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PATENT SPECIFICATION

962,462



NO DRAWINGS

962,462

Date of Application and filing Complete Specification: Aug. 29, 1960.
No. 26144/63.
Application made in Switzerland (No. 77491) on Aug. 28, 1959.
Application made in Switzerland (No. 299) on Jan. 13, 1960.
Application made in Switzerland (No. 2108) on Feb. 25, 1960.
(Patent of Addition to No. 862,297 dated May 8, 1958.)
(Divided out of No. 962,461.)
Complete Specification Published: July 1, 1964.
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Index at acceptance :—C2 C(1G5A, 1G5B, 1G6A1, 1G6B3, 1G6B4, 3A10E3A4, 3A10E5A, 3A10E5E, 3A10E5F1C, 3A10E5F2A, 3A13A3A4, 3A13A3B1, 3A13A3C, 3A13A3L, B4A1, B4A4, B4D, B4M)

International Classification:—C 07 d

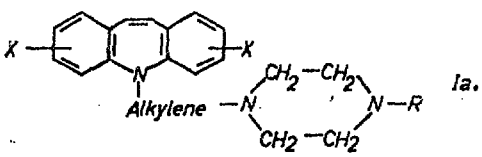
COMPLETE SPECIFICATION

Substituted 5H-Dibenz [b.f] Azepines and processes for their production

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 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 substituted 5H - dibenz[b,f]azepines having valuable pharmacological properties, as well as processes for the production thereof.

Specification No. 862,297 discloses and claims 5 - dibenzo[b.f]azepines having the general formula



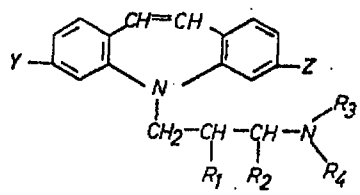
Ia.

wherein

X is hydrogen, halogen or a methyl group,
Alkylene is an alkylene radical having from 2 to 6 carbon atoms and having at least two bridging members between the two nitrogen atoms and
R is an alkyl radical containing 1 to 4 carbon atoms, an alkanoyloxyalkyl or hydroxyalkyl radical.

Specification No. 862,297 also discloses and claims various processes for the production of compounds of the general formula Ia as defined above.

It has now been found that certain 5H - dibenzo[b,f]azepines not disclosed in Specification No. 862,297, and having the general formula



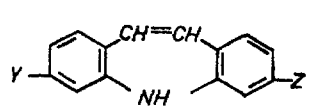
I.

wherein

Y represents hydrogen or a halogen atom,
Z represents hydrogen or a halogen atom,
one of the symbols R_1 and R_2 represents the methyl group and the other hydrogen, and
R_3 and R_4 represent alkylene radicals having from 1 to 4 carbon atoms which are bound to each other by way of an oxygen atom or an alkylimino, alkanoyloxyalkylimino or hydroxyalkylimino group, each of said groups having a total of at most 4 carbon atoms,

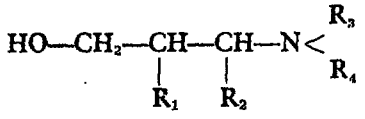
have valuable pharmacological properties, in particular spasmolytic, anti-allergic, sedative, anticonvulsive and anti-emetic activity.

The compounds of the above defined general formula I may be produced by reacting an iminostilbene of the general formula



II.

wherein Y and Z have the meanings given above, in the presence of an acid-binding agent, with a reactive ester of a basic alcohol of the general formula



III

wherein R_1, R_2, R_3 and R_4 have the meanings given above.

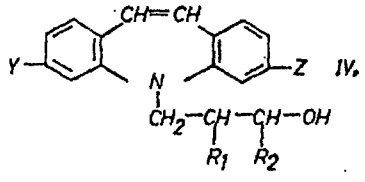
Particularly suitable condensing agents are sodium amide, lithium amide, potassium amide, sodium or potassium, butyl lithium, phenyl lithium, sodium hydride or lithium hydride. The reaction can be performed in the presence or absence of an inert organic solvent, of which examples are benzene, toluene and xylene.

In addition to iminostilbene itself, suitable starting materials of the general formula II are, for example, 3,7-dichloro-iminostilbene, and 3,7-dibromo-iminostilbene as well as the mono-substituted compounds 3-chloro-iminostilbene and 3-bromo-iminostilbene. They may be produced, for example, by treating 3,5 - diacetyl - iminodibenzyl with hydrazoic acid according to Schmidt hydrazoic acid reaction followed by partially hydrolysing the acetamido compound to form 3-amino-5-acetyl-iminodibenzyl, diazotising this, reacting the diazonium halides with cuprous halides according to Sandmeyer and brominating the 3 - halogen - 5 - acetyl - iminodibenzyls obtained in the 10-position with N-bromosuccinimide, splitting off hydrogen halide and hydrolysing, for example with caustic alkalies in the cold, to form 3-halogen-iminostilbenes.

As reactive esters of basic alcohols of the general formula III, in particular the halides, aryl sulphonic acid esters and methane sulphonic acid esters are used. Examples thereof are γ - morpholino - n - butyl chloride, γ - (4 - methyl - piperazino) - n - butyl chloride and the corresponding bromides and toluene - *p* - sulphonic acid esters, as well as γ - morpholino - β - methylpropyl chloride, γ - (4 - methyl - piperazino) - β - methylpropyl chloride, γ - (4 - hydroxyethyl - piperazino) - β - methylpropyl chloride and γ - (4 - acetoxyethyl - piperazino)-β-methylpropyl chloride. The first group of reactive esters of basic alcohols is obtained, for example, starting from 1,3-butylene glycol by reacting it with acetyl chloride to form 3-chloro-n-butyl acetate, reacting the latter with a suitable secondary amine and converting the 3-tertiary amino - n - butanol obtained into its chloride, bromide or toluene sulphonic acid ester.

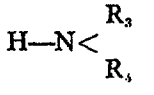
The N-substituted β-methylpropyl chlorides can be obtained for example, by adding hydrogen bromide in the presence of dibenzoylperoxide to β-methallyl chloride and reacting the γ-bromo-β-methylpropyl chloride obtained with suitable secondary amines.

A modified process for the production of compounds of the general formula I consists in reacting a reactive ester of a hydroxy compound of the general formula



IV.

wherein R_1, R_2, Y and Z have the meanings given above, e.g. a halide, an aryl sulphonic acid ester or methane sulphonic acid ester, with a secondary amine of the general formula

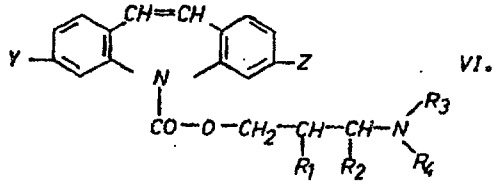


V

wherein R_3 and R_4 have the meanings given above. The reaction can be performed, for example, at a moderately raised temperature of, e.g. 80—120° C., in an inert solvent such as, e.g. a low molecular weight alkanol or alkanone, an excess of the amine being reacted being advantageously used as acid-binding agent. Depending on the boiling point of the amine used and of the solvent as well as on the reaction temperature necessary, the reaction is sometimes to be performed in a closed vessel. Reactive esters of hydroxy compounds of the general formula IV are obtained, for example, by reacting alkali metal compounds of optionally substituted iminostilbene of the general formula II with 1 - bromo - 3 - chlorobutane, 1,3 - dichlorobutane or γ - bromo - β - methylpropyl chloride or with halogen butyl aryl sulphonic acid esters or halogen butyl methane sulphonic acid esters.

Secondary amines of the general formula V are morpholine, N - methyl - piperazine, N - hydroxyethyl - piperazine and N - acetoxyethyl-piperazine.

Compounds of the general formula I are obtained according to a further process by heating a compound of the general formula



VI.

wherein Y, Z, R_1, R_2, R_3 and R_4 have the meanings given above, until one molecular proportion of carbon dioxide has been split off. The compounds of the general formula VI are obtained in their turn, for example,

by reacting phosgene with compounds of the general formula II and reacting the possibly substituted 5 - chlorocarbonyl-iminostilbenes obtained with basic alcohols of the general formula III.

The compounds of the general formula I form salts with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methane sulphonic acid, ethane disulphonic acid, acetic acid, citric acid, malic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, benzoic acid, phthalic acid and 8-chlorotheophyllin. Some of these salts are water soluble.

The following examples further illustrate the production of the new compounds according to the invention. Where not otherwise stated, parts are given as parts by weight and their relationship to parts by volume is as that of grammes to cubic centimetres. The temperatures are in degrees Centigrade.

EXAMPLE 1

19.3 Parts of iminostilbene are dissolved in 360 parts by volume of anhydrous toluene. A suspension of 5 parts of sodium amide in toluene is added dropwise at 60° while stirring well whereupon the reaction mixture is refluxed for 16 hours. At the end of this time, a solution of 21 parts of 3 - (4^1-methylpiperazinyl - 1^1) - 2 - methylpropyl chloride in 150 parts by volume of anhydrous toluene is added dropwise also at 60° while stirring. The whole is then refluxed for 14 hours, whereupon water is added to the reaction mixture and the basic portions are removed from the toluene phase by extracting three times with dilute hydrochloric acid. The combined extracts are made basic and extracted with ether, the ethereal solution is dried over potassium carbonate and concentrated. The residue is distilled in a high vacuum whereupon 5 - [γ - (4^1 - methylpiperazinyl - 1^1) - β - methylpropyl] - iminostilbene passes over at 171—174° under 0.0005 mm. The base crystallises from acetone in the form of yellow rhombs which melt at 99°. The yellow dihydrochloride prepared with alcoholic hydrochloric acid and recrystallised from anhydrous ethanol melts at 246°.

EXAMPLE 2

19.3 Parts of iminostilbene are dissolved in 275 parts by volume of anhydrous toluene. A suspension of 5 parts of sodium amide in toluene is added dropwise at 60° while stirring vigorously whereupon the reaction mixture is refluxed for 2 hours. A solution of 22 parts of 1-chloro-2-methyl-3-bromopropane in 100 parts by volume of anhydrous toluene is then added dropwise while stirring strongly at 60—70° whereupon the whole is refluxed for 12 hours. Water is then added to the reaction mixture, the toluene solution is dried over potassium carbonate and evaporated. The oily residue is boiled for a short time in petroleum ether, the mixture is filtered and concentrated.

25.5 Parts of the crude 5 - (γ-chloro-β-methylpropyl)iminostilbene so obtained are dissolved in 200 parts by volume of butanone and the solution, with 16.4 parts of 4-(2^1-hydroxyethyl) - piperazine and 15 parts of sodium iodide, is refluxed for 17 hours while stirring vigorously. The solvent is then distilled off *in vacuo* and the residue is dissolved in ether. The basic portions are removed from the ethereal phase by extracting three times with dilute hydrochloric acid. The combined extracts are made alkaline and extracted with ether, the ethereal solution is dried over potassium carbonate and concentrated. The residue which consists of 5 - γ - [4^1-(2^{11}-hydroxyethyl) - piperazinyl - 1^1] - β - methylpropyl-iminostilbene, crystallises from acetone in the form of yellow microcrystals which melt at 110°.

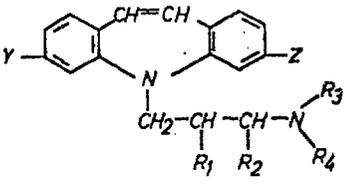
The yellow dihydrochloride prepared with alcoholic hydrochloric acid and recrystallised from anhydrous ethanol melts at 212—216°.

5 - γ - [4^1 - (2^{11} - acetoxyethyl) - piperazinyl - 1^1] - β - methylpropyl-iminostilbene is obtained by acetylation with acetic anhydride.

On using 3 - chloro - iminostilbene and γ - morpholino - β - methylpropyl chloride, 5 - (γ - morpholino - β - methylpropyl) - 3 - chloro-iminostilbene is obtained in an analogous manner, and on using iminostilbene and γ - (4 - methyl - piperazinyl - 1) - n - butyl chloride, 5 - [γ - (4^1 - methyl - piperazinyl-1^1)-n-butyl]-iminostilbene is obtained.

WHAT WE CLAIM IS:—

1. New N - heterocyclic compounds of the general formula



1.

wherein

Y represents hydrogen or a halogen atom,

Z represents hydrogen or a halogen atom,

one of the symbols R_1 and R_2 represents the methyl group and the other represents hydrogen, and

R_3 and R_4 represent alkylene radicals having from 1 to 4 carbon atoms which are bound to each other by way of an oxygen atom, or an alkylimino, alkanoyloxyalkylimino or hydroxyalkylimino group, each of said groups having a total of at most 4 carbon atoms.

2. Process for the production of new

by reacting phosgene with compounds of the general formula II and reacting the possibly substituted 5 - chlorocarbonyl-iminostilbenes obtained with basic alcohols of the general formula III.

The compounds of the general formula I form salts with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methane sulphonic acid, ethane disulphonic acid, acetic acid, citric acid, malic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, benzoic acid, phthalic acid and 8-chlorotheophyllin. Some of these salts are water soluble.

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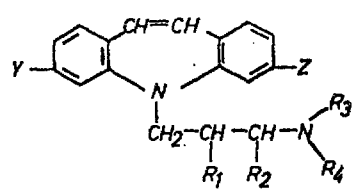
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On using 3 - chloro - iminostilbene and γ - morpholino - β - methylpropyl chloride, 5 - (γ - morpholino - β - methylpropyl) - 3 - chloro-iminostilbene is obtained in an analogous manner, and on using iminostilbene and γ - (4 - methyl - piperazinyl - 1) - n - butyl chloride, 5 - [γ - (4^1 - methyl - piperazinyl-1^1)-n-butyl]-iminostilbene is obtained.

WHAT WE CLAIM IS:—

1. New N - heterocyclic compounds of the general formula



1.

wherein

Y represents hydrogen or a halogen atom,

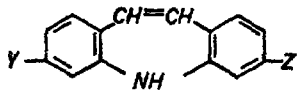
Z represents hydrogen or a halogen atom,

one of the symbols R_1 and R_2 represents the methyl group and the other represents hydrogen, and

R_3 and R_4 represent alkylene radicals having from 1 to 4 carbon atoms which are bound to each other by way of an oxygen atom, or an alkylimino, alkanoyloxyalkylimino or hydroxyalkylimino group, each of said groups having a total of at most 4 carbon atoms.

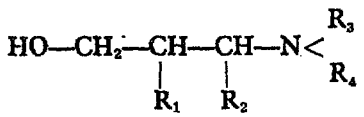
2. Process for the production of new

heterocyclic compounds of the general formula I as defined in claim 1, which comprises reacting, in the presence of an acid-binding agent, an iminostilbene of the general formula



II.

with a reactive ester of a basic alcohol of the general formula

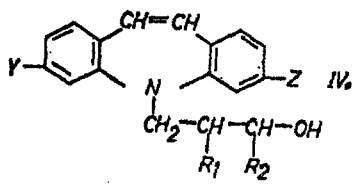


III

wherein

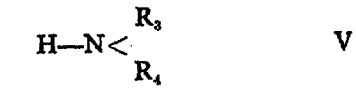
Y, Z, R_1, R_2, R_3 and R_4 have the meanings given in claim 1.

3. Process for the production of heterocyclic compounds of the general formula I as defined in claim 1, which comprises reacting a reactive ester of a hydroxy compound of the general formula



IV.

with a secondary amine of the general formula

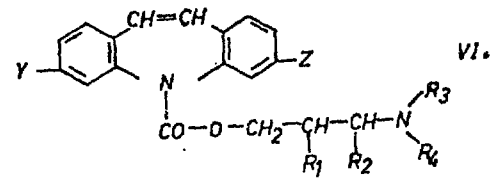


V

wherein

Y, Z, R_1, R_2, R_3 and R_4 have the meanings given in claim 1.

4. Process for the production of heterocyclic compounds of the general formula I as defined in claim 1, which comprises heating a compound of the general formula



VI.

wherein

Y, Z, R_1, R_2, R_3 and R_4 have the meanings given in claim 1, until 1 molecular proportion of carbon dioxide is split off.

5. New N - heterocyclic compounds as herein described with reference to and as illustrated in the foregoing Examples.

6. Process for the production of new N-heterocyclic compounds substantially as herein described with reference to and as illustrated in the foregoing Examples.

W. P. THOMPSON & CO.,
12, Church Street, Liverpool 1,
Chartered Patent Agents.

Reference has been directed in pursuance of Section 9, subsection (1) of the Patents Act, 1949, to patent No. 914,717.

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* C L M S *