

PATENT SPECIFICATION

(11) 1248429

NO DRAWINGS

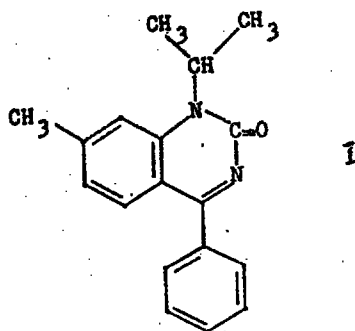
- (21) Application No. 5791/71 (22) Filed 28 Oct. 1968
 (62) Divided out of No. 1248428
 (31) Convention Application No. 679201 (32) Filed 30 Oct. 1967
 (31) Convention Application No. 707932 (32) Filed 26 Feb. 1968
 (31) Convention Application No. 741804 (32) Filed 1 July 1968 in
 (33) United States of America (US)
 (45) Complete Specification published 6 Oct. 1971
 (51) International Classification C 07 d 51/48 A 61 k 27/00
 (52) Index at acceptance
 C2C 3A14A3A 3A14A8A



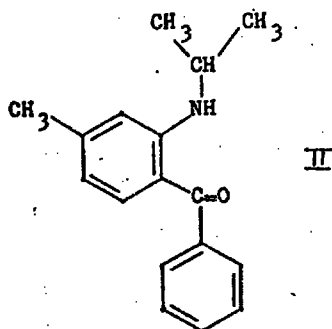
(54) 4-PHENYL-QUINAZOLINONE DERIVATIVE

(71) We, SANDOZ LTD. of Lichtstrasse 35, 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 provides 1 - isopropyl - 7 - methyl - 4 - phenyl - quinazolinone of formula I,



The compound of formula I may be produced by cyclising 4 - methyl - 2 - isopropyl-amino - benzophenone of formula II,

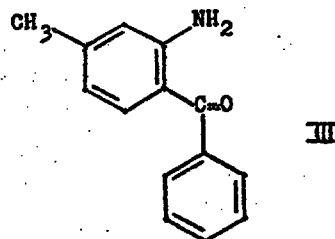


with an alkyl carbamate in which the alkyl radical contains from 1 to 5 carbon atoms, at a temperature of at least 140°C and in the presence of a Lewis acid.

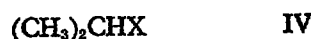
The cyclisation is preferably carried out in the presence of a catalytic amount of a Lewis acid at a temperature of from 160° to 200°C, the preferred Lewis acid being zinc chloride and the preferred carbamate being ethyl carbamate. If desired, the reaction may be carried out in the presence of a suitable inert organic solvent. However, the use of a solvent is not necessary since an excess of the carbamate can be used for this purpose.

The resulting compound of formula I may be recovered and purified using conventional techniques.

The compound of formula II may be produced by reacting 4 - methyl - 2 - amino-benzophenone of formula III,



with a compound of formula IV,



in which X signifies a bromine or iodine atom.

In this process, the compound of formula IV is preferably isopropyl iodide. Desirably, the reaction is carried out in the presence of an inorganic base as acid binding agent, e.g. an alkali metal carbonate such as sodium carbonate, to take up the hydrogen halide liberated during the reaction. If desired, the reaction may be carried out in any suitable

inert organic solvent, e.g. dioxane, benzene and toluene. However, the use of a solvent is not necessary since an excess of the isopropyl halide of formula IV can be utilised for this purpose. The reaction is most conveniently effected at elevated temperatures. Desirably, the reaction is carried out at a temperature of from 60°C to 100°C. Preferably, the reaction is conducted at the reflux temperature of the system. However, the particular temperature employed is not critical and somewhat lower temperatures or higher temperatures and elevated pressures can be employed.

The compound of formula III is either known or can be prepared in manner known *per se*.

The compound of formula I has pharmacological activity. In particular it has anti-inflammatory activity as indicated by the Carrageen-induced edema test on rats, and is indicated for use as an anti-inflammatory agent.

Suitable indicated daily dosages range from 60 mg to 600 mg, preferably given in divided dosages of from 12 mg to 200 mg three to five times a day or in retard form.

The compound of formula I also has analgesic activity and is therefore indicated for use as an analgesic agent. Suitable indicated daily dosages are from 40 to 600 mg, preferably given in divided dosages of from 8 to 200 mg, three to five times daily or in retard form.

The compound may be used in association with, e.g. a physiologically acceptable diluent or carrier, and such other conventional adjuvants as may be desired, and administered orally in such forms as tablets, capsules, elixirs, suspensions or solutions or parenterally in such forms as injectable solutions and suspensions.

A representative formulation is a tablet prepared by conventional tableting techniques and containing, by weight, 50 parts of the compound of formula I, 2 parts of tragacanth, 39.5 parts of lactose, 5 parts of corn starch, 3 parts of talcum and 0.5 parts of magnesium stearate.

The following Example illustrates the invention; the starting material is produced in accordance with Example 9 of Application No. 50943/68, U.K. Specification No. 1248428.

EXAMPLE

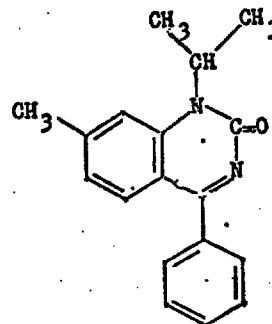
1 - isopropyl - 7 - methyl - 4 - phenyl - quinazolinone

A mixture of 5.9 g of 4 - methyl - 2 - isopropylamino - benzophenone, 13.9 g of urethane and 500 milligrams of zinc chloride is heated at a temperature of 190°C. for 1 1/2 hours. There is then additionally added 7 g. of urethane and 250 milligrams of zinc chloride, and the heating continued at a tem-

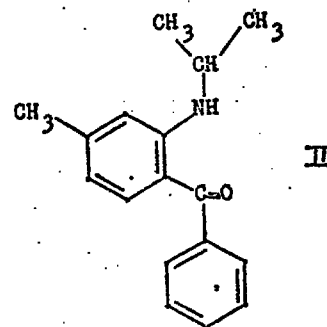
perature of 190°C. for an additional 2 1/2 hours. The resulting mixture is cooled to about 100°C. and diluted with chloroform. The resulting mixture is then filtered and the filtrate washed first with water and then with brine. The organic phase is separated, dried over anhydrous sodium sulfate and concentrated *in vacuo* to remove substantially all of the chloroform and obtain an oily residue which is dissolved in a small amount of about 20 ml. of methylene chloride. The resulting solution is then diluted with about 40 ml. of ethyl acetate and concentrated *in vacuo* to crystallize 1 - isopropyl - 7 - methyl - 4 - phenyl - 2(1H) - quinazolinone; m.p. 137° to 138°C.

WHAT WE CLAIM IS:—

1. A process for the production of 1 - isopropyl - 7 - methyl - 4 - phenyl - quinazolinone of formula I,



characterised in that 4 - methyl - 2 - isopropylaminobenzophenone of formula II,



is cyclised with an alkyl carbamate in which the alkyl radical contains 1 to 5 carbon atoms, at a temperature of at least 140°C and in the presence of a Lewis acid.

2. A process according to claim 1, which is effected at a temperature from 160° to 200°C, employing zinc chloride as the Lewis acid, and ethyl carbamate as the alkyl carbamate.



inert organic solvent, e.g. dioxane, benzene and toluene. However, the use of a solvent is not necessary since an excess of the isopropyl halide of formula IV can be utilised for this purpose. The reaction is most conveniently effected at elevated temperatures. Desirably, the reaction is carried out at a temperature of from 60°C to 100°C. Preferably, the reaction is conducted at the reflux temperature of the system. However, the particular temperature employed is not critical and somewhat lower temperatures or higher temperatures and elevated pressures can be employed.

The compound of formula III is either known or can be prepared in manner known *per se*.

The compound of formula I has pharmacological activity. In particular it has anti-inflammatory activity as indicated by the Carrageen-induced edema test on rats, and is indicated for use as an anti-inflammatory agent.

Suitable indicated daily dosages range from 60 mg to 600 mg, preferably given in divided dosages of from 12 mg to 200 mg three to five times a day or in retard form.

The compound of formula I also has analgesic activity and is therefore indicated for use as an analgesic agent. Suitable indicated daily dosages are from 40 to 600 mg, preferably given in divided dosages of from 8 to 200 mg, three to five times daily or in retard form.

The compound may be used in association with, e.g. a physiologically acceptable diluent or carrier, and such other conventional adjuvants as may be desired, and administered orally in such forms as tablets, capsules, elixirs, suspensions or solutions or parenterally in such forms as injectable solutions and suspensions.

A representative formulation is a tablet prepared by conventional tableting techniques and containing, by weight, 50 parts of the compound of formula I, 2 parts of tragacanth, 39.5 parts of lactose, 5 parts of corn starch, 3 parts of talcum and 0.5 parts of magnesium stearate.

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EXAMPLE

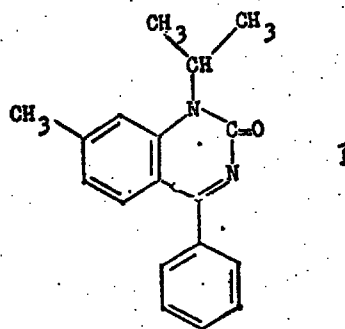
1 - isopropyl - 7 - methyl - 4 - phenyl - quinazolinone

A mixture of 5.9 g of 4 - methyl - 2 - isopropylamino - benzophenone, 13.9 g of urethane and 500 milligrams of zinc chloride is heated at a temperature of 190°C. for 1 1/2 hours. There is then additionally added 7 g. of urethane and 250 milligrams of zinc chloride, and the heating continued at a tem-

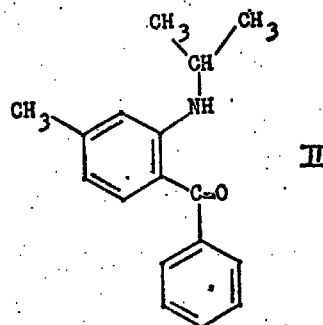
perature of 190°C. for an additional 2 1/2 hours. The resulting mixture is cooled to about 100°C. and diluted with chloroform. The resulting mixture is then filtered and the filtrate washed first with water and then with brine. The organic phase is separated, dried over anhydrous sodium sulfate and concentrated *in vacuo* to remove substantially all of the chloroform and obtain an oily residue which is dissolved in a small amount of about 20 ml. of methylene chloride. The resulting solution is then diluted with about 40 ml. of ethyl acetate and concentrated *in vacuo* to crystallize 1 - isopropyl - 7 - methyl - 4 - phenyl - 2(1H) - quinazolinone; m.p. 137° to 138°C.

WHAT WE CLAIM IS:—

1. A process for the production of 1 - isopropyl - 7 - methyl - 4 - phenyl - quinazolinone of formula I,



characterised in that 4 - methyl - 2 - isopropylaminobenzophenone of formula II,

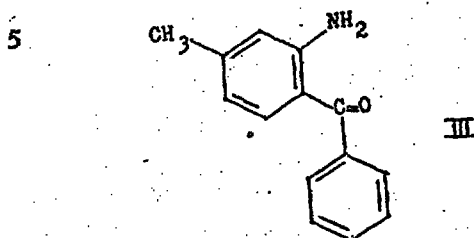


is cyclised with an alkyl carbamate in which the alkyl radical contains 1 to 5 carbon atoms, at a temperature of at least 140°C and in the presence of a Lewis acid.

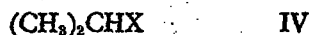
2. A process according to claim 1, which is effected at a temperature from 160° to 200°C, employing zinc chloride as the Lewis acid, and ethyl carbamate as the alkyl carbamate.



3. A process according to Claim 1 or 2, in which the compound of formula II is produced by reacting a compound of formula III,



with a compound of formula IV,



in which X signifies a bromine or iodine atom.

4. A process according to Claim 3, in which the compound of formula IV is isopropyl iodide.

5. A process according to Claim 3 or 4, in which the reaction of the compound of formula III with the compound of formula IV, is carried out in the presence of an in-

organic base to take up the hydrogen halide liberated during the reaction, and at a temperature of from 60° to 100°C.

6. A process for the production of the compound of formula I stated in Claim 1, substantially as herein described, with reference to the Example.

7. The compound of formula I, stated in Claim 1, whenever produced by a process according to any one of the preceding Claims.

8. The compound of formula I, stated in Claim 1.

9. A pharmaceutical composition incorporating the compound of formula I, stated in Claim 1, in association with a physiologically acceptable diluent or carrier.

10. A pharmaceutical composition according to Claim 9, substantially as hereinbefore described.

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Reference has been directed in pursuance of Section 9, Subsection (1) of the Patents Act, 1949, to patent No. 1,181,570.

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1971.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.