1,077,276

PATENT SPECIFICATION

NO DRAWINGS

1,077,276

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Int. Cl.:—C 07 d 93/38, C 07 d 93/44

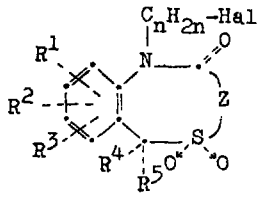
COMPLETE SPECIFICATION

Novel Thiaza Heterocyclics

We, F. HOFFMANN-LA ROCHE & Co., AKTIENGESELLSCHAFT, a Swiss Company of 124—184 Grenzacherstrasse, 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 is concerned with novel thiaza heterocyclics.

The novel thiaza heterocyclics provided by the invention are compounds of the general formula



(I)

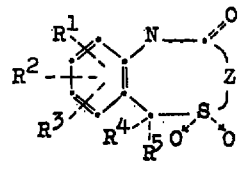
wherein Z represents *either* an orthophenylene group *or* a methylene group which may carry lower-alkyl or lower-carboxyalkyl and/or lower-alkyl or lower-alkanoyloxy substitution *or* an ethylene group which may carry similar substitution at one of its carbon atoms, R^1, R^2 and R^3 each stand for a halogen atom or a lower-alkyl or lower-alkoxy group, R^4 represents a lower-alkyl group, R^5 represents a lower-alkyl, phenyl or halo-phenyl group, *n* stands for 2,3,4,5,6 or 7 and Hal stands for chlorine, bromine or iodine atom and wherein the broken lines denote that the groups or atoms attached thereby are optional. They are useful in that they can be converted into the correspondingly substituted thiaza heterocyclics carrying a substituted amino group in place of the halogen atom on the alkylene chain which form part of the subject matter of our copending Application for Letters Patent No. 14252/66 (now serial no: 1077272) and which, in turn, are useful as antidepressants.

The term "lower alkyl" is used in this description and in the accompanying claims to mean both straight-chain and branched-chain alkyl groups containing not more than seven carbon atoms such as methyl, ethyl, propyl and *iso*propyl. The term "halogen" is used to connote chlorine, bromine, iodine and fluorine unless otherwise specified. Similarly, the terms "lower carboxylalkyl" and "lower alkanoyloxy" are used to mean carboxalkyl and alkanoyloxy groups respectively containing not more than seven carbon atoms. Again, the term "lower alkoxy" is used to mean a straight-chain or branched-chain alkoxy group containing not more than seven carbon atoms such as methoxy, ethoxy or *iso*propoxy.

It will be evident from the foregoing formula that the novel thiaza heterocyclics provided by the invention are benzthiaz[4,1]epines, benzthiaz[4,1]ocines and dibenz[b,f]thiaz[5,1]ocines. The preferred thiaza heterocyclics are the 3,5 - dihydro - benzthiaz[4,1]epinone - (2)s, particularly those in which R^2 and R^3 are absent. Preferably R^4 and R^5 are absent and the methylene group at the 3-position is unsubstituted. R^1 (when present) is preferably in the 8-position and represents a halogen atom (particularly a chlorine atom). The most preferred thiaza heterocyclic is 8-chloro - 1 - (3 - chloro - propyl) - 3,5 - dihydro - benzthiaz[4,1]epinone - (2).

The novel thiaza heterocyclics aforesaid can be prepared by reacting a compound of the general formula

[*Price 4s. 6d.*]



(II)

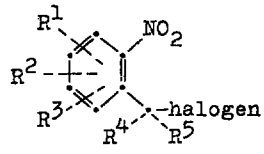
, wherein Z, R^1, R^2, R^3, R^4, R^5 and the broken lines have the significance given earlier, with a compound of the general formula

$$X—C_nH_{2n}—Hal$$

(III)

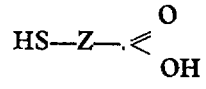
wherein X stands for a halogen atom or a sulphonyloxy group and Hal has the significance given earlier.

The starting materials of formula II hereinbefore can be obtained, for example, by reacting a compound of the general formula



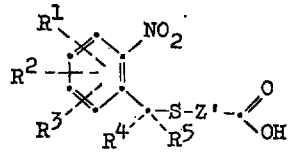
(IV)

with a mercapto acid of the general formula



(V)

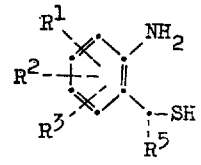
, reducing and cyclising the resulting compound of the formula



(VI)

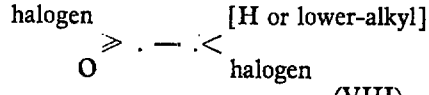
(after oxidising the thio group therein to the sulphonyl group if desired), converting the carbonyl group in the product to the methylene group if desired, oxidising any thio group present to a sulphinyl or sulphonyl group if desired and introducing a lower-alkanoyloxy group on to the carbon atom adjacent to the thio atom if required; in which formulae R^1, R^2, R^3, R^4, R^5 and the broken lines have the significance given earlier and Z′ represents *either* an orthophenylene group *or* a methylene group which may carry a lower-alkyl or lower-carboxyalkyl group as one substituent and a lower-alkyl group as an optional second substituent *or* an ethylene group which may be similarly monosubstituted or disubstituted at one of its carbon atoms.

Those starting materials of formula II in which the carbonyl group adjacent to the nitrogen atom is present, R^4 is absent, Z represents a methylene group which may carry a lower-alkyl group as a substituent and no S-oxide is present may be prepared by treating a compound of the general formula



(VII)

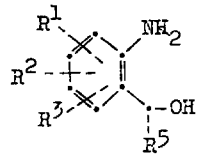
, wherein R^1, R^2, R^3, R^5 and the broken lines have the significance given earlier, with a haloacyl halide of the general formula



(VIII)

, preferably in an alkaline medium. The alkaline medium can be provided by any suitable base. Examples of suitable bases are alkali-metal hydroxides (e.g. sodium hydroxide and potassium hydroxide) and alkaline-earth-metal hydroxides. Temperature is not critical and, accordingly, the treatment can be carried out at any suitable temperature.

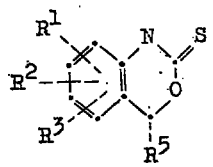
The compounds of formula VII hereinbefore can, in turn, be produced by reacting a compound of the general formula



(IX)

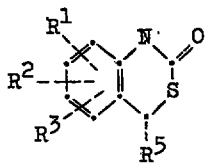
, wherein R^1, R^2, R^3, R^5 and the broken lines have the significance given earlier, with carbon disulphide in the presence of a tertiary amine (e.g. triethylamine) and any suitable inert organic solvent (e.g. an alkanol containing not more than seven carbon atoms such

as ethanol). The resulting product is a compound of the formula



(X)

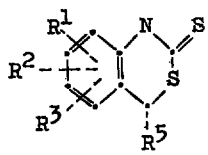
, wherein R^1, R^2, R^3, R^5 and the broken lines have the significance given earlier, which is heated to yield a compound of the formula



(XI)

wherein R^1, R^2, R^3, R^5 and the broken lines have the significance given earlier. The compound of formula XI is then ring-opened to the corresponding compound of formula VII by treatment with an aqueous-alkaline medium such as potassium hydroxide in water.

Compounds of formula XI can also be prepared from the corresponding compounds of formula IX by treatment with carbon disulphide and a base such as potassium hydroxide in the presence of any suitable inert organic solvent such as an alkanol containing not more than seven carbon atoms (e.g. ethanol or methanol) to yield a compound of the formula



(XII)

wherein R^1, R^2, R^3, R^5 and the broken lines have the significance given earlier, which is then treated with an oxidising agent which may be hydrogen peroxide in the presence of any suitable base such as potassium hydroxide to give the corresponding compounds of formula XI.

In the process for the preparation of the compounds of formula I, the symbol X in the compounds of formula III preferably represents a chlorine, bromine or iodine atom or a sulphonyloxy group such as an arylsulphonyloxy group (e.g. tosyloxy) or an alkylsulphonyloxy group (e.g. mesyloxy). In an especially preferred embodiment, X in the compound of formula III is bromine and Hal is chlorine. Further, a compound of formula II is preferably converted into a 1 - (alkali-metal) derivative and this derivative is reacted with a compound of formula III.

The reaction of a compound of formula II with a compound of formula III can be carried out in an inert organic solvent utilizing one or more solvents such as methanol, ethanol, N,N - dimethyl - formamide, benzene, toluene and N - methyl - pyrrolidone. Temperature and pressure are not critical and the reaction can be carried out at room temperature and atmospheric pressure or at elevated temperatures and/or elevated pressures. Any conventional reagent such as an alkali-metal alkoxide containing not more than seven carbon atoms (e.g. sodium methoxide), an alkali-metal hydride (e.g. sodium hydride) or an alkali-metal amide (e.g. sodamide) can be employed to form a 1 - (alkali - metal) derivative, preferably the 1-sodio derivative of compounds of formula II. Advantageously, sodamide is employed. Examples of suitable compounds of formula III are 1 - bromo - 3-chloro - propane, 2 - bromo - ethyl chloride, 1-bromo - 4 - chloro - butane, 1,3 - dibromopropane and 1,3 - dibromo - butane.

The following Examples illustrate the manner in which the novel thiaza heterocyclics provided by the invention can be prepared:

EXAMPLE 1

a) A solution of 18.7 g of sodium methylate in 85 ml of methanol was added at 0°C over a period of 0.25 hour to a suspension of 59.4 g of 8 - chloro - 3,5 - dihydro-benzthiaz[4,1]epinone - (2) in 400 ml of N,N - dimethyl - formamide. The clear solution obtained was stirred at room temperature for 0.25 hour, then 58.2 g of 1-bromo - 3 - chloro - propane in 50 ml of N,N - dimethyl - formamide were added at 0°C over a period of 0.25 hour to the stirred solution. After stirring at room temperature for 1 hour, the mixture was poured into 500 ml of water and extracted three times with methylene chloride. The combined extracts were washed with water, dried over sodium sulphate and evaporated to dryness. From the oily residue, crystalline 8-chloro - 1 - (3 - chloro - propyl) - 3,5-dihydro - benzthiaz[4,1]epinone - (2) was obtained after trituration with ether; melting point = 136°—140°C.

b) A suspension of 10.8 g of 8-chloro-3,5 - dihydro - benzthiaz[4,1]epinone - (2) and 2.44 g of sodamide in 100 ml of dioxan was heated at reflux with stirring for 15 hours. After cooling to 60°C, 8 g of 1-bromo - 3 - chloro - propane were added and

the resulting mixture was heated at reflux for 4 hours. The mixture was then filtered and the filtrate evaporated to dryness *in vacuo*. The residue was chromatographed on activated magnesium silicate and the various fractions were characterised by thin layer chromatography [Silica gel G; solvent; benzene/(ethyl acetate) (8:2)]. Elution with (ethyl acetate)/benzene (1:1) gave 8 - chloro - 1-(3 - chloro - propyl) - 3,5 - dihydro - benzthiaz [4,1]epinone - (2). After recrystallization from acetone, the product was found to have a melting point of 141°—144°C.

EXAMPLE 2

A) The preparation of the starting material:

53 g. (0.5 mol) of thiolactic acid and 40 g (1 mol) of sodium hydroxide in 300 ml of water were carefully added with stirring at 0°C to a solution of 125 g (0.5 mol) of 4-chloro - 2 - nitro - benzyl bromide in 200 ml of acetone. The mixture obtained was stirred at room temperature for 24 hours, then made alkaline with 2-*N* sodium hydroxide and extracted with five 300 ml portions of methylene chloride. The alkaline aqueous layer was acidified with acetic acid and extracted with five 300 ml portions of methylene chloride. The last-mentioned methylene chloride extracts were combined, washed with water, dried over anhydrous sodium sulphate and evaporated to dryness to give crude oily 2-(4 - chloro - 2 - nitro - benzylmercapto)-propionic acid. This acid was dissolved in 1200 ml of methanol and 20 g of 10% palladium - on - carbon catalyst were added. The suspension obtained was hydrogenated under 50—140 pounds per square inch pressure at room temperature until the theoretical amount of hydrogen had been absorbed. The catalyst was then removed by filtration and the filtrate was evaporated to dryness. The crystalline residue was recrystallized from ether/hexane (melting point = 107°—109°C) and then from ether to give 2 - (2 - amino-4 - chloro - benzylmercapto) - propionic acid of melting point 105°—105.5°C.

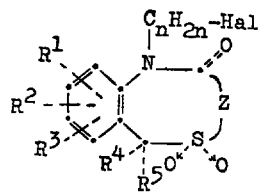
The 2 - (2 - amino - 4 - chloro - benzylmercapto) - propionic acid obtained was dissolved in 600 ml of dry xylene and the solution was heated at reflux for 5 hours, with removal of water formed when refluxing. After cooling, the crystalline precipitate was separated by filtration, washed with xylene and dried to yield 8 - chloro - 3 - methyl - 3,5 - dihydro-benzthiaz[4,1]epinone - (2). After recrystallization from methanol, the melting point of the product was 229°—230°C.

B) The process:

4.3 g (0.11 mol) of sodamide were added to a solution of 22.7 g (0.1 mol) of 8 - chloro-3 - methyl - 3,5 - dihydro - benzthiaz[4,1] epinone - (2) in 150 ml of anhydrous N,N-dimethyl - formamide and 150 ml of anhydrous tetrahydrofuran, and the mixture was stirred for 2 hours at room temperature and for 1 hour at 50°C. After cooling to room temperature, 78 g of 1 - bromo - 3-chloro - propane were added. The resulting mixture was stirred overnight, then diluted with water and extracted with ether. The ether extract was washed with water, dried over anhydrous sodium sulphate and evaporated to dryness. The residue was crystallized from ether to give 8 - chloro - 1 -(3-chloro - propyl) - 3 - methyl - 3,5 - dihydro-benzthiaz[4,1]epinone - (2) of melting point 118°—119°C after recrystallization from ethyl acetate.

WHAT WE CLAIM IS:—

1. Compounds of the general formula



wherein Z represents *either* an orthophenylene group *or* a methylene group which may carry lower-alkyl or lower-carboxyalkyl and/or lower-alkyl or lower-alkanoyloxy substitution *or* an ethylene group which may carry similar substitution at one of its carbon atoms, R^1, R^2 and R^3 each stand for a halogen atom or a lower-alkyl or lower-alkoxy group, R^4 represents a lower-alkyl group, R^5 represents a lower-alkyl, phenyl or halo-phenyl group, *n* stands for 2,3,4,5,6 or 7 and Hal stands for a chlorine, bromine or iodine atom and wherein the broken lines denote that the groups or atoms attached thereby are optional.

2. 3,5 - Dihydro - benzthiaz[4,1]epinone-(2)s as set forth in claim 1, wherein R^2 and R^3 are absent.

3. 3,5 - Dihydro - benzthiaz[4,1]epinone-(2)s as set forth in claim 2, wherein R^1 (when present) is in the 8-position.

4. An 8 - halo - 1 - (halo - alkyl) - 3,5-dihydro - benzthiaz[4,1]epinone - (2) as set forth in claim 1.

5. 8 - Chloro - 1 - (3 - chloro - propyl)-3,5 - dihydro - benzthiaz[4,1]epinone - (2).

the resulting mixture was heated at reflux for 4 hours. The mixture was then filtered and the filtrate evaporated to dryness *in vacuo*. The residue was chromatographed on activated magnesium silicate and the various fractions were characterised by thin layer chromatography [Silica gel G; solvent; benzene/(ethyl acetate) (8:2)]. Elution with (ethyl acetate)/benzene (1:1) gave 8 - chloro - 1-(3 - chloro - propyl) - 3,5 - dihydro - benzthiaz [4,1]epinone - (2). After recrystallization from acetone, the product was found to have a melting point of 141°—144°C.

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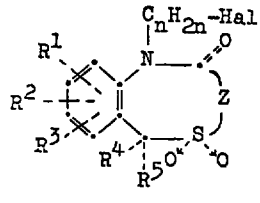
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4.3 g (0.11 mol) of sodamide were added to a solution of 22.7 g (0.1 mol) of 8 - chloro-3 - methyl - 3,5 - dihydro - benzthiaz[4,1] epinone - (2) in 150 ml of anhydrous N,N-dimethyl - formamide and 150 ml of anhydrous tetrahydrofuran, and the mixture was stirred for 2 hours at room temperature and for 1 hour at 50°C. After cooling to room temperature, 78 g of 1 - bromo - 3-chloro - propane were added. The resulting mixture was stirred overnight, then diluted with water and extracted with ether. The ether extract was washed with water, dried over anhydrous sodium sulphate and evaporated to dryness. The residue was crystallized from ether to give 8 - chloro - 1 -(3-chloro - propyl) - 3 - methyl - 3,5 - dihydrobenzthiaz[4,1]epinone - (2) of melting point 118°—119°C after recrystallization from ethyl acetate.

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4. An 8 - halo - 1 - (halo - alkyl) - 3,5-dihydro - benzthiaz[4,1]epinone - (2) as set forth in claim 1.

5. 8 - Chloro - 1 - (3 - chloro - propyl)-3,5 - dihydro - benzthiaz[4,1]epinone - (2).

* C L M S *

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