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PATENT SPECIFICATION

942,876

NO DRAWINGS

942,876

Date of Application and filing Complete Specification: March 27, 1961.

No. 11077/61.

Two Applications made in Switzerland (Nos. 4965 and 4966) on April 29, 1960.

Complete Specification Published: Nov. 27, 1963.

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Index at acceptance:—Class C2, C(B4A2, B4C, B4M).

International Classification:—C 07 d.

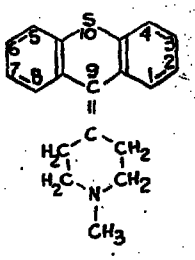
COMPLETE SPECIFICATION

Improvements in or relating to Piperidylidene-Thiaxanthene

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: —

The present invention relates to a novel thiaxanthene derivative and a process for its production.

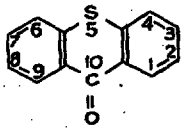
The present invention provides 9 - (N - methyl - piperidylidene - 4¹) - thiaxanthene of the formula I,



I

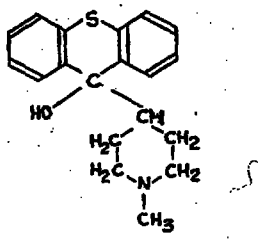
its acid addition salts and pharmaceutical compositions containing, in addition to an inert carrier, said compound I and/or an acid addition salt thereof.

The Ring Index 1940, formula No. 2019, also shows that the thiaxanthone nucleus can be numbered as follows:



but the numbering system shown in formula I above is used throughout this specification.

The present invention further provides a process for the production of the compound I and its acid addition salts, characterized in that 9 - (N - methyl - piperidyl - 4¹) - thiaxanthenol - (9) of the formula II,

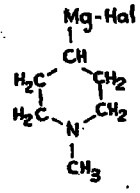


II

is treated with an agent for splitting off water, and, when it is desired to produce an acid addition salt, salification with an acid is effected. Examples of acids for effecting salification are hydrochloric, hydrobromic, sulphuric, citric, oxalic, tartaric, succinic, maleic, acetic, benzoic, hexahydrobenzoic, methanesulphonic, fumaric, gallic and hydriodic acid.

The splitting off of the water may be effected by heating with a dehydration agent, for example phosphorus oxychloride, phosphorus pentachloride, sulphuryl chloride or concentrated hydrochloric acid solution.

In the process of the invention compound II above may be first produced by reacting thiaxanthone-(9) with an organic magnesium compound of the general formula III,



III

wherein Hal represents a chlorine, bromine or iodine atom, and hydrolysing the resulting reaction product. Since the compound II is a base, it may, of course, be converted to its acid addition salt. Compound II and the method of its production mentioned herein are described and claimed in Patent Specification No.

[*Price 4s. 6d.*]

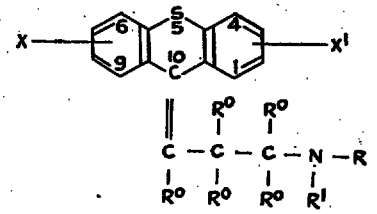
942,877 (Application No. 6404/63).

In one method of carrying out the process of the invention the compound I may be produced by heating compound II above with phosphorus oxychloride. Isolation of the resulting compound I, after removal of any excess phosphorus oxychloride present, may be effected by running the reaction product onto ice, making alkaline with an alkali metal hydroxide and extracting with a water immiscible inert organic solvent (for example chloroform). After removal of the solvent, purification in manner known *per se* may be effected.

When concentrated hydrochloric acid solution is used for splitting off water from the compound II above, it is advantageous to effect this operation at room temperature.

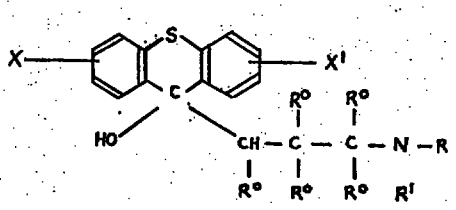
In the production of the compound II above the known Grignard technique is used, it being possible to use, instead of magnesium, a magnesium copper alloy in accordance with Gilman.

In British Patent Specification No. 829,763 there are described and claimed compounds having the general formula:—



in which each of X and X^1 represents a hydrogen or halogen atom, a C_{1-5} alkyl radical, or a C_{1-5} alkoxy radical; each R^o is a hydrogen atom or an alkyl radical, the R^o groups together containing from 0 to 4 carbon atoms,

and $-N<^{R}_{R^1}$ is a tertiary amino group in which R and R^1 are separate or R and R^1 are joined together to form a heterocyclic ring with the nitrogen atom, or R^1 is joined to any R^o group that is not hydrogen to form a heterocyclic ring with the nitrogen atom, and a process for their production which process comprises dehydrating a compound of general formula:



In said prior specification there are exemplified the following, either in the form of the free base or a salt:—

10 - (3 - dimethylaminopropylidene) - thiaxanthene, 2 - chloro - 10 - (3 - dimethyl - aminopropylidene) - thiaxanthene, including its α- and β-isomers,

2 - bromo - 10 - (3 - dimethylaminopropylidene-thiaxanthene,

2 - methoxy - 7 - chloro - 10 - [3 - (4 - morpholinyl) - propylidene - thiaxanthene,

3,8 - dipropoxy - 10 - (3 - dipropylaminopropylidene) - thiaxanthene,

2 - chloro - 8 - ethyl - 10 - (2 - methyl - 3 - dimethylaminopropylidene) - thiaxanthene,

2 - chloro - 10 - [3 - (1 - piperidyl) - propylidene] - thiaxanthene,

7 - propyl - 10 - [3 - (1 - pyrrolidyl) - propylidene] - thiaxanthene, the α- and β-forms of 2 - chloro - 10 - (3 - diethylaminopropylidene) - thiaxanthene,

2 - methoxy - 10 - (3 - dimethylamino - propylidene) - thiaxanthene,

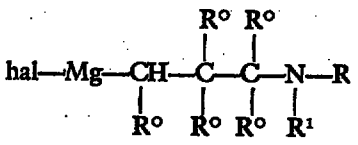
2,8 - dichloro - 10 - (3 - dimethylaminopropylidene) - thiaxanthene,

2 - methyl - 10 - (3 - dimethylaminopropylidene) - thiaxanthene and

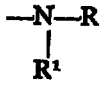
2 - chloro - 10 - (1 - methyl - 3 - piperidylmethylene) - thiaxanthene.

For these previously described compounds only antiemetic properties are mentioned in said prior specification. In contradistinction thereto, the compound of the present invention shows pronounced histamine inhibition, serotonine inhibition and anticholinergic effect; it is able to relieve or abort very quickly acute asthma conditions. For example, status asthmaticus may be aborted rapidly on intravenous injection of 2—4 mg of the free base. Furthermore, the compound of the present invention is able to relieve or abort other types of dispnoea, or allergic conditions, e.g. hay fever; in such cases the compound may be administered orally in the form of a physiologically acceptable acid addition salt.

In Patent Specification No. 829,764 there are, furthermore, described and claimed Grignard compounds having the general formula:

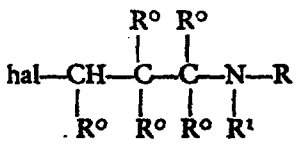


in which hal is a halogen atom; each R^o is a hydrogen atom or an alkyl radical, the R^o groups altogether containing from 0 to 4 carbon atoms; and

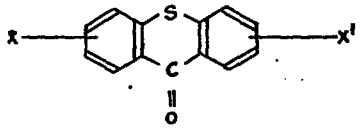


is a tertiary amino group in which R and R^1 are separate hydrocarbon groups or R and R^1 are joined together to form a heterocyclic ring with the nitrogen atom, or R^1 is joined to any

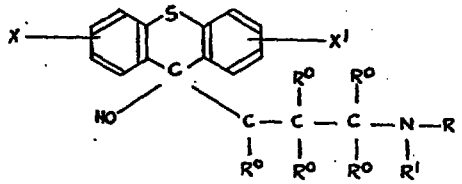
R^o group that is not hydrogen to form a heterocyclic ring with the nitrogen atom; a process for producing a compound as defined above, which comprises reacting a substituted propyl halide having the general formula:—



in which hal, R^o, R and R^1 are as defined above, with magnesium in dry tetrahydrofuran; and the process that comprises reacting a Grignard compound as defined above with a thiaxanthone of formula:



to produce a 10 - (3 - substituted aminopropyl) - 10 - hydroxy - thiaxanthene having the general formula:



in which each of X and X^1 is a hydrogen or halogen atom or a C_{1-5} alkyl or C_{1-5} alkoxy radical, and R^o, R and R^1 are as defined above.

The following Example illustrates the invention without, however, limiting it. The melting points are uncorrected and the temperatures are all stated in degrees Centigrade.

EXAMPLE

9 - (N - methyl - piperidylidene - 4^1) - thiaxanthene

a) 9 - (N - methyl - piperidyl - 4^1) - thiaxanthenol - (9).

The starting material, thiaxanthone - (9) (m.p. 207°) is obtained by condensation of *o*-chlorobenzoic acid with thiophenol and by cyclising the product of the reaction with thionyl chloride and aluminium chloride.

8.77 g of magnesium filings in a well dried apparatus are covered with 175 cc of tetrahydrofuran and activated with an iodine crystal and a few drops of ethyl bromide. 48 g of N - methyl - 4 - chloropiperidine are then added dropwise in such a way that steady reaction is maintained. When all the material has been added, the mixture is refluxed for 10 hours in the course of which nearly all the magnesium reacts. Through an extraction apparatus mounted on the flask 16.4 g. of thiaxanthone-(9) are added and subsequently boiling under reflux for 20 hours is effected. The solvent is then removed in a vacuum and the remaining organomagnesium compound treated with a solution of ammonium chloride, causing a precipitation of the required 9 - (N-methyl - piperidyl - 4^1) - thiaxanthenol - (9) which is crystallized from ethanol. M.p. 187.5—188.5°.

Maleate: 1.19 g of the base thus obtained and 0.45 g of maleic acid are dissolved in 30 cc of abs. ethanol. As the solution cools the maleate precipitates in crystalline form and is then recrystallized from abs. ethanol. M.p. 194—195°.

b) 9 - (N - methyl - piperidylidene - 4^1) - thiaxanthene.

4.0 g of 9 - (N - methyl - piperidyl - 4^1) - thiaxanthenol - (9) (m.p. 187.5—188.5°) are heated to the boil under reflux for 5 hours together with 25 cc of phosphorus oxychloride. Excess phosphorus oxychloride is then removed in a vacuum and the residue dissolved in 40 cc of ice water. The compound is extracted with chloroform from the aqueous solution after this has beeen alkalised with 20 cc of a concentrated caustic soda solution. The solvent is driven off and the required 9 - (N - methyl - piperidylidene - 4^1) - thiaxanthene crystallized from ligroin. M.p. 120—120.5°.

Maleate: 1.10 g of the base thus obtained and 0.44 g of maleic acid are dissolved in 30 cc of abs. ethanol. The maleate of 9 - (N - methyl - piperidylidene - 4^1) - thiaxanthene precipitates in crystalline form as the solution cools. After recrystallization from abs. ethanol, the analytically pure maleate melts at 183—184°.

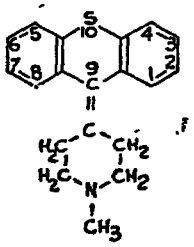
Hydrochloride: M.p. 162—165° from water.

Tartrate: M.p. 192—194° from ethanol.

Acetate: M.p. 103—105° from ether.

WHAT WE CLAIM IS:—

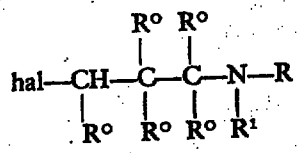
1. A process for the production of 9 - (N-methyl - piperidylidene - 4^1) - thiaxanthene of the formula I,



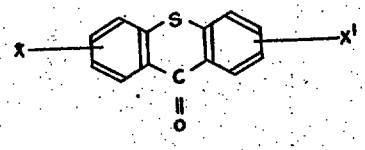
I

and its acid addition salts, characterized in that 9 - (N - methylpiperidyl - 4^1) - thiaxan-

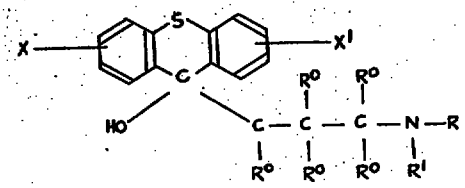
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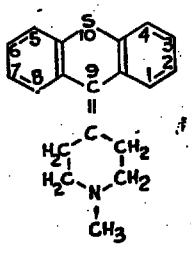
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Tartrate: M.p. 192—194° from ethanol.

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WHAT WE CLAIM IS:—

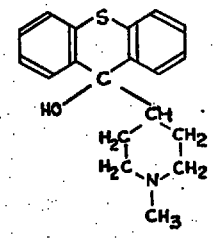
1. A process for the production of 9 - (N-methyl - piperidylidene - 4^1) - thiaxanthene of the formula I,



I

and its acid addition salts, characterized in that 9 - (N - methylpiperidyl - 4^1) - thiaxan-

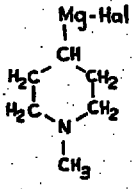
thenol - (9) of the formula II,



II

is treated with an agent for splitting off water, and, when it is desired to produce an acid addition salt, salification with an acid is effected.

2. A process according to Claim 1, in which the compound II is produced by reacting thiaxanthone - (9) with an organic magnesium compound of the general formula III,



III

wherein Hal represents a chlorine, bromine or iodine atom, and hydrolysing the resulting reaction product.

3. A process for the production of the compound I stated in Claim 1 and its acid addition salts substantially as herein described with reference to the Example.

4. The compound I stated in Claim 1 and its acid addition salts whenever produced by the process claimed in any one of the preceding claims.

5. 9 - (N - methyl - piperidylidene-4') - thiaxanthene and its acid addition salts.

6. Pharmaceutical compositions containing, in addition to an inert carrier, a compound claimed in either one of claims 4 and 5.

ERIC POTTER & CLARKSON,
Agents for the Applicants.
317 High Holborn, London, W.C.1.

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SPECIFICATION NO. 942,876

By a direction given under Section 17 (1) of the Patents Act 1949 this application proceeded in the name of WESTMINSTER BANK LIMITED, of 41, Lothbury, London, E.C.2., a British Company.

THE PATENT OFFICE D 86158/1(7)/R.109 200 12/63 PL

