RESERVE COPY.

PATENT SPECIFICATION

943,275

NO DRAWINGS

943,275

Date of Application and filing Complete Specification: Nov. 16, 1960.

No. 39268/60.

Application made in Switzerland (No. 80636) on Nov. 16, 1959.

Complete Specification Published: Dec. 4, 1963.

© Crown Copyright 1963.

Index at acceptance:—Class C2, C(1E6K4, 1F2C6, 1F2D3, 2B4A4, 2B4C, 2B4F, 2B4G1, 2B4G10, 2B9, 3A12A4A, 3A12A4C, 3A12B1, 3A12C1, 3A12C3, 3A14A3C, 3A14A5, 3A14A7A).

International Classification:—C 07 d.

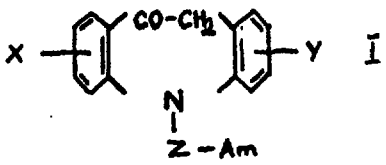
COMPLETE SPECIFICATION

Derivatives of Dibenz[b,f]azepine and process 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 new derivatives of Dibenz[b,f]azepines with valuable pharmacological properties as well as processes for their preparation.

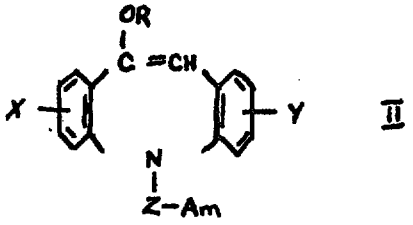
5H - Dibenzo[b,f]azepine - 10(11H) - ones and derivatives thereof have not previously been known. It has now been found that N-derivatives of such compounds corresponding to the general formula



I

in which X signifies hydrogen, a halogen atom or an alkyl radical of at most 3 carbon atoms, Y signifies hydrogen, a halogen atom or an alkyl or alkoxy radical of at most 3 carbon atoms, Z signifies a straight- or branched-chain alkylene residue containing 2—6 carbon atoms, and Am signifies a dialkylamino group of at most 8 carbon atoms, while one of the two alkyl residues of Am may be combined with the alkylene residue Z, or both alkyl residues of Am may be combined among themselves together, directly or via an oxygen atom or an alkylimino-group, possess valuable pharmacological properties, especially anti-allergic, anti-emetic, anti-spasmodic and sedative activities, as well as intensifying the effect of other medicaments, especially of narcotics.

Quaternary ammonium salts, which are derived from the tertiary bases defined above, act as ganglioplegics. The preparation of the new compounds may be effected by hydrolysis of 5-substituted 10-alkoxy- or 10-alkenyloxy-5H-dibenzo[b,f]azepines of the general formula



II

in which R signifies an alkyl or alkenyl radical of at most 4 carbon atoms and X, Y, Z and Am have the meaning given above, preferably in acid medium, for example in dilute hydrochloric acid. Suitable starting substances of the general formula II are, for example,

5 - (β - dimethylamino - ethyl) - 10-methoxy - 5H - dibenzo[b,f]azepine,

5 - (γ - dimethylamino - propyl) - 10-methoxy - 5H - dibenzo[b,f]azepine,

5 - (γ - dimethylamino - propyl) - 10-ethoxy - 5H - dibenzo[b,f]azepine,

5 - (β - pyrrolidino - ethyl) - 10 - ethoxy-5H - dibenzo[b,f]azepine,

5 - (γ - piperidino - propyl) - 10 - methoxy - 5H - dibenzo[b,f]azepine,

5 - (γ - dimethylamino - propyl) - 10 - *n*-butoxy - 5H - dibenzo[b,f]azepine,

5 - [γ - (4¹ - methyl - piperazino)-propyl]-10 - methoxy - 5H - dibenzo[b,f]azepine and

5 - (γ - dimethylamino - propyl) - 10-methoxy - 3,7 - dichloro - 5H - dibenzo[b,f]-azepine, m.p. 96° C.

Compounds of general formula II have

[*Price 4s. 6d.*]

been claimed in copending Application No. 39269/60 (Serial No. 943,276).

By adding reactive esters, especially halides or sulphates, of aliphatic or araliphatic alcohols, e.g. methyl iodide, dimethyl sulphate, ethyl bromide, ethyl iodide or benzyl chloride, to the tertiary amines of the general formula I, monoquaternary ammonium compounds are formed in the usual way, by reaction with the group Am.

With inorganic or organic acids, such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanedisulphonic acid, acetic acid, citric acid, malic acid, succinic acid, fumaric acid, maleic acid, tartaric acid, benzoic acid and phthalic acid, the tertiary bases form salts, some of which are soluble in water.

The following example illustrates in more detail the preparation of the new compounds. Parts signify therein parts by weight, and these are to parts by volume as g are to c.c. The temperatures are given in degrees Centigrade.

10 parts of 5 - (β - dimethylamino - ethyl)- 10 - methoxy - 5H - dibenzo[b,f]azepine are boiled under reflux in 80 parts by volume of 2 N-hydrochloric acid for an hour. After cooling, the reaction solution is made alkaline with concentrated ammonia and the oil which separates is dissolved in ether. The ethereal solution is washed with water, dried and evaporated. When the residue is distilled in high vacuum, 5 - (β - dimethylamino - ethyl)- 5H - dibenzo [b,f]azepine - 10(11H) - one of b.p.$_{0,01}$ 174—175°, m.p. 80° is obtained.

The following are obtained in a similar way:

5 - (γ - dimethylamino - propyl) - 5H-dibenzo[b,f]azepine - 10(11H) - one, b.p.$_{0,005}$ 174°,

5 - (β - morpholino - ethyl) - 5H - dibenzo-[b,f]azepine - 10(11H) - one, b.p.$_{0,01}$ 202°,

5 - (γ - piperidino - propyl) - 5H - dibenzo-[b,f]azepine - 10(11H) - one, b.p.$_{0,005}$ 188°,

5 - [γ - (4^1 - methyl - piperazino)-propyl]- 5H - dibenzo[b,f]azepine - 10(11H) - one, m.p. 122°,

5 - (γ - dimethylamino - propyl) - 3,7-dichloro - 5H - dibenzo[b,f]azepine-10(11H)-one, m.p. 87°,

5 - (γ - dimethylamino - propyl) - 3,7-dimethyl - 5H - dibenzo[b,f]azepine-10(11H)-one,

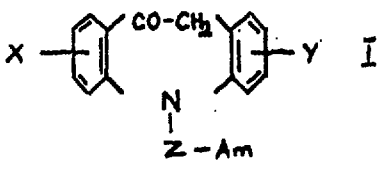
5 - (γ - dimethylamino - propyl) - 2-methoxy - 5H - dibenzo[b,f]azepine-10(11H)-one,

5 - (β - methyl - γ - dimethylamino-propyl) - 5H - dibenzo[b,f]azepine-10(11H)-one, b.p.$_{0,015}$ 178°, and

5 - [β - (1^1 - methyl - piperidyl - 2^1)-ethyl] - 5H - dibenzo[b,f]azepine - 10(11H)-one, b.p.$_{0,01}$ 202°.

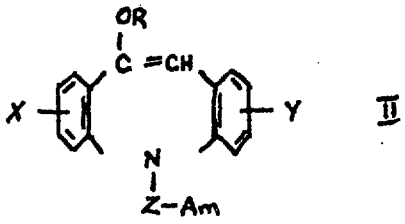
WHAT WE CLAIM IS:—

1. Process for the production of New N-heterocyclic compounds, characterised in that compounds of the general formula



I

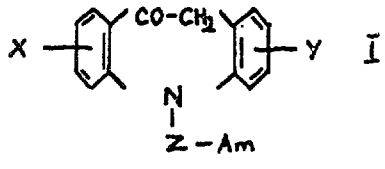
in which X signifies hydrogen, a halogen atom or an alkyl radical of at most 3 carbon atoms, Y signifies hydrogen, a halogen atom or an alkyl or alkoxy radical of at most 3 carbon atoms, Z signifies a straight or branched chain alkylene residue containing 2—6 carbon atoms, and Am signifies a dialkylamino group of at most 8 carbon atoms, while one of the two alkyl residues of Am may be combined with the alkylene residue Z or both alkyl residues of Am may be combined among themselves together, directly or via an oxygen atom or an alkylimino group, and if desired their acid-addition salts or quaternary ammonium compounds, are prepared by hydrolysing a 5-substituted 10-alkoxy- or 10-alkenyloxy- 5H - dibenzo[b,f]azepine - 10(11H)-one of the general formula



II

in which R signifies an alkyl or alkenyl radical of at most 4 carbon atoms residue, and if desired converting the tertiary base so obtained into its salts with inorganic or organic acids, or into a quaternary ammonium compound by adding a reactive ester of an aliphatic or araliphatic alcohol.

2. N - heterocyclic compounds of the general formula



I

in which X, Y, Z and Am have the meanings given in claim 1, as well as their acid addition salts and the quaternary ammonium compounds formed by adding on reactive esters of aliphatic or araliphatic alcohols.

3. N-Heterocyclic compounds of the general formula I defined in claim 1, sub-

been claimed in copending Application No. 39269/60 (Serial No. 943,276).

By adding reactive esters, especially halides or sulphates, of aliphatic or araliphatic alcohols, e.g. methyl iodide, dimethyl sulphate, ethyl bromide, ethyl iodide or benzyl chloride, to the tertiary amines of the general formula I, monoquaternary ammonium compounds are formed in the usual way, by reaction with the group Am.

With inorganic or organic acids, such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanedisulphonic acid, acetic acid, citric acid, malic acid, succinic acid, fumaric acid, maleic acid, tartaric acid, benzoic acid and phthalic acid, the tertiary bases form salts, some of which are soluble in water.

The following example illustrates in more detail the preparation of the new compounds. Parts signify therein parts by weight, and these are to parts by volume as g are to c.c. The temperatures are given in degrees Centigrade.

10 parts of 5 - (β - dimethylamino - ethyl)-10 - methoxy - 5H - dibenzo[b,f]azepine are boiled under reflux in 80 parts by volume of 2 N-hydrochloric acid for an hour. After cooling, the reaction solution is made alkaline with concentrated ammonia and the oil which separates is dissolved in ether. The ethereal solution is washed with water, dried and evaporated. When the residue is distilled in high vacuum, 5 - (β - dimethylamino - ethyl)-5H - dibenzo [b,f]azepine - 10(11H) - one of $b.p._{0,01}$ 174—175°, m.p. 80° is obtained.

The following are obtained in a similar way:

5 - (γ - dimethylamino - propyl) - 5H-dibenzo[b,f]azepine - 10(11H) - one, $b.p._{0,005}$ 174°,

5 - (β - morpholino - ethyl) - 5H - dibenzo-[b,f]azepine - 10(11H) - one, $b.p._{0,01}$ 202°,

5 - (γ - piperidino - propyl) - 5H - dibenzo-[b,f]azepine - 10(11H) - one, $b.p._{0,005}$ 188°,

5 - [γ - (4¹ - methyl - piperazino)-propyl]-5H - dibenzo[b,f]azepine - 10(11H) - one, m.p. 122°,

5 - (γ - dimethylamino - propyl) - 3,7-dichloro - 5H - dibenzo[b,f]azepine-10(11H)-one, m.p. 87°,

5 - (γ - dimethylamino - propyl) - 3,7-dimethyl - 5H - dibenzo[b,f]azepine-10(11H)-one,

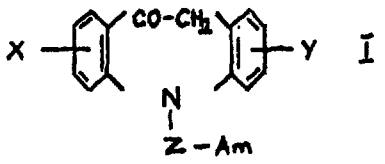
5 - (γ - dimethylamino - propyl) - 2-methoxy - 5H - dibenzo[b,f]azepine-10(11H)-one,

5 - (β - methyl - γ - dimethylamino-propyl) - 5H - dibenzo[b,f]azepine-10(11H)-one, $b.p._{0,015}$ 178°, and

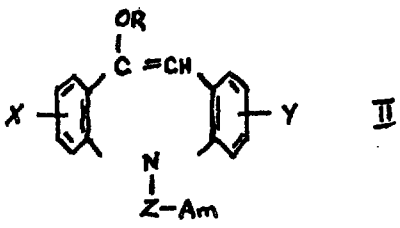
5 - [β - (1¹ - methyl - piperidyl - 2¹)-ethyl] - 5H - dibenzo[b,f]azepine - 10(11H)-one, $b.p._{0,01}$ 202°.

WHAT WE CLAIM IS:—

1. Process for the production of New N-heterocyclic compounds, characterised in that compounds of the general formula

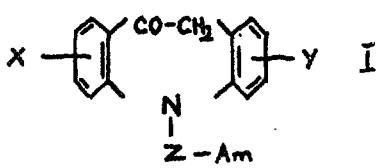


in which X signifies hydrogen, a halogen atom or an alkyl radical of at most 3 carbon atoms, Y signifies hydrogen, a halogen atom or an alkyl or alkoxy radical of at most 3 carbon atoms, Z signifies a straight or branched chain alkylene residue containing 2—6 carbon atoms, and Am signifies a dialkylamino group of at most 8 carbon atoms, while one of the two alkyl residues of Am may be combined with the alkylene residue Z or both alkyl residues of Am may be combined among themselves together, directly or via an oxygen atom or an alkylimino group, and if desired their acid-addition salts or quaternary ammonium compounds, are prepared by hydrolysing a 5-substituted 10-alkoxy- or 10-alkenyloxy- 5H - dibenzo[b,f]azepine - 10(11H)-one of the general formula



in which R signifies an alkyl or alkenyl radical of at most 4 carbon atoms residue, and if desired converting the tertiary base so obtained into its salts with inorganic or organic acids, or into a quaternary ammonium compound by adding a reactive ester of an aliphatic or araliphatic alcohol.

2. N - heterocyclic compounds of the general formula



in which X, Y, Z and Am have the meanings given in claim 1, as well as their acid addition salts and the quaternary ammonium compounds formed by adding on reactive esters of aliphatic or araliphatic alcohols.

3. N-Heterocyclic compounds of the general formula I defined in claim 1, sub-

stantially
to and as i
4. Proc
heterocycli
I defined

Lea
(Le

The followi
Examiner, acting

Page 2, lin

THE PATENT OFFIC
9th June, 196

stantially as herein described with reference to and as illustrated in the foregoing examples.

4. Process for the manufacture of N-heterocyclic compounds of the general formula I defined in claim 1, 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.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press (Leamington) Ltd.—1963. Published by The Patent Office, 25 Southampton Buildings, London, W.C.2, from which copies may be obtained.

ERRATUM

SPECIFICATION No. 943,275

Page 2, line 65, *for* "New N-" *read* "new N-"

THE PATENT OFFICE
23rd March 1964

CORRECTION OF CLERICAL ERROR

SPECIFICATION NO. 943,275

The following correction is in accordance with the Decision of the Superintending Examiner, acting for the Comptroller-General, dated the 9th day of April, 1964.

Page 2, line 89, *delete* "residue",

THE PATENT OFFICE,
9th June, 1964

D 6281/1(6)/R.109 200 5/64 PL