PATENT SPECIFICATION

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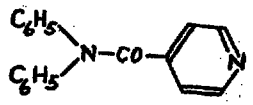
International Classification:—C07d.

COMPLETE SPECIFICATION

N,N-Diphenyl-Isonicotinamide

We, SOCIETA FARMACEUTICI ITALIA, a Body Corporate organised and existing under the laws of Italy, of 1—2, Largo Guido Donegani, Milan, Italy, 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 invention relates to a tranquillizer that is a new chemical product having activity on the central nervous system and to a process of preparing it. The new chemical product is N,N-diphenylisonicotinamide having the following structural formula:



which can be therapeutically employed as a tranquillizer.

N,N-diphenylisonicotinamide, both as the free base in solid form or in suspension, and as a salt aqueous solution with organic or inorganic acids, such as hydrochloric acid, sulphuric acid, phosphoric acid or tartaric acid, is particularly useful in therapy, in the treatment of neurotic anxiety and of the insomnia which is frequently present in the forms of anxiety and in the psychic agitations of a normal patient. N,N-diphenylisonicotinamide may be prepared by condensing a derivative of isonicotinic acid, capable of reacting with an amine to yield the corresponding acid amide, with diphenylamine.

According to the invention N,N-diphenylisonicotinamide may be prepared, in high yield, by condensing crude isonicotinic acid chloride hydrochloride (preferably prepared by chlorination of isonicotinic acid with thionyl chloride) with diphenylamine dissolved in an inert organic solvent, such as dioxane, optionally in the presence of tertiary amines such as pyridine.

Reaction will take place in the cold, but it is better to operate at 80°C—100°C preferably for about one hour.

N,N-diphenylisonicotinamide hydrochloride, formed by this condensation, is isolated by eliminating the solvent, then dissolved in water and treated with alkali, such as sodium or potassium carbonate, bicarbonate or hydroxide, preferably until it becomes alkaline. The N,N-diphenylisonicotinamide precipitates from the aqueous medium and is separated and purified. The preferred purification method consists of dissolving the crude free base in warm acidic water, then decolourizing with carbon, cooling and finally neutralizing with alkali.

N,N-diphenylisonicotinamide may be transformed into aqueous solution of one of its salts, such as the hydrochloride, sulphate, phosphate, tartrate or citrate, by dissolving the free base in an aqueous solution of the corresponding acid.

N,N-diphenylisonicotinamide is a white microcrystalline powder, stable both to heat and light. It is preferably administered orally as a pharmaceutical composition, in the form of a pill, tablet, capsule, suspension or other dosage unit for oral administration, particularly orally with a significant quantity of a pharmaceutically acceptable solid or liquid carrier or diluent. Among pharmaceutically acceptable carriers or diluents are starch, lactose, talc, magnesium stearate, pectins and gelatins. The percentage of the active ingredient may vary according to the particular pharmaceutical form but in general pharmaceutical compositions contain from 0.5 to 80% by weight with respect to the composition of N,N-diphenylisonicotinamide.

Pharmaceutical compositions included in the invention may contain N,N-diphenylisonicotinamide in admixture with one or more therapeutically active products.

The following Example illustrates the invention:

EXAMPLE

Crude isonicotinic acid chloride hydrochloride (which is obtained by chlorination

[*Price 4s. 6d.*]

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of 50 g of isonicotinic acid with 180 cc thionyl chloride ($SOCl_2$) with refluxing for about 1 hour and after that by evaporation of the excess thionyl chloride) is dissolved in 180 cc dioxane and 60 cc anhydrous pyridine. To the solution 60 g diphenylamine dissolved in 90 cc dioxane is added and warmed on a water bath for 1 hour. The solvent is eliminated under vacuum and the residue is pulped with a 10% aqueous solution of sodium carbonate until it becomes alkaline (after about 650 cc have been added). The whitish product is filtered, washed with water and dried: Yield: 90 g crude N,N-diphenylisonicotinamide, melting at 162—165°C. The crude product is dissolved in 4 litres warm water to which concentrated hydrochloric acid is added to effect complete dissolution (about 80—85 cc are required). The resulting solution is boiled with decolouring carbon, filtered in the warm, cooled and neutralized with a 10% aqueous solution of sodium carbonate. The white product is filtered, washed with water and dried. 80 g pure N,N-diphenylisonicotinamide melting at 164—166°C is obtained.

Pharmacology of N,N-diphenylisonicotinamide

N,N-diphenylisonicotinamide has been administered orally, intravenously and intraperitoneously as suspension in a 5% solution of gum arabic.

The tranquillizing dose of N,N-diphenylisonicotinamide has been determined in mouse according to the Beeman Test (Phisiol Zool. (1947), *20*, 273) and in rat according to the Jacobsen test (Acta Pharm. Toxicol (1955) *11*, 135).

The "mouse tranquillizing dose" (that is the amount of drug expressed in mg/kg, capable of abolishing the evident attitude of violent hostility which is shown by an animal placed in the same room with another one in 50% of couples of treated male fully grown mice) is 75 mg/kg (intraperitoneously).

The "rat tranquillizing dose" (that is the amount of drug expressed in mg/kg, capable of abolishing the evident signs of violent agitation and tension in the intervals between one painful stimulation and the next in 50% of treated rats) is equal to 180 mg/kg (intraperitoneously).

The hypothermizing dose (that is the amount of drug, expressed in mg/kg, able to produce in mice or in rats a fall of rectal temperature of 1 degree Celsius when animals are kept at a room temperature of 22°C) is equal to 45 mg/kg (mouse) and to 50 mg/kg (rat).

This hypothermizing effect lasts about 90 minutes. The ratio between the hypothermizing dose orally administered and that intraperitoneously administered is 8.

The lethal dose (that is the amount of drug expressed in mg/kg, which when intraperitoneously administered is able to kill 50% of the treated animals in 48 hours) is equal to 600 mg/kg in mouse and more than 1000 mg/kg in rat.

Doses of 400 mg/kg in mouse and 900 mg/kg in rat do not abolish the righting reflexes.

N,N-diphenylisonicotinamide orally administered in dogs, at a dose of 100 mg/kg daily for 30 days, does not cause alterations either to the hematic crasis, or to the hepatic and renal functions.

N,N-diphenylisonicotinamide, both intravenously and intraperitoneously administered at a dose of 100 mg/kg in dogs under narcosis by 5,5-diallylbarbituric acid does not modify either the arterial blood pressure, or the rhythm and breathing amplitude, or the vascular response to adrenaline, acetylcholine or histamine.

WHAT WE CLAIM IS:—

1. N,N-diphenylisonicotinamide.
2. A pharmaceutical composition in the form of a tablet, pill, capsule, suspension or other dosage unit for oral administration which contains as an active ingredient N,N-diphenylisonicotinamide in an amount of from 0.5 to 80% by weight with respect to the composition with a significant quantity of a pharmaceutically acceptable solid or liquid carrier or diluent.
3. A process of preparing N,N-diphenylisonicotinamide in which a derivative of isonicotinic acid, capable of reacting with an amine to yield the corresponding acid amide, preferably isonicotinic acid chloride hydrochloride, is condensed with diphenylamine dissolved in an inert organic solvent.
4. A process as defined by Claim 3 wherein the inert organic solvent is dioxane.
5. A process as defined by Claim 3 or Claim 4 which is carried out in the presence of a tertiary amine.
6. A process as defined by any of Claims 3 to 5 which is carried out at 80°—100°C.
7. A process of preparing N,N-diphenylisonicotinamide as described in the Example.
8. N,N-diphenylisonicotinamide prepared by a process as defined by any of Claims 3 to 7.

ERIC POTTER AND CLARKSON,
Chartered Patent Agents,
317 High Holborn, London, W.C.1.

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