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3,551,435

# CERTAIN 4-(PYRIDYLMETHYLENE)-3,4-DIHYDRO-1-BENZOTHIEPIN-5(2H)-ONES

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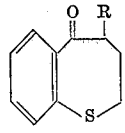
No Drawing. Application Aug. 12, 1968, Ser. No. 753,018, which is a continuation-in-part of applications Ser. No. 462,403, June 8, 1965, and Ser. No. 635,389, May 2, 1967. Divided and this application July 22, 1969, Ser. No. 870,932
Int. Cl. C07d 31/50
U.S. Cl. 260—294.8 4 Claims

## ABSTRACT OF THE DISCLOSURE

The compounds are of the class of dihydrobenzothiepin-5(2H)-ones, useful for their respective pharmacological properties, such as hypotensive, vasopressor or anti-inflammatory activity, depending upon the type of derivative considered.

This application is a division of my co-pending application Ser. No. 753,018, filed Aug. 12, 1968, which in turn is a continuation-in-part of application Ser. No. 635,389, filed May 2, 1967 and application Ser. No. 462,403, filed June 8, 1965, both now abandoned.

This invention relates to certain novel dihydrobenzothiepin-5(2H)-ones. More particularly, this invention is concerned with dihydrobenzothiepin-5(2H)-ones having the formula




wherein R is a member selected from the group consisting of diloweralkylaminomethyl, pyridylmethylene and piperidinomethyl; and the non-toxic, acid addition salts and the therapeutically active loweralkyl quaternary ammonium derivatives thereof.

As used herein loweralkyl may be straight or branch chained and have from 1 to 6 carbon atoms, such as, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl and the like.

The therapeutically active non-toxic acid addition salts of these compounds are prepared by treatment with an appropriate acid such as an inorganic said, e.g., hydrochloric, hydrobromic, hydroidic, sulfuric, nitric or phosphoric; an organic acid such as acetic, propionic, glycolic, lactic, pyruvic, malonic, succinic, maleic, malic, fumaric, tartaric, citric, benzoic, mandelic, cinnamic, methane sulfonic, benzene sulfonic, salicylic, 2-phenoxybenzoic. Conversely, the salt form may be converted in the usual manner into the free base.

The novel compounds may be converted into the corresponding quaternary ammonium compounds by reaction of the tertiary bases with alkylating agents, i.e., alkyl or aralkyl halides or esters formed by reacting alkanols with an oxygen-containing acid such as methyl iodide, ethyl bromide, propyl chloride; lower alkenyl halides—allyl bromide; dilower alkylsulfates—dimethylsulfate, diethylsulfate; lower alkylarylsulfonates—methyl p-toluenesulfonate or aralkyl halides—benzyl chloride. The quaternizing reaction may be performed in the presence or absence of a solvent, at room temperature or under cooling, at atmospheric pressure or in a closed vessel under pressure. Suitable solvents for this purpose are ethers such as diethylether and tetrahydrofuran, hydrocarbons such as benzene and heptane, ketones such as acetone and butanone, lower alkanols such as ethanol, propanol or butanol; or organic acid amides such as formamide or dimethylformamide. When lower alkyl halogenides are used as quaternizing agents, diethyl ether and benzene are the preferred solvents.



The compounds of this invention have been found to possess valuable pharmacological properties. For example, in those compounds in which R is piperidinomethyl, a hypotensive (blood pressure lowering) effect of 40–66 mm. of Hg is observed following intraveneous administration to anesthetized dogs at doses of 10 mg./kg. of body weight. Those compounds in which R is diloweralkylaminomethyl are vasopressor agents in dogs. For example, doses of 2 mg./kg. of body weight, administered intraveneously, cause the blood pressure to rise 12 mm. of Hg. Those compounds in which R is pyridylmethylene are useful as anti-inflammatory agents as judged by their ability to inhibit kaolin induced edema in the rat paw. For example, an 18% inhibition is observed after oral administration of about 100 mg./kg. of body weight. The corresponding acid addition salts have the same utilities as the basic compounds.

The compounds of this invention wherein R is diloweralkylaminomethyl are prepared by reacting 3,4-dihydro-1-benzothiepin-5(2H)-one with a diloweralkylamine hydrochloride and formaldehyde or a polymer thereof such as paraformaldehyde in a suitable solvent such as ethanol in the presence of an acid such as concentrated hydrochloric acid under reflux conditions.

The compounds of this invention wherein R is a pyridylmethylene are prepared by reacting a mixture of 3,4-dihydro-1-benzothiepin-5(2H)-one and a pyridinecarboxaldehyde with an alkali such as potassium hydroxide dissolved in a suitable solvent such as methanol.

The compound of this invention wherein R is piperidinomethyl is prepared by reacting a solution of piperidine in a suitable solvent such as ethanol together with 3,4-dihydro-1-benzothiepin-5(2H)-one and formaldehyde or a polymer thereof such as paraformaldehyde under acidic conditions such as that provided by the addition of an acid, for example, concentrated hydrochloric acid, and under reflux conditions.

The following examples are intended to illustrate, but not to limit, the scope of the present invention.

### EXAMPLE I

A solution of 11.2 g. (0.16 mole) of hydroxylamine hydrochloride in 16 ml. of water is added to a stirred slurry of 17.8 g. (0.1 mole) of 3,4-dihydro-1-benzothiepin-5(2H)-one in 60 ml. of 95% ethanol. Aqueous potassium hydroxide (15 g., 0.28 mole of potassium hydroxide in 15.7 ml. of water) is then added and the slurry is heated under reflux for 2 hours, cooled, poured into ice water and acidified with concentrated hydrochloric acid. White crystals form. The crystals are recovered by filtration. Three recrystallizations from 95% ethanol yield white crystals of 3,4-dihydro-1-benzothiepin-5(2H)-one oxime; M.P. 97–99° C.

### EXAMPLE II

A mixture of 17.8 g. (0.1 mole) of 3,4-dihydro-1-benzothiepin - 5(2H) - one, 10.6 g. (0 13 mole) of dimethylamine hydrochloride, 3.96 g. (0.044 mole) of paraformaldehyde and 0.2 ml. of concentrated hydrochloric acid in 20 ml. of 95% ethanol is refluxed with stirring for 3 hours. After slight cooling 80 ml. of acetone is added. Cooling in the refrigerator yields white crystals. Two recrystallizations from 95% ethanol-acetone produces white crystals of 4-dimethylaminomethyl-3,4-dihydro-1-benzothiepin-5(2H)-one hydrochloride; M.P. 182–184° C.

EXAMPLE III

To a stirred mixture of 7.1 g. (0.04 mole) of 3,4-dihydro-1-benzothiepin-5(2H)-one and 4.28 g. (0.04 mole) of 2-pyridinecarboxaldehyde is added dropwise 40 ml. of a solution of 2 g. of potassium hydroxide in 50 ml. of methanol. The solution is stirred for 3 hours whereupon crystals appear, and then for an additional hour in an ice bath. The crystals are recovered by filtration. Two recrystallizations from ethyl acetate produce white crystals of 4 - (2 - pyridylmethylene) - 3,4-dihydro-1-benzothiepin-5(2H)-one; M.P. 120–122° C.

EXAMPLE IV

A solution of 13.2 g. (0.16 mole) of piperidine in ethanol, 21.4 g. (0.12 mole) of 3,4-dihydro-1-benzothiepin-5(2H)-one, 4.8 g. of paraformaldehyde and enough concentrated hydrochloric acid to make the solution acidic is heated under reflux for 18 hours. After removal of some of the ethanol in vacuo, the solution is cooled and poured into ice water to yield crystals of piperidinomethyl-3,4-dihydro-1-benzothiepin-5(2H) - one hydrochloride. The hydrochloride salt is converted to the free base and then to crystalline acid fumarate salt by the addition of methanolic fumaric acid to the free base. The fumarate salt is recrystallized twice from methanol to give piperidinomethyl-3,4-dihydro - 1 - benzothiepin-5(2H)-one fumarate; M.P. 150–151° C.

EXAMPLE V

Using the procedure of Example II and replacing dimethylamine hydrochloride with an equivalent amount of diethylamine hydrochloride, dipropylamine hydrochloride, diisobutylamine hydrochloride and dibutylamine hydrochloride the appropriate 4-diloweralkylaminomethyl-3,4 - dihydro - 1 - benzothiepin - 5(2H)-one is produced, namely:

4 - diethylaminomethyl - 3 ' - dihydro-1-benzothiepin-5(2H)-one;

4 - dipropylaminomethyl - 3,4 - dihydro - 1 - benzothiepin-5(2H)-one;



4 - diisobutylaminomethyl - 3,4 - dihydro - 1 - benzothiepin-5(2H)-one;

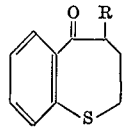
4 - dibutylaminomethyl - 3,4 - dihydro - 1 - benzothiepin-5(2H)-one.

EXAMPLE VI

Using the procedure of Example III and replacing 2-pyridinecarboxaldehyde with an equivalent amount of 3-pyridinecarboxaldehyde and 4-pyridinecarboxaldehyde, the products obtained are 4-(3-pyridylmethylene)-3,4-dihydro-1-benzothiepin-5(2H)-one and 4-(4-pyridylmethylene)-3,4-dihydro-1-benzothiepin-5(2H)-one.

We claim:

**1.** A member selected from the group consisting of dihydrobenzothiepin-5(2H)-ones having the formula




wherein R is a member selected from the group consisting of pyridylmethylene and the non-toxic acid addition salts thereof.

**2.** 4 - (2 - pyridylmethylene) - 3,4 - dihydro - 1 - benzothiepin-5(2H)-one.

**3.** 4 - (3 - pyridylmethylene) - 3,4-dihydro - 1 - benzothiepin-5(2H)-one.

**4.** 4 - (4 - pyridylmethylene) - 3,4 - dihydro - 1 - benzothiepin-5(2H)-one

**References Cited**

UNITED STATES PATENTS

389,144 6/1968 Mohrbacher et al. ... 260—294.8

ALAN L. ROTMAN, Primary Examiner

U.S. Cl. X.R.

260—293.4, 327, 999

PO-1050
(5/69)

# UNITED STATES PATENT OFFICE
# CERTIFICATE OF CORRECTION

Patent No. 3,551,435 Dated December 29, 1970

Inventor(s) Mohrbacher & Paragamian

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

In Column 1, line 52, "said" should read -- acid --. In Column 2, line 53, "15 g." should read -- 15.7 g. --. Same Column, line 64, " (0 13 mole) " should read -- (0.13 mole) --. Under References Cited, the patent number should read -- 3,389,144 --.

SIGNED AND
SEALED
MAR 9 1971

(SEAL)
Attest:

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