PATENT SPECIFICATION

NO DRAWINGS

921,961

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No. 27521/59.
Application made in Switzerland (No. 62880) on Aug. 13, 1958.
(Patent of Addition to No. 862,297 dated May 8, 1958.)
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International Classification:—C07d.

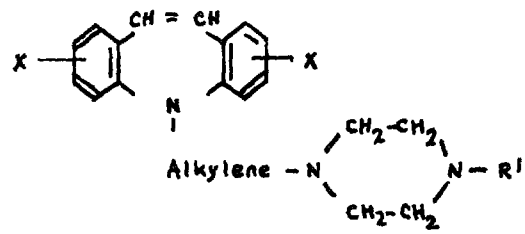
COMPLETE SPECIFICATION

New Iminostilbene Derivatives and method of preparing them

We, J. R. GEIGY A.G. a body corporate organised according to the laws of Switzerland, of 215, Schwarzwaldallee, Basle, Switzerland, do hereby declare the invention, for which 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 concerns improvements in the iminostilbene derivatives and the processes for their production described and claimed in British Patent Specification No. 862,297.

The present invention relates to a process for the production of ~~imonostilbene~~ iminostilbene derivatives of the general formula:

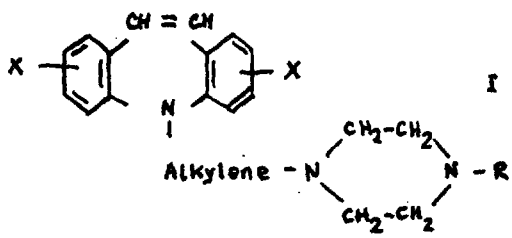


Ia

wherein both X's represent hydrogen, chlorine or the same alkyl radicals which can contain from 1 to 4 carbon atoms.

Alkylene represents an alkylene radical having from 2 to 6 carbon atoms.

R^1 represents an alkanoyloxyalkyl radical containing a total of from 2 to 8 carbon atoms, which comprises esterifying a compound of the general formula:

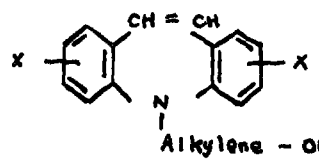


I

wherein X and alkylene have the meanings given above and R represents a hydroxyalkyl radical containing from 1 to 4 carbon atoms.

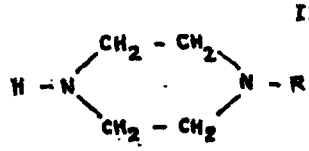
The invention further relates to a process for the production of compounds of the general formula I as defined above comprising reacting a reactive ester of a hydroxyl compound of the general formula:

II



wherein X and Alkylene have the meanings given above with an N-substituted piperazine of the general formula:

III



wherein R has the meaning given above.

[*Price 4s. 6d.*]

The compounds of general formulae I and Ia have valuable pharmacological properties, in particular sedative, anticonvulsive, antiallergic, antiemetic, antiphlogistic and antipyretic activity.

Suitable reactive esters of compounds of the general formula II are, in particular, their halides and aryl sulphonic acid esters. The reaction is performed advantageously in the presence of one mol of an alkali iodide in an inert organic solvent which is boiled under reflux. Examples of suitable starting materials are 5 - (β - chlorethyl)-, 5 - (β - chloropropyl)-, 5 - (γ - chloropropyl)-, 5 - (δ - chlorobutyl)-, 5 - (β - *p* - toluene sulphonyloxyethyl)- and 5 - (γ - *p* - toluene sulphonyloxypropyl)- iminostilbene, -3.7 - dichloro - iminostilbene and -3.7 - dimethyl - iminostilbene. These compounds are, in their turn, obtained, for example, by reacting iminostilbene or derivatives thereof with reactive diesters of alkane diols, in particular with those having two different acid components such as, e.g. α - bromo - β - chloralkanes, α - bromo - ω - chloralkanes and aryl sulphonic acid esters of chloralkanols and bromalkanols.

Examples of N-substituted piperazines of the general formula III are N - (β - hydroxyethyl) - piperazine, N - (γ - hydroxypropyl) - piperazine and N - (δ - hydroxybutyl) - piperazine.

The tertiary bases form mono- and di-acid salts, some of which are water soluble, with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methane sulphonic acid, ethane sulphonic acid, ethane disulphonic acid, acetic acid, succinic acid, furmaric acid, maleic acid, malic acid, tartaric acid, citric acid, benzoic acid and phthalic acid.

The following examples illustrate the production of the new compounds. Parts are given therein as parts by weight unless otherwise stated, and their relationship to parts by volume is as that of grammes to cubic centimetres. The temperatures are in degrees Centigrade.

Example 1

19 Parts of iminostilbene and 20 parts of 1-chloro-3-bromopropane are dissolved in 800 parts by volume of abs. benzene and 4.4 parts of sodium amide in toluene are added dropwise while stirring strongly, the addition being made within half an hour at 50°. On completion of the dropwise addition, the whole is stirred for another 3 hours at 50—60° and then refluxed for 3 hours. After cooling, water is added to the reaction mixture and the benzene phase is separated, washed with water, dried and concentrated. The oily residue is dissolved in 400 parts by volume of petroleum ether, any undissolved iminostilbene is filtered off and the solvent is evaporated. Oily 5 - (3^1 - chloropropyl) - iminostilbene remains which, after recrystallisation from abs. ether, melts at 67°.

19 Parts of the oily residue are dissolved in 130 parts by volume of butanone and, after the addition of 10 parts of sodium iodide, are stirred under reflux for 16 hours with 19 parts of N - (β - hydroxyethyl) - piperazine. The solvent is then distilled off, water is added and the whole is thoroughly extracted with ether. After thoroughly washing with water, the ethereal solution is extracted three times with diulted hydrochloric acid. The acid extracts are made alkaline and the precipitated base is dissolved in ether. After drying the ethereal solution with sodium sulphate and evaporating the solvent, 5 - (3^1 - (4^{11} - hydroxyethyl - piperazino) -propyl) - iminostilbene remains. M.P. 100°.

The dihydrochloride prepared with alcoholic hydrochloric acid melts at 228—230°.

The following compounds can be produced in an analogous manner:

5 - [3^1 - (4^{11} - hydroxyethyl - piperazino) - propyl] - 3.7 - dichloro - iminostilbene,

5 - [2^1 - (4^{11} - γ - hydroxypropyl - piperazino) - ethyl] - 2.8 - dichloro - iminostilbene,

5 - [3^1 - (4^{11} - hydroxyethyl - piperazino) - propyl] - 3.7 - dimethyl - iminostilbene.

Example 2

1 Part of 5 - [3^1 - (4^{11} - hydroxyethyl - piperazino) - propyl] - iminostilbene and 5 parts of acetic acid anhydride are refluxed for 4 hours. The excess acetanhydride is evaporated in the vacuum, the residue is dissolved in cold water, the solution is filtered and the filtrate is made alkaline with sodium carbonate solution. The precipitate is dissolved in ether, the ether solution is washed with water, dried over sodium sulphate and the solvent is distilled off. The residue is dissolved in petroleum ether, the solution is filtered and the filtrate is concentrated. 5 - [3^1 - (4^{11} - acetoxyethyl - piperazino) - propyl] - iminostilbene is obtained as a yellow oil.

1 Part of this oil is dissolved in as little acetone as possible and then the calculated amount of abs. alcoholic hydrochloric acid is added. After some time the dihydrochloride crystallises out and, when recrystallised from alcohol, it melts at 209—212°.

In an analogous manner, 5 - [3^1 - (4^{11} - acetoxyethyl - piperazino) - propyl] - 3.7 - dichloro - iminostilbene and its dihydrochloride are obtained from 5 - [3^1 - (4^{11} - hydroxyethyl - piperazino) - propyl] - 3.7 - dichloro - iminostilbene.

WHAT WE CLAIM IS:—

1. A process for the production of iminostilbene derivatives of the general formula:

The compounds of general formulae I and Ia have valuable pharmacological properties, in particular sedative, anticonvulsive, antiallergic, antiemetic, antiphlogistic and antipyretic activity.

Suitable reactive esters of compounds of the general formula II are, in particular, their halides and aryl sulphonic acid esters. The reaction is performed advantageously in the presence of one mol of an alkali iodide in an inert organic solvent which is boiled under reflux. Examples of suitable starting materials are 5 - (β - chlorethyl)-, 5 - (β - chloropropyl)-, 5 - (γ - chloropropyl)-, 5 - (δ - chlorobutyl)-, 5 - (β - *p* - toluene sulphonyloxyethyl)- and 5 - (γ - *p* - toluene sulphonyloxypropyl)- iminostilbene, -3.7 - dichloro - iminostilbene and -3.7 - dimethyl - iminostilbene. These compounds are, in their turn, obtained, for example, by reacting iminostilbene or derivatives thereof with reactive diesters of alkane diols, in particular with those having two different acid components such as, e.g. α - bromo - β - chloralkanes, α - bromo - ω - chloralkanes and aryl sulphonic acid esters of chloralkanols and bromalkanols.

Examples of N-substituted piperazines of the general formula III are N - (β - hydroxyethyl) - piperazine, N - (γ - hydroxypropyl) - piperazine and N - (δ - hydroxybutyl) - piperazine.

The tertiary bases form mono- and di-acid salts, some of which are water soluble, with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methane sulphonic acid, ethane sulphonic acid, ethane disulphonic acid, acetic acid, succinic acid, furmaric acid, maleic acid, malic acid, tartaric acid, citric acid, benzoic acid and phthalic acid.

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5 - [2^1 - (4^{11} - γ - hydroxypropyl - piperazino) - ethyl] - 2.8 - dichloro - iminostilbene,

5 - [3^1 - (4^{11} - hydroxyethyl - piperazino) - propyl] - 3.7 - dimethyl - iminostilbene.

EXAMPLE 2

1 Part of 5 - [3^1 - (4^{11} - hydroxyethyl - piperazino) - propyl] - iminostilbene and 5 parts of acetic acid anhydride are refluxed for 4 hours. The excess acetanhydride is evaporated in the vacuum, the residue is dissolved in cold water, the solution is filtered and the filtrate is made alkaline with sodium carbonate solution. The precipitate is dissolved in ether, the ether solution is washed with water, dried over sodium sulphate and the solvent is distilled off. The residue is dissolved in petroleum ether, the solution is filtered and the filtrate is concentrated. 5 - [3^1 - (4^{11} - acetoxyethyl - piperazino) - propyl] - iminostilbene is obtained as a yellow oil.

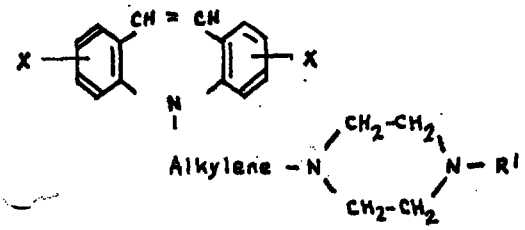
1 Part of this oil is dissolved in as little acetone as possible and then the calculated amount of abs. alcoholic hydrochloric acid is added. After some time the dihydrochloride crystallises out and, when recrystallised from alcohol, it melts at 209—212°.

In an analogous manner, 5 - [3^1 - (4^{11} - acetoxyethyl - piperazino) - propyl] - 3.7 - dichloro - iminostilbene and its dihydrochloride are obtained from 5 - [3^1 - (4^{11} - hydroxyethyl - piperazino) - propyl] - 3.7 - dichloro - iminostilbene.

WHAT WE CLAIM IS:—

1. A process for the production of iminostilbene derivatives of the general formula:

* C L M S *

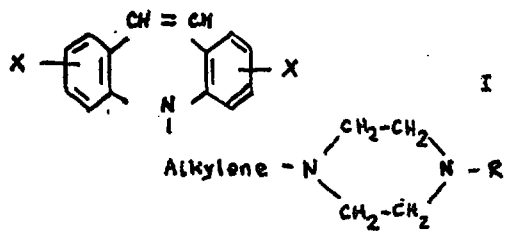


Ia

wherein both X's represent hydrogen, chlorine or the same alkyl radicals which can contain from 1 to 4 carbon atoms,

Alkylene represents an alkylene radical having from 2 to 6 carbon atoms and

R^1 represents an alkanoyloxyalkyl radical containing a total of from 2 to 8 carbon atoms which comprises esterifying a compound of the general formula:

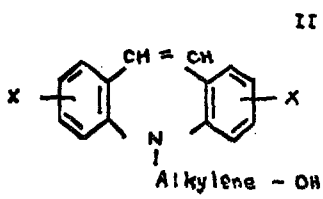


I

wherein X and Alkylene have the meanings given above and

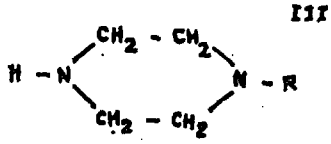
R represents a hydroxyalkyl radical containing from 1 to 4 carbon atoms.

2. A process for the production of iminostilbene derivatives of general formula I, as defined in claim 1, comprising reacting a reactive ester of a hydroxyl compound of the general formula II:



II

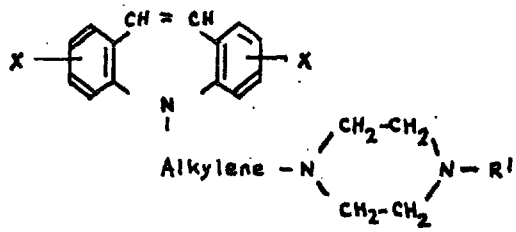
wherein X and Alkylene have the meanings defined in claim 1, with an N-substituted piperazine of the general formula III:



III

wherein R has the meaning given in claim 1.

3. Process for the preparation of iminostilbene derivatives of the general formula:



Ia

wherein X, Alkylene and R^1 have the meanings defined in claim 1 substantially as hereinbefore described with reference to and as illustrated by Example 2.

4. Process for the preparation of iminostilbene derivatives of the general formula I, as defined in claim 1, substantially as hereinbefore described with reference to and as illustrated by Example 1.

5. 5 - [3^1 - (4^{11} - hydroxyethyl - piperazino) - propyl] - iminostilbene.

6. 5 - [3^1 - (4^{11} - hydroxyethyl - piperazino) - propyl] - 3,7 - dichloro - iminostilbene.

7. 5 - [2^1 - (4^{11} - β - hydroxypropyl - piperazino) - ethyl] - 2,8 - dichloro - iminostilbene.

8. 5 - [3^1 - (4^{11} - hydroxyethyl - piperazino) - propyl] - 3,7 - dimethyl - iminostilbene.

9. 5 - [3^1 - (4^{11} - acetoxyethyl - piperazino) - propyl] - 3,7 - dichloro - iminostilbene.

10. Iminostilbene derivatives of the general formula Ia as defined in claim 1, whenever produced by a process as claimed in claim 1.

11. Iminostilbene derivatives of the general formula I as defined in claim 1, whenever produced by a process as claimed in claim 2.

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* C L M S *