—96°C. The mother liquor is evaporated in vacuo and afterwards treated with 200 ml of ether. It is poured with slight stirring into ca 70 ml of petroleum ether of low boiling point until turbidity sets in and stirred for 4 hours. After suction filtration and washing of the crystallisate with a small amount of cold ether, there is obtained a further amount of 5-acetyl-iminodibenzyl of melting point 94°—96°C.

1800 g (13.5 mol) of aluminium chloride in 3600 ml of methylene chloride, dried over molecular sieves, are charged under an inert gas into a 20 litre round flask provided with a stirrer, condenser, thermometer, dropping funnel with gas-inlet tube and exhaust apparatus for hydrochloric acid gas. To this mixture is added dropwise within ca 0.5 hour at room temperature a solution of 712 g (3 mol) of 5-acetyl-iminodibenzyl in 1800 ml of methylene chloride dried over molecular sieves and the resulting mixture is left to stir for a further ca 10 minutes. There is then added dropwise within 0.5 hour at room temperature a solution of 830 ml (9 mol) of oxalic acid monomethyl ester chloride and 1200 ml of methylene chloride. In so doing, the internal temperature slowly rises to 33°C. The mixture is left to stir at room temperature overnight (or during 16 hours). After completion of the reaction, 3000 ml of 3-N hydrochloric acid are cautiously added dropwise while cooling well with ice so that the temperature does not exceed 20°C. Since, in so doing, the flask content becomes an unstirrable thick mass, it must be diluted with 5000 ml of ethyl acetate. The mixture is cautiously treated with 2000 ml of distilled water while stirring intensively. The flask content is transferred to a 30 litre stirring vessel and, after treatment with a further 5000 ml of ethyl acetate, stirred. The aqueous phase is re-extracted once with 4000 ml of ethyl acetate. The organic phases are washed five times with 4000 ml of dilute sodium chloride solution each time (2000 ml of saturated aqueous sodium chloride solution and 2000 ml of water). Concentration is then carried out in vacuo without drying. The water is removed by azeotropic distillation with 1500 ml of toluene. After completion of the evaporation, there is obtained a resin which is dissolved in 3800 ml of methanol on a steam-bath and charged into a 20 litre stirring flask. The methanolic solution, cooled with an ice-bath, is treated, with further cooling, with 4550 ml of 1-N aqueous

sodium hydroxide in such a manner that the temperature does not exceed 15°C. After completion of the saponification, the flask content is poured on to 8000 ml of ice-water and adjusted Congo-acidic with ca 850 ml of concentrated hydrochloric acid while stirring. The mixture is extracted once with 12 litres and once with 4 litres of ethyl acetate. The organic phases are washed individually six times with 4 litres of water. The combined ethyl acetate phases are concentrated in vacuo without drying to a volume of ca 1—2 litres, water still remaining being azetropically distilled off with toluene. The crystal mass obtained after concentration is cooled to room temeprature while stirring, stirred at this temperature for 2—3 hours, and then filtered under suction. The filter cake is washed portionwise with a total of 1 litre of ice-cold ethyl acetate and dried in vacuo at 40°C. There is obtained thin-layer chromatographically uniform 5-acetyl-3-oxalyl-iminodibenzyl of melting point ca 205°C.

658 g (11.7 mol) of potassium hydroxide are dissolved in 5 litres of water in a 20 litre four-necked flask provided with a stirrer, condenser, thermometer and inert gas inlet tube, the temperature rising to ca 45°C. 1000 g (3.2 mol) of 5-acetyl-3-oxalyl-iminodibenzyl are introduced into this solution with inert gasification and the mixture is left to stir at an oil-bath temperature of 135°C for about 24 hours until complete saponification is achieved. The flask content is cooled down to room temperature and treated with 100 ml of ethyl acetate in order to avoid a foam formation. There is then added dropwise at 15°—20°C within 1.5 hours a solution consisting of 2 litres of water, 540 ml of glacial acetic acid and 448 g (6.5 mol) of hydroxylamine hydrochloride. After completion of the addition, the mixture is stirred for 5—5.5 hours and then the flask content is stirred into 12 litres of ethyl acetate. The mixture is acidified to pH 1—2 with concentrated hydrochloric acid, the aqueous phase is separated and re-extracted once with 5 litres of ethyl acetate. The organic phases are washed individually five times with 5 litres of water each time (total 25 litres) and then dried over sodium sulphate and evaporated. The thus-obtained crude product is dissolved in 3 litres of tetrahydrofuran and introduced dropwise within ca 1.5—2 hours into 12 litres of boiling water in a 20 litre stirring flask while stirring well and simultaneously distilling off the tetrahydrofuran, whereby the internal temperature should lie at between 85°C and 95°C. There is now added dropwise within 0.25 hour a solution of 28.6 g (0.4 mol) of hydroxylamine hydrochloride in 200 ml of water and the mixture is left to stir at 90°—95°C for 5 hours. In due course there results a resinous rubber-like precipitate and the aqueous phase is clear. When this condition is reached, the mixture is worked-up as follows:

The supernatant aqueous clear solution is decanted off and rejected. The residue is dissolved in 12 litres of methylene chloride and washed twice with 5 litres of water each time. The aqueous phases are back-extracted once with 2 litres of methylene chloride. The combined organic phases are concentrated to a volume of about 5 litres, the nitrile crystallising out. In order to achieve complete crystallisation, the mixture is left to stand in a refrigerator overnight and the crystallisate is then filtered off. The mother liquor obtained is filtered through a column containing 4.5 kg of aluminium oxide (activity grade II; neutral) with methylene chloride and the thin-layer chromatographically uniform fractions are combined and evaporated in vacuo. The thus-obtained residue is combined with the aforementioned crystallisate and suspended in about 1 litre of ether/methylene chloride (3:1). The suspension is filtered and the crystallisate again back-washed with a small amount of ether/methylene chloride (3:1). After drying in vacuo at 40°C, there is obtained thin-layer chromatographically uniform 3-cyano-iminodibenzyl of melting point 164°—165°C.

Example 2.

1.10 g (0.005 mol) of 3-cyano-iminodibenzyl and 0.25 g (0.0025 mol) of potassium acetate are heated to 210°C. At this temperature there is added dropwise within 15 minutes 1.74 g (0.010 mol) of dimethylaminopropyl dimethylcarbamate. The mixture is subsequently heated to 250°C for 3 hours. The mixture is then cooled down to room temperature. The mixture is treated with 20 ml of water and then extracted twice with 20 ml of chloroform each time. The combined chloroform phases are washed with 20 ml of water and then the basic constituents are separated from neutral constituents by extraction with 10 ml of 5% methanesulphonic acid each time. The aqueous phase is now made alkaline with 28% aqueous sodium hydroxide solution and extracted with chloroform. After drying over magnesium sulphate, concentration is carried out under reduced pressure. The residue is distilled at 200°C/0.05 mmHg. The resulting light yellow distillate crystallises spontaneously. There is obtained 3-cyano-N-(N,N-dimethylaminopropyl)-iminobenzyl of melting point 55°—57°C.

Example 3.

1.30 g (0.0036 mol) of 3-bromo-N-(N,N-dimethylaminopropyl)-iminodibenzyl and 0.41 g (0.0046 mol) of copper-I-cyanide are boiled under reflux for 6 hours in the presence of 5 ml of dimethylformamide. The mixture is cooled down to room temperature, 20 ml of chloroform are added thereto and the resulting mixture is filtered. The chloroform phase is washed with water, dried and evaporated. As the residue there remains a brown oil having the following composition (in accordance with gas chromatography): 72% of 3-cyano-N-(N,N-dimethylaminopropyl)-iminodibenzyl, 4% of 3-bromo-N-(N,N-dimethylaminopropyl)-iminodibenzyl, 16% of 3-cyano-iminodibenzyl and 1% of 3-bromo-iminodibenzyl. Purification of the crude product can be carried out as follows:

The brown oil is dissolved in 20 ml of chloroform and extracted three times with 10 ml of 5% methanesulphonic acid. The acidic portion is washed with 20 ml of ethyl acetate and made alkaline with concentrated aqueous sodium hydroxide. The resulting emulsion is extracted twice with 20 ml of chloroform each time. The chloroform phases are combined, washed with 50 ml of water, dried over magnesium sulphate and evaporated under reduced pressure. The oily residue is distilled under strongly reduced pressure. There is obtained 3-cyano-N-(N,N-dimethylaminopropyl)-iminodibenzyl in the form of a yellow oil of boiling point 240°C/0.12 mmHg which crystallises overnight; melting point 53°—55°C.

The 3-bromo-N-(N,N-dimethylaminopropyl)-iminodibenzyl used as the starting material can be prepared as follows:

1.50 g of sodium hydride dispersion (50% in mineral oil) are washed with 10 ml of n-hexane and suspended in 5 ml of N,N-dimethylformamide. This suspension is added dropwise at room temeprature and within 10 minutes to a solution of 2.2 g of 3-bromo-iminodibenzyl in 5 ml of dimethylformamide. The resulting solution is stirred at 70°C for 0.25 hour, cooled down to room temperature and treated dropwise with a solution of 3.67 g of N,N-dimethylaminopropyl chloride in 4 ml of dimethylformamide. The mixture is stirred at 60°C for 16 hours and subsequently treated with 40 ml of water. The resulting emulsion is extracted twice with 20 ml of ethyl acetate. The ethyl acetate extracts are combined, washed eight times with 50 ml of water and extracted three times with 20 ml of 10% methanesulphonic acid. The acidic portion is washed twice with 20 ml of ethyl acetate and again made alkaline with concentrated sodium hydroxide solution. The basic product is extracted twice with 30 ml of chloroform, dried over magnesium sulphate and concentrated under reduced pressure. The brown oily residue is distilled under strongly reduced pressure. There is obtained 3-bromo-N-(N,N-dimethlaminopropyl)-iminodibenzyl of boiling point 230°C/0.08 mmHg.

Example 4.

1.90 g of 3-cyano-iminodibenzyl-5-carboxylic acid (N,N-dimethylaminopropyl ester) are heated under reduced pressure to 170°C for 3 hours and to 210°C for 1 hour. The brown oil obtained is taken up in 30 ml of chloroform and extracted twice with 20 ml of 1-N methanesulphonic acid. The acidic extracts are washed with 30 ml of ethyl acetate and subsequently made alkaline with concentrated sodium hydroxide solution. The resulting basic product is extracted twice with 20 ml of chloroform each time. The organic solution is washed with water, dried over magnesium sulphate and evaporated. There is obtained 3-cyano-N-(N,N-dimethylaminopropyl)-iminodibenzyl of melting point 53°—55°C.

The 3-cyano-iminodibenzyl-5-carboxylic acid (N,N-dimethylaminopropyl ester) used as the starting material can be prepared as follows:

2.70 g of 3-cyano-iminodibenzyl are dissolved in 20 ml of orthoxylene. A light stream of phosgene, dried with sulphuric acid, is conducted into the solution, which is warmed to 100°C, for 7 hours. Subsequently, the solution is stirred at the same temperature for 3 hours and then the solvent is evaporated. There is obtained 3-cyano-5-chlorocarbonyl-iminodibenzyl of melting point 129°—130°C.

2.89 g of 3-cyano-5-chlorocarbonyl-iminodibenzyl are dissolved, together with 1.13 g of 3-dimethylaminopropanol, in 20 ml of benzene and the mixture is heated under reflux for 18 hours under argon gasification. The resulting solution is made alkaline with 5 ml of 2-N aqueous sodium hydroxide and washed four times with 70 ml of water each time. The benzene phase is extracted twice with 50 ml of 1-N aqueous methane-sulphonic acid each time and the aqueous phases are washed with 20 ml of ethyl acetate. The aqueous phases are combined, made alkaline with concentrated aqueous sodium hydroxide and extracted twice with 30 ml of chloroform each time. The chloroform phases are combined, washed with water, dried over mag-

nesium sulphate and concentrated under reduced pressure. There is obtained 3-cyano-iminodibenzyl-5-carboxylic acid (N,N-dimethylaminopropyl ester) in the form of a brown oil.

The following Examples illustrate pharmaceutical preparations provided by the present invention and the production of same:

Example A.

Production of tablets:	
Active ingredient	50 g
Lactose	202 g
Maize starch	80 g
Hydrolysed maize starch	20 g
Calcium stearate	8 g
	360 g

The active ingredient, the lactose, the maize starch and the hydrolysed maize starch are mixed and granulated with water to a viscous paste. This paste is passed through a sieve and subsequently dried at 45°C overnight. The dried granulate is passed through a sieve and subsequently mixed with the calcium stearate. The mixture obtained is pressed to tablets weighing 360 mg and having a diameter of about 10 mm.

Example B.

Production of tablets:	
Active ingredient	25.0 g
Lactose	114.0 g
Maize starch	50.0 g
Gelatinised maize starch	8.0 g
Calcium stearate	3.0 g
	200.0 g

The active ingredient, the lactose, the maize starch and the gelatinised maize starch are intimately mixed with one another. The mixture is passed through a comminuting machine and subsequently moistened with water to a thick paste. The moist mass is passed through a sieve. The moist granulate is dried at 45°C. The dried granulate is mixed thoroughly with the calcium stearate. The granulate is now pressed to tablets weighing 200 mg and having a diameter of about 8 mm.

Example C.

Production of capsules:	
Active ingredient	25.0 g
Lactose	160.0 g
Maize starch	30.0 g
Talc	5.0 g
	220.0 g

The active ingredient, the lactose and the maize starch are intimately mixed with one another and passed through a comminuting machine. The mixture is now mixed thoroughly with the talc and filled into hard shell gelatin capsules.

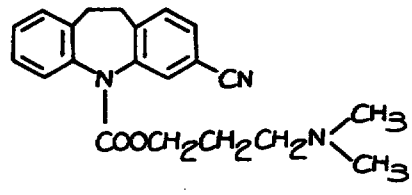
Example D.

Production of a parenteral dosage form:	
Each 1 ml ampoule contains:	
Active ingredient	10.20 mg (2% excess)
Methanesulphonic acid for injection	2.22 mg
Glucose for injection purposes	40.0 mg
Water for injection purposes q.s. ad	1 ml

22.2 g of methanesulphonic acid for injection, 102 g of active ingredient and 400 g of glucose are successively dissolved in 8000 ml of water for injection in a glass vessel while stirring at room temperature. Subsequently, water for injection is added until the total volume is 10000 ml. The solution is either filtered sterile, filled into colourless ampoules, gassed with nitrogen and sealed or filled into colourless ampoules, gassed with nitrogen, sealed and subsequently sterilised for 30 minutes with flowing steam or autoclaved at 120°C.

WHAT WE CLAIM IS:—

1) 3-Cyano-N-(N,N-dimethylaminopropyl)-iminodibenzyl of the formula

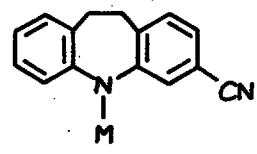


(I)

and acid addition salts thereof.

2) 3-Cyano-N-(N,N-dimethylaminopropyl)-iminodibenzyl hydrochloride.

3) A process for the manufacture of 3-cyano-N-(N,N-dimethylaminopropyl)-iminodibenzyl of formula I given in claim 1 and acid addition salts thereof, which process comprises reacting a compound of the general formula



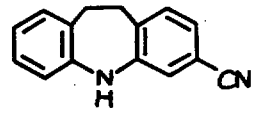
(II)

wherein M represents an alkali metal atom, with a compound of the general formula



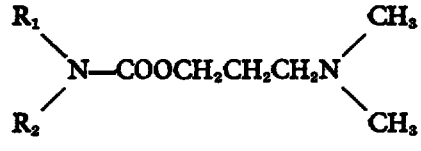
(III)

wherein Z represents a leaving atom or group, or reacting 3-cyano-iminodibenzyl of the formula



(IV)

with a compound of the general formula



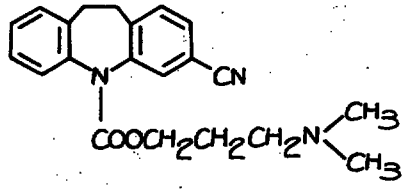
(V)

wherein R_1 and R_2 each represent a hydrogen atom or a lower alkyl group or R_1 and R_2 together with the nitrogen atom to which they are attached represent a 5-membered or 6-membered saturated heterocyclic group, or heating 3-cyano-iminodibenzyl-5-carboxylic acid (N,N-dimethylaminopropyl ester) of the formula

22.2 g of methanesulphonic acid for injection, 102 g of active ingredient and 400 g of glucose are successively dissolved in 8000 ml of water for injection in a glass vessel while stirring at room temperature. Subsequently, water for injection is added until the total volume is 10000 ml. The solution is either filtered sterile, filled into colourless ampoules, gassed with nitrogen and sealed or filled into colourless ampoules, gassed with nitrogen, sealed and subsequently sterilised for 30 minutes with flowing steam or autoclaved at 120°C.

WHAT WE CLAIM IS:—

1) 3-Cyano-N-(N,N-dimethylaminopropyl)-iminodibenzyl of the formula

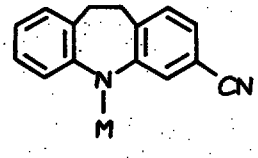


(I)

and acid addition salts thereof.

2) 3-Cyano-N-(N,N-dimethylaminopropyl)-iminodibenzyl hydrochloride.

3) A process for the manufacture of 3-cyano-N-(N,N-dimethylaminopropyl)-iminodibenzyl of formula I given in claim 1 and acid addition salts thereof, which process comprises reacting a compound of the general formula



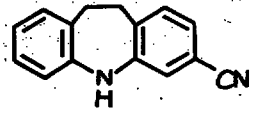
(II)

wherein M represents an alkali metal atom, with a compound of the general formula



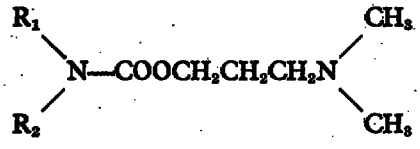
(III)

wherein Z represents a leaving atom or group, or reacting 3-cyano-iminodibenzyl of the formula



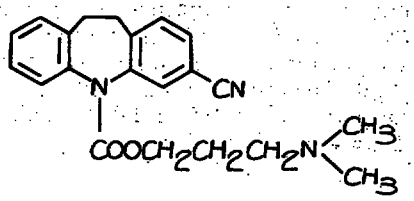
(IV)

with a compound of the general formula



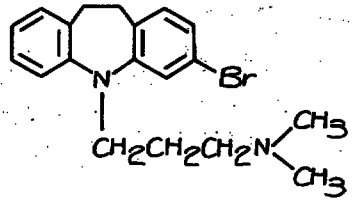
(V)

wherein R_1 and R_2 each represent a hydrogen atom or a lower alkyl group or R_1 and R_2 together with the nitrogen atom to which they are attached represent a 5-membered or 6-membered saturated heterocyclic group, or heating 3-cyano-iminodibenzyl-5-carboxylic acid (N,N-dimethylaminopropyl ester) of the formula



(VI)

or reacting 3-bromo-N-(N,N-dimethylaminopropyl)-iminodibenzyl of the formula



(VII)

with copper-I-cyanide, and, if desired, converting the base of formula I obtained into an acid addition salt.

4) A process according to claim 3, wherein the base of formula I is converted into the hydrochloride.

5) A process according to claim 3 or claim 4, wherein N-sodium-3-cyanoiminodibenzyl is reacted with N,N-dimethylaminopropyl chloride.

6) A process according to claim 5, wherein the reaction is carried out in dimethylformamide at a temperature of from about 20°C to 100°C.

7) A process for the manufacture of 3-cyano-N-(N,N-dimethylaminopropyl)-iminodibenzyl and acid addition salts thereof, substanstially as hereinbefore described with reference to any one of Examples 1 to 4.

8) 3-Cyano-N-(N,N-dimethylaminopropyl)-iminodibenzyl and acid addition salts thereof, when manufactured by the process claimed in any one of claims 3 to 7 inclusive or by an obvious chemical equivalent thereof.

9) A pharmaceutical preparation containing 3-cyano-N-(N,N-dimethylaminopropyl)-iminodibenzyl or an acid addition salt thereof in association with a compatible pharmaceutical carrier material.

For the Applicants,
CARPMAELS & RANSFORD,
Chartered Patent Agents,
43 Bloomsbury Square,
London, WC1A 2RA.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1981.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.