

PATENT SPECIFICATION

NO DRAWINGS

L077.272

L077.272



Date of Application and filing Complete Specification: March 31, 1966.

No. 14252/66.

Application made in United States of America (No. 445264) on April 2, 1962.

Complete Specification Published: July 26, 1967.

© Crown Copyright 1967.

65



Index at acceptance:—C2 C(1E6K4, 1E7D2, 1E7F1, 1E7N5, 1E7P3, 1F2C5, 1F2C6, 1F2C7, 1F2D2, 1F2D3, 1G5B, 1G6B6, 1H1A3, 1H1C2, 1H1C3, 1J3C2, 1M1A, 1M1C2, 1M1C3, 2B3A2, 2B3F, 2B3G5, 2B4A4, 2B4F, 2B4G1, 2B4G4, 2B9, 2D34, 3A12A4C, 3A12B1, 3A12C5)

Int. Cl.:—C 07 d 93/36, C 07 d 99/02

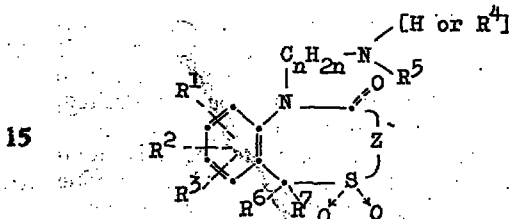
COMPLETE SPECIFICATION

Novel Thiaza Heterocyclics and a Process for the Manufacture Thereof

We, 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 and a process for the manufacture thereof.

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



oxygen atom and which may contain one substituent, R⁶ represents a lower-alkyl group, R⁷ represents a lower-alkyl, phenyl or halo-phenyl group and n stands for 2, 3, 4, 5, 6 or 7 and wherein the broken lines denote that the groups or atoms attached thereby are optional, and acid addition salts thereof.

The compounds of formula I and their pharmaceutically acceptable acid addition salts are characterized by their antidepressant action on the central nervous system and are accordingly useful as antidepressants. They are useful not only in the relief of symptomatology associated with depression of the central nervous system, but also in the prevention and reversal of central nervous system depression caused by exogenous chemical agents. They can be administered internally (for example, parenterally or enterally) in conventional pharmaceutical dosage forms with dosage adjusted to fit the exigencies of a particular therapeutic situation. The pharmaceutical dosage forms may be prepared by incorporating the active ingredient in conventional liquid or solid vehicles to provide elixirs, suspensions, tablets, capsules and powders according to accepted pharmaceutical practice.

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, R¹, R² and R³ each stand for a halogen atom or a lower-alkyl or lower-alkoxy group, R⁴ and R⁵ each stand for a lower-alkyl or benzyl group or jointly, together with the nitrogen atom to which they are attached, form a 5- or 6-membered heteromonocyclic ring which may contain one further nitrogen or

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 isopropyl. The term "halogen" is used to connote chlorine, bromine, iodine, and fluorine unless otherwise specified. Similarly, the terms "lower carboxyalkyl" and "lower alkanoyloxy" are used to mean carboxyalkyl and alkanoyloxy groups respectively

[Price 4s. 6d.]

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

5 carbon atoms such as methoxy, ethoxy or isopropoxy. R^4 and R^5 may individually represent a benzyl group or a straight-chain or branched-chain lower-alkyl group as herein-

10 before defined (e.g. methyl, ethyl, propyl, *iso*-propyl or butyl). The term "benzyl" is used to mean the benzyl group as well as substituted derivatives thereof (e.g. lower-alkyl

15 benzyl). R^4 and R^5 when taken together with the nitrogen atom to which they are attached, may also form a 5- or 6-membered heteromonocyclic ring. Preferably, this ring is a piperazino, piperidino, pyrrolidino or morpholino ring or a substituted derivative thereof.

20 Advantageously, any substituent on the heterocyclic ring is present when the latter contains an additional nitrogen atom and the substituent is on said additional atom. Suitable substituents include branched-chained or straight-chain lower-alkyl groups such as

25 methyl and ethyl and lower-hydroxyalkyl groups. The term "lower hydroxyalkyl" is used in this specification to mean both straight-chain and branched-chain hydroxyalkyl groups containing not more than seven carbon atoms (e.g. hydroxyethyl). Advantageously, R^4 and R^5 are both lower-alkyl or R^4 is absent and R^5 is lower-alkyl.

When R^4 and R^5 combine with the N-atom to which they are attached to form a

35 ring, the ring contains 5- or 6-members and is preferably saturated. Thus, R^4 and R^5 , when taken together with the said nitrogen atom and containing, at the most, one further oxygen or nitrogen atom and, at the most,

40 one substituent on the ring, can represent, for example, a N-(lower alkyl)-piperazino, N-(lower hydroxyalkyl)-piperazino, pyrrolidino, piperazino, morpholino or piperidino group. Thus, R^4 and R^5 can together represent,

45 for example, an alkylene chain of four or five carbon atoms, an alkylene-oxa-alkylene chain containing three or four carbon atoms or an alkylene-aza-alkylene chain containing three or four carbon atoms which may

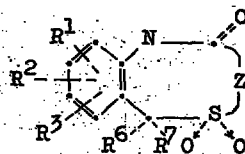
50 be substituted at the aza atom by a lower-alkyl or lower-hydroxyalkyl group. It will be evident from the foregoing formula that the novel thiaza heterocyclics provided by the invention are benzthiaz[4,1]

55 epines, benzthiaz[5,1]ocines and dibenz[b,f]thiaz[5,1]ocines and their acid addition salts. The preferred thiaza heterocyclics are the 3,5 - dihydro - benzthiaz[4,1]epinone - (2)s and their acid addition salts, particularly

60 those in which R^1 and R^3 are absent. Preferably, R^6 and R^7 are absent, the methylene group at the 3-position is unsubstituted and R^4 (when present) and R^5 each represent a lower-alkyl group. R^1 (when present) is preferably in the 8-position and represents a

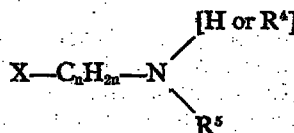
chlorine atom or the methoxy group. The most preferred thiaza heterocyclics are the 8 - halo - 1 - [di(lower alkyl)amine - alkyl] - 3,5 - dihydro - benzthiaz[4,1]epinone - (2)s and their salts with pharmaceutically acceptable acids.

According to the process provided by the invention, the novel thiaza heterocyclics aforesaid are manufactured by reacting a compound of the general formula



II

either with a compound of the general formula



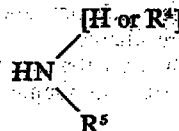
III

or with a compound of the general formula



IV

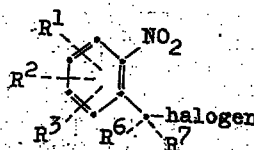
and treating the reaction product with an amine of the general formula



V

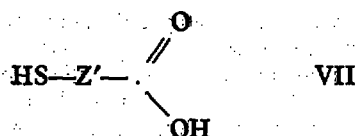
and, in either case, converting any carbonyl group present into a methylene group if desired, oxidising any thio group present to a sulphinyl or sulphonyl group if desired, introducing a lower-alkanoyloxy group on to the carbon atom adjacent to the thia atom if required and, also if desired, converting the product into an acid addition salt; in which formulae n , Z , R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 and the broken lines have the significance given earlier, X stands for a halogen atom or a sulphonyloxy group and Hal stands for a chlorine, bromine or iodine atom.

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

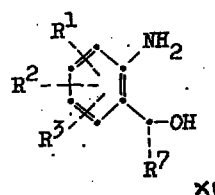
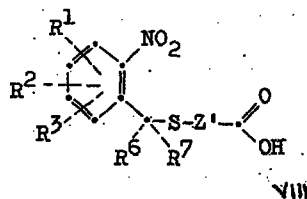


VI

with a mercapto acid of the general formula

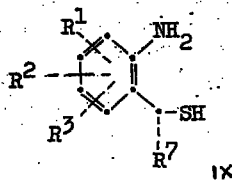


reducing and cyclising the resulting compound of the formula

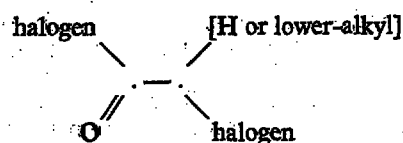


- 5 (after oxidising the thio group therein to the sulphonyl group if desired), converting the carbonyl group in the product to the methylene group if desired, oxidising any thio group present to a sulphonyl or sulfonyl group if desired and introducing a lower-alkanoyloxy group on to the carbon atom adjacent to the thio atom if required; in which formulae R¹, R², R³, R⁶, R⁷ and the broken lines have the significance given earlier and Z' represents
- 10 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 ethylene group which may be
- 15 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, R⁶ 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



- 30 wherein R¹, R², R³, R⁷ and the broken lines have the significance given earlier, with a halo-acyl halide of the general formula

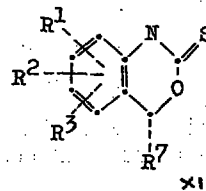


- 35 preferably in an alkaline medium. The alkaline medium can be provided by the suitable base. Examples of suitable bases are alkali

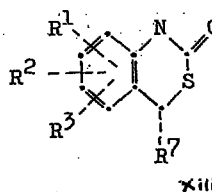
metal hydroxides (e.g. sodium hydroxide and potassium hydroxide) and alkaline-earth-metal hydroxides. Temperature is not critical and, accordingly, the treatment can be carried out at any suitable temperature.

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

wherein R¹, R², R³, R⁷ 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



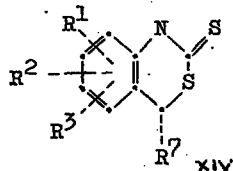
wherein R¹, R², R³, R⁷ and the broken lines have the significance given earlier, which is heated to yield a compound of the formula



wherein R¹, R², R³, R⁷ and the broken lines have the significance given earlier. The compound of formula XIII is then ring-opened to the corresponding compound of formula IX by treatment with an aqueous-alkaline medium such as potassium hydroxide in water.

Compounds of formula XIII can also be prepared from the corresponding compounds of formula XI by treatment of the latter with carbon disulphide and a base such as potas-

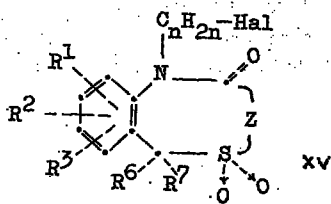
sium hydroxide in the presence of any suitable inert organic solvent such as an alkanol containing not more than seven carbon atoms (e.g. ethanol or methanol) to yield a compound of the formula



wherein R^1 , R^2 , R^3 , R^7 and the broken lines have the significance given earlier, which is then treated with an oxidizing agent which may be hydrogen peroxide in the presence of any suitable base such as potassium hydroxide to give the corresponding compounds of formula XIII.

In the process provided by the present invention, the symbol X in the compounds of formula III and IV 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 one embodiment of the process, a compound of formula II, preferably after conversion thereof into a 1-(alkali metal) derivative, is reacted with a compound of formula IV and the resulting compound of the formula



wherein R^1 , R^2 , R^3 , R^6 , R^7 , Z , n , Hal and the broken lines have the significance given earlier, is treated with a primary or secondary amine of formula V. In a preferred embodiment X in the compounds of formula IV is bromine and Hal is chlorine.

The first stage of the foregoing embodiment ($II + IV \rightarrow X$) 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 IV are 1-bromo-3-chloro-propane, 2-bromo-ethyl chloride, 1-bromo-4-chloro-butane, 1,3-dibromo-propane and 1,3-dibromo-butane.

The second stage of the foregoing embodiment ($XV + V \rightarrow I$) can be carried out in an inert organic solvent medium utilizing one or more inert organic solvents; for example, ethers such as dioxane, and N,N-dimethyl-formamide. Here again, temperature and pressure are not critical and the reaction can be carried out at or below room temperature and at atmospheric pressure or at elevated temperatures and/or elevated pressures. This stage is preferably carried out in the presence of an alkali-metal halide such as, for example, sodium iodide.

Any primary or secondary amine of the formula V can be suitably employed in the aforementioned second stage. If a secondary amine is used, the two carbon atoms joined to the nitrogen atom of the amine can form a part of a group which exists independently of the other group. Therefore, such carbon atoms can individually comprise a part of a straight-chain or branched-chain lower-alkyl radical such as methyl, ethyl, propyl or isopropyl. Alternatively, such carbon atoms can comprise part of a divalent radical and such radicals can combine with each other directly or through an additional nitrogen or oxygen atom to form a group such as pentamethylene, tetramethylene, ethylene-oxa-ethylene and ethylene-aza-ethylene.

In another embodiment of the process, a compound of formula II is reacted, preferably after conversion thereof into a 1-(alkali metal) derivative, with a compound of the formula III. Preferably, the compound of formula II is converted into a 1-sodio derivative.

The reaction can be carried out in an inert organic solvent utilizing one or more inert organic solvents (e.g. dioxane, an alkanol such as methanol, and N,N-dimethyl-formamide). Temperature and pressure are not critical and the reaction can be carried out at or below room temperature and atmospheric pressure or at elevated temperatures and/or elevated pressures. Here again, conventional reagents such as an alkali-metal alkoxide containing not more than seven carbon atoms such as sodium methoxide, an alkali-metal hydride such as sodium hydride or an alkali-metal amide such as sodamide can be

utilized to form the 1-(alkali metal) derivative, preferably the 1-sodio derivative, of compounds of formula II.

Compounds of formula I in which a carbonyl group is present in the thiaza ring can be reduced if desired. This reduction is preferably carried out by treatment with lithium aluminium hydride or with diisobutyl aluminium hydride at a temperature of from minus 20°C to 120°C (preferably minus 5°C to 120°C) in the presence of an inert organic solvent such as tetrahydro-furan, an ether such as diethyl ether or methyl ethyl ether or a hydrocarbon such as toluene or benzene.

Compounds of formula I in which a thio group is present in the 4-position can be oxidized by treatment with an oxidizing agent. For example, by treatment with an alkali-metal periodate (preferably with sodium periodate) a 4-oxide is formed.

Compounds of formula I in which Z represents a methylene or ethylene group which is substituted by a lower alkanoyloxy group can be obtained from the corresponding compounds in which said group is absent by treatment with the appropriate lower-alkanoylating agent such as an anhydride derived from an alkanic acid containing not more than seven carbon atoms (e.g. acetic acid anhydride).

The compounds of formula I form salts with one or more mols of acid depending on the number of basic nitrogen atoms present. The preferred salts are the pharmaceutically acceptable acid addition salts and these are formed, for example, with pharmaceutically acceptable inorganic acids such as hydrochloric acid, hydrobromic acid, sulphuric acid and phosphoric acid and with pharmaceutically acceptable organic acids such as citric acid, tartaric acid, salicylic acid, toluene-sulphonic acid, ascorbic acid, maleic acid, succinic acid, formic acid and acetic acid.

The compounds of formula XV hereinbefore are claimed *per se* in the specification of our copending Application for Letters Patent no: 9997/67 (now serial no: 1077276).

The following Examples illustrate the process provided by the invention:

EXAMPLE 1

A suspension of 10.8 g of 8 - chloro - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) and 2.44 g sodamide in 100 ml of absolute dioxan was stirred and heated at reflux for 20 hours. After cooling to 60°C, 8.1 g of 2 - diethylamino - ethyl chloride in 20 ml of dioxan were added over a period of 0.5 hour. The mixture was stirred and heated at reflux for 4 hours, after which time 5 ml of methanol were added. The resulting mixture was filtered and the filtrate was evaporated to dryness *in vacuo*. The residual oil was evaporated in ethyl acetate and the solution was extracted twice with dilute hydro-

chloric acid. The aqueous extracts were combined, washed with ether, made alkaline by the addition of 3-N sodium hydroxide and extracted twice with ethyl acetate. The combined ethyl acetate extracts were washed with water, dried over sodium sulphate and evaporated to dryness *in vacuo*. 8 - Chloro - 1 - (2 - diethylamino - ethyl) - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) was obtained as an oil. The oily base was dissolved in isopropanolic hydrochloric acid and yielded crystalline 8 - chloro - 1 - (2 - diethylaminoethyl) - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) hydrochloride upon the addition of ether. After recrystallization from methanol/ether, the hydrochloride was found to have a melting point of 214°—215°C.

EXAMPLE 2

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 absolute dioxan was heated at reflux with stirring for 20 hours. After cooling to 60°C, the mixture was added to 3 - dimethylamino - propylchloride (liberated from a concentrated solution of 15 g of the hydrochloride with 6-N sodium hydroxide and extracted with ether, dried over sodium sulphate and evaporated to dryness *in vacuo*) in dioxan. The resulting mixture was heated at reflux with stirring for 4 hours. After the addition of 5 ml of methanol, the mixture was filtered and the filtrate evaporated to dryness *in vacuo*. The oily residue was dissolved in ethyl acetate and the solution extracted twice with dilute hydrochloric acid. The aqueous extracts were washed with ether, made alkaline by the addition of 3-N sodium hydroxide and extracted twice with ethyl acetate. The extracts were combined and washed with water. After drying over sodium sulphate and evaporation to dryness *in vacuo*, 8 - chloro - 1 - (3 - dimethylamino - propyl) - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) was obtained as an oil. The oily base was dissolved in isopropanolic hydrochloric acid and, after adding ether, yielded 8 - chloro - 1 - (3 - dimethylamino - propyl) - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) hydrochloride of melting point 199°—201°C. After recrystallization from methanol/acetone, the hydrochloride melted at 201°—202°C.

EXAMPLE 3

A suspension of 8.5 g of 8 - chloro - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) and 1.75 g of sodamide in 100 ml of absolute dioxan was heated at reflux with stirring for 14 hours. To the thus stirred mixture there was added over a period of 0.5 hour a solution of 4.2 g of 1 - (2 - chloro - ethyl) - piperidine in 10 ml of dioxan. The resulting mixture was heated at reflux with stirring for 20 hours. The mixture was then filtered

and the solvent was removed *in vacuo* to leave a brown oil which was dissolved in ethyl acetate. The resulting mixture was extracted twice with 3-N hydrochloric acid. The ethyl acetate extracts were washed with ethyl acetate, made alkaline with 3-N sodium hydroxide and extracted three times with methylene chloride. The methylene chloride extracts were combined, washed with water, dried over sodium sulphate and evaporated to dryness. On addition of ether to the oily residue, there formed a crystalline product which was removed by filtration. The crystalline product and its mother liquor were dissolved in methanol and treated with isopropanolic hydrochloric acid. Upon addition of ether, 8-chloro-1-(2-piperidino-ethyl)-3,5-dihydro-benzthiaz[4,1]epinone-(2) hydrochloride was obtained in crystalline form; melting point=242°—243°C. After heating at reflux with charcoal in methanol and recrystallization from methanol/ether, the hydrochloride melted at 245°—246°C.

6 g of 8-chloro-1-(2-piperidino-ethyl)-3,5-dihydro-benzthiaz[4,1]epinone-(2) hydrochloride were dissolved in 76 ml of methanol containing 1.73 g of sodium methylate. The solution obtained was evaporated to dryness *in vacuo*. The residue was suspended in methylene chloride and the suspension was filtered. The solvent was removed *in vacuo* to yield the free base, 8-chloro-1-(2-piperidino-ethyl)-3,5-dihydro-benzthiaz[4,1]epinone-(2).

EXAMPLE 4

A) The preparation of the starting material:

A mixture of 20 ml of methyl amine and 28.6 g of benzaldehyde in 100 ml of ethanol was kept at 60°C and 3 atmospheres hydrogen pressure for 4 days. After cooling, 11.8 g of sodium borohydride were added and the mixture was stirred at room temperature for 4 hours. The solvent was then removed under reduced pressure and the residue was suspended in water and extracted twice with chloroform. The organic extracts were combined, washed with water and dried over sodium sulphate. The solvent was then removed *in vacuo* to leave an oil. The oil was dissolved in 100 ml of water and 11.1 g of ethylene oxide were added at room temperature. The mixture was kept for 5 hours at 3°C and for 24 hours at room temperature, then extracted with chloroform. The extract was washed with water, dried over sodium sulphate and evaporated *in vacuo*. The oily residue was distilled under reduced pressure to give 2-(N-methyl-benzylamino)-ethanol of boiling point 73°C/0.08 mm.

3.5 ml of thionyl chloride in 10 ml of benzene were added dropwise to a stirred, ice-cold solution of 7.15 g of 2-(N-methyl-benzylamino)-ethanol in 20 ml of

benzene. The mixture was stirred at room temperature for 4 hours. The solvent was then removed and the resulting solid residue was dissolved in water. The aqueous solution thus formed was made alkaline with an aqueous sodium carbonate solution. After repeated extractions with chloroform, the organic extracts were combined, washed with water, dried over sodium sulphate and evaporated to dryness to give 2-(N-methyl-benzylamino)-ethyl chloride as an oil.

B) The process:

A suspension of 8.5 g of 8-chloro-3,5-dihydro-benzthiaz[4,1]epinone-(2) and 1.75 g of sodamide in 100 ml of absolute dioxan was heated at reflux with stirring for 14 hours. To the hot stirred mixture there were added dropwise 7.8 g of 2-(N-methyl-benzylamino)-ethyl chloride in 10 ml of dioxan. The mixture obtained was heated at reflux with stirring for 4 hours. After the addition of 5 ml of methanol, the mixture was filtered and the filtrate evaporated to dryness under reduced pressure. The oily residue was dissolved in ethyl acetate and extracted with dilute hydrochloric acid. The aqueous extract was washed with ether, made alkaline by the addition of 3-N sodium hydroxide and extracted twice with ethyl acetate. The combined ethyl acetate extracts were washed with water, dried over sodium sulphate and evaporated to dryness *in vacuo* to give 8-chloro-1-[2-(N-methyl-benzylamino)-ethyl]-3,5-dihydro-benzthiaz[4,1]epinone-(2) as an oil. The oily base was dissolved in 1-N methanolic hydrochloric acid and treated with ether to yield crystalline 8-chloro-1-[2-(N-methyl-benzylamino)-ethyl]-3,5-dihydro-benzthiaz[4,1]epinone-(2) hydrochloride of melting point 236°—237°C. The hydrochloride melted at 236°C after recrystallization from methanol/ether.

EXAMPLE 5

i) 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.

ii) A mixture of 10 g of 8 - chloro - 1 - (3 - chloro - propyl) - 3,5 - dihydro - benzthiaz[4,1]epinone - (2), 4.45 g of sodium iodide and 13.85 g of 1 - methyl - piperazine in 100 ml of dioxan was heated at reflux with stirring for 20 hours. After cooling, the mixture was filtered and the filtrate evaporated to dryness *in vacuo*. The solid residue was dissolved in methylene chloride and the solution was extracted twice with 2-N hydrochloric acid. The combined aqueous extracts were washed with methylene chloride, made alkaline with 3-N sodium hydroxide and extracted twice with methylene chloride. The organic extracts were combined, washed with water, dried over sodium sulphate and evaporated to dryness to yield 8 - chloro - 1 - [3 - (4 - methyl - piperazino) - propyl] - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) as a crystalline material. The base was dissolved in 26.4 ml of 1-N methanolic hydrochloric acid. Treatment of the solution with ether yielded crystalline 8 - chloro - 1 - [3 - (4 - methyl - piperazino) - propyl] - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) dihydrochloride of melting point 274°—280°C.

EXAMPLE 6

A suspension of 19.4 g of 8 - chloro - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) and 4 g of sodamide in 200 ml of dioxan was stirred and heated at reflux for 20 hours. After cooling to 60°C, 9.78 g of 3 - (4 - methyl - piperazino) - propyl chloride [obtained by reaction of 3 - (4 - methyl - piperazino) - propanol hydrochloride with thionyl chloride followed by liberation of the free base with sodium methylate] in 30 ml of dioxan were added over a period of 0.5 hour. The mixture was stirred and heated at reflux for 4 hours. After the addition of 10 ml of methanol, the mixture was filtered and the filtrate evaporated to dryness *in vacuo*. The

residual oil was dissolved in ethyl acetate and the solution was extracted twice with 3-N hydrochloric acid. The aqueous extracts were washed with ethyl acetate, made alkaline with 3-N sodium hydroxide and extracted twice with chloroform. The organic extracts were combined, washed with water, dried over sodium sulphate and evaporated to dryness *in vacuo* to yield 8 - chloro - 1 - [3 - (4 - methyl - piperazino) - propyl] - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) as an oil. The oily residue was dissolved in methanol. After the addition of isopropanolic hydrochloric acid, crystalline 8 - chloro - 1 - [3 - (4 - methyl - piperazino) - propyl] - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) dihydrochloride of melting point 283°—284°C was obtained.

EXAMPLE 7

A mixture of 10 g of 8 - chloro - 1 - (3 - chloro - propyl) - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) and 20 ml of methyl amine in 100 ml of dioxan was shaken under hydrogen at 5 atmospheres and at a temperature of 30°C for 2 days. The reaction mixture was then diluted with 100 ml of methylene chloride, washed twice with water and extracted twice with dilute hydrochloric acid. The extracts were combined, washed with methylene chloride and made alkaline with 6-N sodium hydroxide. Repeated extraction with methylene chloride, washing of the combined organic extracts with water, drying over sodium sulphate and evaporation to dryness *in vacuo* yielded 8 - chloro - 1 - (3 - methylamino - propyl) - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) as an oil. The oily base was dissolved in a mixture of methanol/ether (1:1). After addition of isopropanolic hydrochloric acid, crystalline 8 - chloro - 1 - (3 - methylamino - propyl) - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) hydrochloride of melting point 229°—233°C was obtained. After recrystallization from methanol/(ethyl acetate), the hydrochloride was found to have a melting point of 230°—232°C.

EXAMPLE 8

A suspension of 10 g of 8 - chloro - 1 - (3 - chloro - propyl) - 3,5 - dihydro - benzthiaz[4,1]epinone - (2), 4.45 g of sodium iodide and 18 g of 1 - (2 - hydroxy - ethyl) - piperazine in 100 ml of dioxan was heated at reflux with stirring for 20 hours. The mixture was then diluted with methylene chloride and washed twice with water. The resulting mixture was extracted twice with 1-N hydrochloric acid. The combined aqueous extracts were washed with methylene chloride, made alkaline with 6-N sodium hydroxide and extracted twice with methylene chloride. The extracts were combined, washed with water, dried over sodium sulphate and evaporated to dryness to yield 8 - chloro - 1 - [3 - (4 - (2 - hydroxy - ethyl) - piperazino) - propyl] -

3,5 - dihydro - benzthiaz[4,1]epinone - (2) as an oil. The oily base was dissolved in methanolic hydrochloric acid and, after the addition of ether, crystalline 8 - chloro - 1 - (3 - [4 - (2 - hydroxy - ethyl) - piperazino] - propyl) - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) dihydrochloride of melting point 217°—219°C was obtained. After recrystallization from methanol/ether the dihydrochloride was found to have a melting point of 216°—218°C.

EXAMPLE 9

A mixture of 10 g of 8 - chloro - 1 - (3 - chloro - propyl) - 3,5 - dihydro - benzthiaz[4,1]epinone - (2), 4.45 g of sodium iodide and 12 g of morpholine in 100 ml of dioxan was heated at reflux with stirring for 15 hours. After cooling, the mixture was filtered and the filtrate evaporated to dryness. The residue was dissolved in methylene chloride and the solution was extracted twice with 1-N hydrochloric acid. The aqueous extracts were combined, washed with methylene chloride, made alkaline with 6-N sodium hydroxide and extracted twice with methylene chloride. The organic extracts were combined, washed with water, dried over sodium sulphate and evaporated to dryness *in vacuo* to yield 8 - chloro - 1 - (3 - morpholino - propyl) - 3,5 - dihydro - benzthiaz[4,1]epinone - (2). The base was dissolved in 1-N methanolic hydrochloric acid and, after the addition of ether, crystalline 8 - chloro - 1 - (3 - morpholino - propyl) - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) hydrochloride was obtained. After recrystallization from methanol/ether, the hydrochloride was found to have a melting point of 246°—248°C.

EXAMPLE 10

A suspension of 20 g of 3,5 - dihydro - benzthiaz[4,1]epinone - (2) in 400 ml of absolute toluene was carefully added to a suspension of 5.4 g of sodamide in 220 ml of absolute toluene. On heating to 60°C, the stirred mixture became clear and after an additional 0.5 hour at this temperature became turbid again. After cooling to room temperature, 16 g of 3 - dimethylamino - propyl chloride were added to the stirred mixture over a period of 20 minutes. The resulting mixture was heated at reflux with stirring for 15 hours and then filtered. The filtrate was extracted twice with dilute hydrochloric acid. The combined aqueous extracts were washed with chloroform made alkaline with 3-N sodium hydroxide and extracted twice with methylene chloride. The combined organic extracts were washed with water, dried over sodium sulphate and evaporated to dryness *in vacuo* to give a brown oil. 13.8 g. of this oil were chromatographed on activated magnesium silicate. Elution with chloroform/benzene (1:1), chloroform/meth-

anol (2:8) and methanol gave 1* (3 - dimethylamino - propyl) - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) as an oil which crystallized on standing; melting point=61°—64°C from ether/petroleum ether (30°—60°C). The free base was dissolved in 50 ml of methanol. 60 ml of a 5% solution of oxalic acid in ether were slowly added and 1 - (3 - dimethylamino - propyl) - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) oxalate of melting point 184°—187°C was obtained. After recrystallization from methanol/ether, the oxalate was found to have a melting point of 186°—187°C.

EXAMPLE 11

A) The preparation of the starting material:

A mixture of 35 g of 5 - methoxy - 2 - nitro - toluene, 37.1 g of N - bromo - succinimide and 3.5 g of dibenzoyl peroxide in 350 ml of carbon tetrachloride was heated at reflux for 6 hours by means of a 250W-Infrared lamp (G.E.). After cooling, the mixture was filtered and the filtrate was washed with dilute sodium hydroxide solution and water, dried over sodium sulphate and evaporated to dryness *in vacuo*. The residue was dissolved in 90 ml of acetone and the solution carefully added to a stirred solution of 16.9 g of sodium hydroxide and 24.3 g of 80% mercapto-acetic acid in 200 ml water at 0°C. The mixture obtained was stirred for 4 days at room temperature, then diluted with water and extracted with methylene chloride. The aqueous medium remaining was made acidic with glacial acetic acid and extracted twice with methylene chloride. The methylene chloride extracts were combined, washed with water, dried over sodium sulphate and evaporated to dryness *in vacuo*. The residual oil was crystallized with ether/petroleum ether (30°—60°C) to give 2 - (5 - methoxy - 2 - nitro - benzylmercapto) - acetic acid of melting point 105°—107°C. After recrystallization from ether, the product was found to have a melting point of 107°—109°C.

A solution of 52.3 g of 2 - (5 - methoxy - 2 - nitro - benzylmercapto) - acetic acid in 1,200 ml of ethanol was hydrogenated at 30°C and 6 atmospheres in the presence of 5 g of 10% palladium-on-charcoal until the hydrogen uptake was completed. The mixture was then filtered and the filtrate evaporated to dryness *in vacuo*. 500 ml of xylene were added to the residue and the mixture was heated at reflux for 12 hours. From the cooled mixture, a crude crystalline precipitate of melting point 196°—198°C was obtained. From the mother liquor there was obtained a crude material of melting point 192°—196°C. The two solids were combined and dissolved in methanol. Charcoal was added and the resulting mixture was heated at reflux for 3

hours. After filtering off the charcoal and distilling off part of the solvent on the steam-bath, crystalline 7 - methoxy - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) was obtained. After recrystallization from methanol, the product was found to have a melting point of 202°—203°C.

B) The process:

A stirred suspension of 15 g of 7 - methoxy - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) in 150 ml of N,N - dimethyl - formamide was cooled to 0°C. A solution of 4.67 g of sodium methylate in 23.1 ml of methanol was added to the cooled suspension. After stirring at 0°C for 0.25 hour, 14 g of 3 - dimethylamino - propyl chloride were added dropwise thereto; then stirring was continued for 2 hours at 50°C and for 16 hours at room temperature. After removal of most of the solvent *in vacuo*, the residue was suspended in methylene chloride. The suspension was washed with water and extracted twice with 3-N hydrochloric acid. The acidic extracts were combined, washed with ether, made alkaline with 6-N sodium hydroxide and extracted twice with methylene chloride. The combined methylene chloride extracts were washed with water, dried over sodium sulphate and evaporated to dryness *in vacuo* to yield 1 - (3 - dimethylamino - propyl) - 7 - methoxy - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) as an oil. The oily residue was dissolved in an excess of 1-N methanolic hydrochloric acid and, after the addition of ether, 1 - (3 - dimethylamino - propyl) - 7 - methoxy - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) hydrochloride of melting point 199°—202°C was obtained. After recrystallization from methanol/ether, the hydrochloride was found to have a melting point of 200°—202°C.

EXAMPLE 12

A) The preparation of the starting material:

A mixture of 50 g of 2 - chloro - 6 - nitro - toluene, 52 g of N - bromo - succinimide and 1 g of dibenzoyl peroxide in 400 ml of carbon tetrachloride was heated at reflux for 24 hours. After cooling, the mixture was filtered and the filtrate was washed with dilute sodium hydroxide solution and water, dried over sodium sulphate and evaporated to dryness. The residue was dissolved in 100 ml of acetone and carefully added to a stirred solution of 33.3 g (80%) of mercapto-acetic acid and 23.1 g of sodium hydroxide in 300 ml of water at 0°C. The mixture was stirred for 3 days at room temperature, then diluted with water, washed twice with chloroform and acidified with glacial acetic acid. Extraction with methylene chloride, washing of the extracts with water, drying over sodium sulphate and evaporating to dryness *in vacuo* yielded a brown oil. The oil was dissolved

in 165 ml of ethanol and hydrogenated at room temperature and at 3 atmospheres in the presence of 3 g of 10 per cent palladium-on-charcoal until the hydrogen uptake was completed. The catalyst was then filtered off and the filtrate was evaporated to dryness. 80 ml of xylene were added to the residue and the mixture was heated at reflux for 8 hours. After cooling, crystalline 6 - chloro - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) was obtained. After recrystallization from acetone, the product was found to have a melting point of 205°—206°C.

B) The process:

A suspension of 9.6 g of 6 - chloro - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) and 2.2 g of sodamide in 100 ml dioxan was heated at reflux with stirring for 20 hours. After the mixture was cooled to 60°C, 6.6 g of 3 - dimethylamino - propyl chloride in 10 ml of dioxan were carefully added and the heating at reflux and stirring were continued for 4 hours. The mixture was then cooled, 5 ml of methanol were added and the solvent was removed *in vacuo*. The residue was heated with 150 ml of ethyl acetate and extracted twice with 2-N hydrochloric acid. The aqueous extracts were washed with ethyl acetate, made alkaline with 3-N sodium hydroxide and extracted twice with methylene chloride. The organic extracts were combined, washed with water, dried over sodium sulphate and evaporated to dryness *in vacuo* to yield 6 - chloro - 1 - (3 - dimethylamino - propyl) - 3,5 - dihydro - benzthiaz[4,1]epinone - (2). The residue was dissolved in an excess of 1-N methanolic hydrochloric acid and, after the addition of ether, 6 - chloro - 1 - (3 - dimethylamino - propyl) - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) hydrochloride of melting point 205°—207°C was obtained. After recrystallization from methanol/ether, the hydrochloride was found to have a melting point of 206°—208°C.

EXAMPLE 13

A) The preparation of the starting material:

A mixture of 100.8 g of 4 - methoxy - 2 - nitro - toluene, 106.5 g of N - bromo - succinimide and 7 g of dibenzoyl peroxide in 1000 ml of carbon tetrachloride was heated at reflux for 3 hours. After cooling, the mixture was filtered and the filtrate was washed with dilute sodium hydroxide solution and water, dried over sodium sulphate and evaporated to dryness. The residue was dissolved in 240 ml of acetone and added slowly to a stirred mixture of 70 g of 80% mercapto-acetic acid and 48.5 g of sodium hydroxide in 360 ml of water at 0°C. After stirring for 3 days at room temperature, the mixture was diluted with 300 ml of water.

After addition to the mixture of 500 ml of methylene chloride, there was obtained a

crystalline precipitate which was filtered off and dissolved in 400 ml of water. The aqueous layer of the filtrate was separated and added to this solution. After acidifying with glacial acetic acid and repeated extraction with methylene chloride, the combined organic extracts were washed with water, dried over sodium sulphate and evaporated to dryness *in vacuo*. The oily residue was crystallized with ether/[petroleum ether (30°—60°)] to yield 2 - (4 - methoxy - 2 - nitro - benzylthio) - acetic acid of melting point 75°—77°C. After two recrystallizations from ether/[petroleum ether (30°—60°C)], the product was found to have a melting point of 79°—80.5°C.

A solution of 80 g of 2 - (4 - methoxy - 2 - nitro - benzylthio) - acetic acid in 3000 ml of ethanol was hydrogenated at 13 atmospheres and room temperature in the presence of 8 g of 10% palladium-on-charcoal until the hydrogen uptake was completed. The mixture was then filtered and the filtrate was evaporated to dryness *in vacuo*. 1000 ml of xylene were added to the residue and the mixture was heated at reflux for 10 hours. Upon cooling, the mixture yielded 8 - methoxy - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) of melting point 198°—201°C. The product was dissolved in methanol and charcoal was added to the resulting solution. The mixture was heated at reflux for 3 hours. After removal of the charcoal by filtration and cooling the filtrate, the crystalline product precipitated. Upon recrystallization from methanol, the product was found to have a melting point of 202°—204°C.

B) The process:

A stirred suspension of 20.9 g of 8-methoxy - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) and 4.7 g of sodamide in 200 ml of dioxan was heated at reflux for 20 hours. After cooling to 60° C, 15.2 g of 3-dimethylamino-propyl chloride were added and heating at reflux and stirring were continued for 4 hours. The solvent was then removed *in vacuo* and the residue was treated with ethyl acetate and extracted twice with 2-N hydrochloric acid. The combined aqueous extracts were washed with ethyl acetate and made alkaline with 3-N sodium hydroxide. Extraction with methylene chloride, washing of the combined extracts with water, drying over sodium sulphate and evaporation to dryness yielded 1 - (3 - dimethylamino - propyl) - 8 - methoxy - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) as an oil. The oily base was dissolved in an excess of 1-N methanolic hydrochloric acid. The solution was evaporated to dryness *in vacuo* and the residue crystallized from methanol/acetone to yield 1 - (3 - dimethylamino - propyl) - 8 - methoxy - 3,5 - dihydrobenzthiaz[4,1]epinone - (2) hydrochloride of melting point 179°—183° C. After recrystallization from

methanol/ether, the product was found to have a melting point of 205°—206° C.

EXAMPLE 14

A) The preparation of the starting material:

A mixture of 51.4 g of 3 - chloro - 2 - nitro - toluene, 52 g of N-bromo-succinimide and 5 g of dibenzoyl peroxide in 500 ml of carbon tetrachloride was heated at reflux for 24 hours. The mixture was then heated at reflux with heat supplied by a 250W-Infrared lamp for a further 15 hours. The resulting mixture was filtered and the filtrate washed with dilute sodium hydroxide solution and water. After drying over sodium sulphate and evaporation to dryness, the residue was dissolved in 100 ml of acetone and added slowly to a stirred mixture of 34.2 g of 80% mercapto-acetic acid and 24.8 g of sodium hydroxide in 300 ml of water at 0° C. After stirring for 3 days at room temperature, the mixture was diluted with 500 ml of water, washed twice with methylene chloride and acidified with glacial acetic acid. Repeated extraction with methylene chloride, washing of the combined organic extracts with water, drying over sodium sulphate and evaporation to dryness *in vacuo* yielded an oil. The oil was crystallized from ether/[petroleum ether (30°—60° C)] to yield 2 - (3 - chloro - 2 - nitro - benzylthio) - acetic acid of melting point 131°—134° C. After two recrystallizations from ether, the product was found to have a melting point of 135°—137° C.

A solution of 17.2 g of 2 - (3 - chloro - 2 - nitro - benzylthio) - acetic acid in 165 ml of ethanol was hydrogenated at room temperature and 3 atmospheres in the presence of 2 g of 10% palladium-on-charcoal until the hydrogen uptake was completed. The mixture was then filtered and the filtrate was evaporated to dryness *in vacuo*. 100 ml of xylene were added to the residue and the mixture was heated at reflux for 10 hours. After cooling, the crystalline precipitate which formed was filtered and recrystallized from acetone to yield 9 - chloro - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) of melting point 192°—193° C.

B) The process:

A mixture of 24.5 g of 9 - chloro - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) and 5.6 g of sodamide in 250 ml of dioxan was heated at reflux with stirring for 40 hours. After cooling to 60° C, 16.9 g of 3-dimethylamino-propyl chloride were added dropwise thereto and heating at reflux and stirring were continued for 18 hours. The mixture was then diluted with 300 ml of ethyl acetate and extracted twice with 2-N hydrochloric acid. The aqueous extracts were combined, washed with ethyl acetate, made alkaline with 3-N sodium hydroxide and extracted twice with methylene chloride. The combined organic

extracts were washed with water, dried over sodium sulphate and evaporated to dryness *in vacuo* to yield, as the residue, 9 - chloro - 1 - (3 - dimethylamino - propyl) - 3,5 - dihydro - benzthiaz[4,1]epinone - (2). The residue was dissolved in an excess of 1-N methanolic hydrochloric acid and the solvent was removed *in vacuo*. The residue was crystallized from methanol/ethyl acetate to yield 9 - chloro - 1 - (3 - dimethylamino - propyl) - 3,5 - dihydro - benzthiaz[4,1] - epinone - (2) hydrochloride. The hydrochloride was dissolved in methanol, charcoal was added and the mixture was heated at reflux for 4 hours. After removal of the charcoal by filtration, ethyl acetate was added and the solvent partially evaporated. From the cooled mixture, the hydrochloride of melting point 209°—211° C was obtained.

EXAMPLE 15

A solution of 7 g of 8 - chloro - 1 - (3 - dimethylamino - propyl) - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) hydrochloride in 280 ml of methanol containing 1.12 g of sodium methylenate was evaporated to dryness *in vacuo*. Methylene chloride was added to the residue and after filtration of the resulting mixture the filtrate was evaporated to dryness to yield 8 - chloro - 1 - (3 - dimethylamino - propyl) - 3,5 - dihydro - benzthiaz[4,1]epinone - (2). The free base thus obtained was dissolved in 300 ml of absolute tetrahydro-furan and the solution obtained was carefully added over a period of 1 hour to an ice-cold suspension of 3.5 g of lithium aluminium hydride in 350 ml of absolute tetrahydro-furan. After stirring the mixture for 30 hours at room temperature, a saturated aqueous sodium sulphate solution and some solid sodium sulphate were added. The resulting mixture was filtered and the filtrate was evaporated to dryness *in vacuo* to leave an oily brown residue. The oily brown residue was chromatographed on activated magnesium silicate. With benzene/(ethyl acetate) (1:1) 8-chloro - 1 - (3 - dimethylamino - propyl) - 1,2,3,5 - tetrahydro - benzthiaz[4,1]epine was eluted as a yellow oil. The eluate was dissolved in methanol and an excess of a 5% ethereal solution of oxalic acid was added. Crystalline 8 - chloro - 1 - (3 - dimethyl - amino - propyl) - 1,2,3,5 - tetrahydro - benzthiaz[4,1]epine oxalate of melting point 100°—125° C was obtained. Recrystallization from methanol/ether yielded the oxalate of melting point 142°—145° C.

EXAMPLE 16

10 g of 8 - chloro - 1 - (2 - diethylamino - ethyl) 3,5 - dihydro - benzthiaz[4,1]epinone - (2) hydrochloride were dissolved in 64 ml of methanol containing 1.548 g of sodium. After removal of the solvent *in vacuo*, the residue was suspended in methylene chloride. The sus-

pension was filtered and the filtrate evaporated to dryness *in vacuo*. The oily residue was dissolved in 200 ml of methanol and, with cooling and stirring, 60 ml of 0.5-N sodium periodate solution were added dropwise thereto. The solution was then stirred at room temperature for 3 days, filtered and the solvent removed *in vacuo* to yield 8 - chloro - 1 - (2 - diethylamino - ethyl) - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) 4-oxide as an oil. The oily residue was dissolved in methanol and treated with isopropanolic hydrochloric acid. Addition of ether yielded 8-chloro - 1 - (2 - dimethylamino - ethyl) - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) 4-oxide hydrochloride of melting point 216°—218° C. After recrystallization from methanol/ether, the hydrochloride melted at 219°—220° C.

EXAMPLE 17

A) The preparation of the starting material:

A solution of 25 g of 2 - amino - 5 - chloro - benzhydrol 2.5 ml of triethyl amine and 20 ml of carbon disulphide in 250 ml of ethanol was heated to reflux for 18 hours. The mixture was then concentrated *in vacuo* until a crystalline precipitate appeared. On cooling, 6 - chloro - 4 - phenyl - 1,4 - dihydro - 2H - benzoxaz[3,1]methione - (2) was obtained as white needles which melted at 197°—200° C after recrystallization from a mixture of methylene chloride and petroleum ether.

Distillation of 6 - chloro - 4 - phenyl - 1,4 - dihydro 2H - benzoxaz[3,1]methione - (2) in a bulb tube at ca 0.1 mm and ca 200° C (bath temperature) gave a white solid which, after recrystallization from a mixture of methylene chloride and ether, melted at 209°—211° C. This compound was found to be 6 - chloro - 4 - phenyl - 1,4 - dihydro - 2H - benzthiaz[3,1]inone - (2).

A solution of 67 g of 6 - chloro - 4 - phenyl - 1,4 - dihydro - 2H - benzthiaz[3,1]inone - (2) and 5 g of sodium hydrosulphite ($\text{Na}_2\text{S}_2\text{O}_4$) in 500 ml of an aqueous 20% solution of potassium hydroxide was heated at reflux for 4 hours. The mixture was then cooled, neutralized with acetic acid and extracted with methylene chloride. The organic phase was washed with water and dried and the solvent was removed *in vacuo* to yield crude α - phenyl - 2 - amino - 5 - chloro - benzylmercaptan as an oil.

A solution of 44 g of the crude mercaptan in 1050 ml of ether was shaken with 19.9 ml of chloroacetyl chloride and 225 ml of 2-N sodium hydroxide; these reagents were added in turns in small portions so that the aqueous phase remained basic. There precipitated a solid which was collected on a filter and, after recrystallization from a mixture of methylene chloride and ether, yielded 7 - chloro - 5 - phenyl - 3,5 - dihydro - benzthiaz[4,1]epi-

none - (2) as white needles melting at 221°—223° C.

B) The process:

To a solution of 4 g of 7-chloro-5-phenyl-3,5-dihydro-benzthiaz[4,1]epinone - (2) in 30 ml of N,N-dimethyl-formamide were added 1.28 g of a 50% suspension of sodium hydride in mineral oil. The mixture was heated to ca 60° C for 5 minutes, then 3.3 g of 3-dimethylamino-propyl chloride were added and the temperature was kept at 60° C for 2 hours. After this time, the mixture was cooled, poured into ice-water and extracted with ether. The ether extract was evaporated to yield 7-chloro-1-(3-dimethylamino-propyl)-5-phenyl-3,5-dihydro-benzthiaz[4,1]epinone - (2) as an oil. The residual oil was dissolved in *n*-butanol. Addition of hydrogen chloride in ether gave crystals of 7-chloro-1-(3-dimethylamino-propyl)-5-phenyl-3,5-dihydro-benzthiaz[4,1]epinone - (2) hydrochloride which, after recrystallization from a mixture of methylene chloride and ether, was found to have a melting point of 249°—251° C.

EXAMPLE 18

A) The preparation of the starting material:

2.5 g of sodium borohydride were added to a solution of 12 g of 2-amino-4-chloro-benzophenone in 40 ml of tetrahydrofuran and 30 ml of ethanol. The mixture was stirred for 16 hours at room temperature, then poured into water. White crystals of 2-amino-4-chloro-benzhydrol melting at 94°—96° C were obtained. The 2-amino-4-chloro-benzhydrol so obtained was added to a solution of 4.8 g of potassium hydroxide in 10 ml of water and 80 ml of ethanol. 10 ml of carbon disulphide were then added and the mixture was heated to reflux overnight. Concentration *in vacuo*, neutralization with acetic acid and extraction with methylene chloride gave 7-chloro-4-phenyl-1,4-dihydro-2H-benzthiaz[3,1]methione - (2) as yellow crystals melting at 173°—177° C.

An aqueous solution of 9.1 g of potassium hydroxide was added to 102 ml of an aqueous 30% solution of hydrogen peroxide cooled in an ice-bath. To the mixture were added 11.7 g of 7-chloro-4-phenyl-1,4-dihydro-2H-benzthiaz[3,1]methione - (2) and 40 ml of ethanol. The suspension obtained was stirred for 18 hours at room temperature and acidified with hydrochloric acid. There was obtained a crystalline precipitate which still contained starting material and which was, therefore, treated again with hydrogen peroxide under the conditions just described. There were obtained white prisms of 7-chloro-4-phenyl-1,4-dihydro-2H-benzthiaz[3,1]inone - (2) which, after recrystallization from a mixture of methylene chloride and ether, melted at 185°—187° C.

A solution of 1 g of 7-chloro-4-phenyl-

1,4-dihydro-2H-benzthiaz[3,1]inone - (2) and 0.1 g of sodium hydrosulphite ($\text{Na}_2\text{S}_2\text{O}_3$) in 10 ml of a 20% aqueous solution of potassium hydroxide was heated to reflux for 2.5 hours. The mixture was then cooled, neutralized with hydrochloric acid and extracted with methylene chloride to yield 8-phenyl-2-amino-4-chloro-benzylmercaptan as an oil. This oil was dissolved in 30 ml of ether and shaken with 0.25 ml of chloroacetyl chloride and dilute sodium hydroxide. There formed a solid precipitate which after recrystallization from a mixture of methylene chloride and ether, gave 8-chloro-5-phenyl-3,5-dihydro-benzthiaz[4,1]epinone - (2) as white prisms melting at 234°—236° C.

B) The process:

To a solution of 2.6 g of 8-chloro-5-phenyl-3,5-dihydro-benzthiaz[4,1]epinone - (2) in 20 ml of N,N-dimethyl-formamide there were added 0.84 g of a 50% suspension of sodium hydride in mineral oil and 2.2 g of 3-dimethylamino-propyl chloride. The mixture was heated to 50°—70° C for 1.75 hours, cooled and poured into ice-water. Extraction with ether gave 8-chloro-1-(3-dimethylamino-propyl)-5-phenyl-3,5-dihydro-benzthiaz[4,1]epinone - (2) as an oil. The oil was dissolved in *n*-butanol and treated with ethereal hydrogen chloride. There was obtained a crystalline material which, after recrystallization from a mixture of methylene chloride and ether, gave 8-chloro-1-(3-dimethylamino-propyl)-5-phenyl-3,5-dihydro-benzthiaz[4,1]epinone - (2) hydrochloride as white needles melting at 253°—256° C.

EXAMPLE 19

A) The preparation of the starting material: 59 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:

i) 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.

ii) A solution of 40 ml of methyl amine in 100 ml of dioxan was combined with a solution of 15.2 g of 8 - chloro - 1 - (3 - chloro - propyl) - 3 - methyl - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) in 50 ml of dioxan and the mixture was kept in a nitrogen atmosphere under 50—60 pounds per square inch pressure at room temperature. After removal of the excess of methyl amine, the reaction mixture was diluted with methylene chloride. After washing with water, the mixture was extracted several times with dilute hydrochloric acid. The acidic extracts were combined and made alkaline with 6-N sodium hydroxide solution. The resulting mixture was extracted with methylene chloride and the extract was washed with water and evaporated to give crude 8 - chloro - 1 - (3 - methylamino - propyl) - 3 - methyl - 3,5 - dihydro - benzthiaz[4,1]epinone - (2). The crude base was dissolved in methanol and, after acidification with isopropanolic hydrochloric acid and addition of ether, 8 - chloro - 1 - (3 - methylamino - propyl) - 3 - methyl - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) hydrochloride crystallized. After recrystallizing

twice from methanol/ether, the hydrochloride melted at 218°—220° C.

EXAMPLE 20

3.02 g of sodium methylate in 12.1 ml of methanol were added at 0° C to a suspension of 11.4 g of 8 - chloro - 3 - methyl - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) in 100 ml of N,N-dimethyl-formamide. The temperature was maintained at 0° C and the mixture stirred for 0.25 hour. 12.4 g of 3 - diethylamino - propyl chloride dissolved in a few ml of toluene were then added and the mixture obtained was heated for 2 hours at 50° C, then left overnight at room temperature. The reaction mixture was subsequently concentrated *in vacuo* and the residue was suspended in methylene chloride. The suspension was washed with water and extracted twice with 3-N hydrochloric acid. The acidic layers were combined, washed with ether, made alkaline with 6-N sodium hydroxide solution and extracted with methylene chloride. The last-mentioned methylene chloride extract was washed with water, dried over anhydrous sodium sulphate and evaporated to dryness to give a brown oily residue containing 8 - chloro - 1 - (3 - diethylamino - propyl) - 3 - methyl - 3,5 - dihydro benzthiaz[4,1]epinone - (2). The oily residue was dissolved in methanol and, after the addition of 0.9 g of oxalic acid and ether, crystalline 8 - chloro - 1 - (3 - diethylamino - propyl) - 3 - methyl - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) oxalate was obtained. After three recrystallizations from methanol/ether, the oxalate had a melting point of 150°—152° C.

63 ml of a toluene solution containing 0.054 mol of diisobutyl aluminium hydride were added to a solution of 6.24 g (0.018 mol) of 8 - chloro - 1 - (3 - diethylamino - propyl) - 3 - methyl - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) in 1000 ml of anhydrous toluene. The resulting mixture was heated at reflux overnight in a nitrogen atmosphere, then cooled in an ice-bath. To the thus cooled medium there was carefully added a mixture of 20 ml of methanol and 10 ml of water; the mixture was filtered and the filtrate was dried over anhydrous sodium sulphate and evaporated to yield crude material containing 8 - chloro - 1 - (3 - diethylamino - propyl) - 3 - methyl - 1,2,3,5 - tetrahydro - benzthiaz[4,1]epine. The crude residue was dissolved in methanol and, after addition of one molar equivalent of oxalic acid, 8 - chloro - 1 - (3 - diethylamino - propyl) - 3 - methyl - 1,2,3,5 - tetrahydro - benzthiaz[4,1]epine oxalate crystallized upon addition of ether. The oxalate melted at 138°—139° C after two recrystallizations from methanol/ether.

EXAMPLE 21

A solution of 3.02 g (0.06 mol) of sodium methylate in 12.1 ml of methanol was added

to a suspension of 11.4 g (0.05 mol) of 8-chloro - 3 - methyl - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) in 100 ml of N,N - dimethyl - formamide at 0° C. The resulting clear solution was stirred for 0.25 hour, 12.2 g of 3 - dimethylamino - propyl chloride in a few ml of toluene were then added in portions. The resulting mixture was stirred for 2 hours at 50° C, then overnight at room temperature, after which it was evaporated to dryness and the residue suspended in methylene chloride. The suspension was washed with water and extracted twice with 3-N hydrochloric acid. The acidic layers were combined, washed with ether, made alkaline with 6-N sodium hydroxide and extracted with methylene chloride. The last-mentioned methylene chloride extract was washed with water, dried over anhydrous sodium sulphate and evaporated to dryness to give 8 - chloro - 1 - (3 - dimethylamino - propyl) - 3 - methyl - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) as a brown oil. It was converted into the hydrochloride which, after three recrystallizations from methanol/ether, had a melting point of 187°—189° C.

A solution of 4 g of 8 - chloro - 1 - (3 - dimethylamino - propyl) - 3 - methyl - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) was carefully added to a suspension of 4.9 g of lithium aluminium hydride in 300 ml of anhydrous tetrahydrofuran. The resulting mixture was heated at reflux for 36 hours. An additional 2.5 g of lithium aluminium hydride were then added and the heating at reflux was continued for a further 12 hours. After cooling, a saturated solution of sodium sulphate was added slowly to destroy the excess of lithium aluminium hydride. Anhydrous sodium sulphate was then added and the resulting mixture filtered. The filtrate was concentrated to dryness, leaving a crude residue containing 8 - chloro - 1 - (3 - dimethylamino - propyl) - 3 - methyl - 1,2,3,5 - tetrahydro - benzthiaz[4,1]epine. 1.8 g of this residue were dissolved in methanol and, after addition of one molar equivalent of oxalic acid, 8 - chloro - 1 - (3 - dimethylamino - propyl) - 3 - methyl - 1,2,3,5 - tetrahydro - benzthiaz[4,1]epine oxalate was precipitated by adding ether. After recrystallization from methanol/ether, the oxalate melted at 158.5°—160° C.

EXAMPLE 22

A solution of 10 g of 8 - chloro - 1 - (3 - chloro - propyl) - 3 - methyl - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) and 4.45 g of sodium iodide in 300 ml of absolute ethanol was saturated with dimethyl amine at 75° C for 5 hours. The resulting mixture was cooled and filtered and the filtrate was evaporated to dryness. The oily residue was dissolved in 500 ml of ethyl acetate and the solution was extracted with 1-N hydrochloric acid. The

acidic extract was washed with ether, then made alkaline with 3-N sodium hydroxide and extracted with 1000 ml of ethyl acetate. The last-mentioned ethyl acetate extract was washed with water, dried over anhydrous sodium sulphate and evaporated to dryness to yield 8 - chloro - 1 - (3 - dimethylamino - propyl) - 3 - methyl - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) as an oil. The oily residue was dissolved in isopropanol saturated with hydrogen chloride and evaporated to dryness. Recrystallization from acetone gave 8 - chloro - 1 - (3 - dimethylamino - propyl) - 3 - methyl - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) hydrochloride of melting point 190°—192° C.

42 ml of a 1-N toluene solution of diisobutyl aluminium hydride (0.042 mol) were added to a solution of 4.2 g (0.014 mol) of 8 - chloro - 1 - (3 - dimethylamino - propyl) - 3 - methyl - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) in 500 ml of anhydrous toluene, and the mixture was heated at reflux in a nitrogen atmosphere for 24 hours. After cooling in an ice-bath, a mixture of 10 ml of methanol and 5 ml of water was added dropwise to the cooled reaction mixture. The solution was filtered and the filtrate was dried over anhydrous sodium sulphate and evaporated to yield a crude residue containing 8 - chloro - 1 - (3 - dimethylamino - propyl) - 3 - methyl - 1,2,3,5 - tetrahydrobenzthiaz[4,1]epine. The residue was dissolved in methanol and, after the addition of one molar equivalent of oxalic acid, 8 - chloro - 1 - (3 - dimethylamino - propyl) - 3 - methyl - 1,2,3,5 - tetrahydro - benzthiaz[4,1]epine oxalate was precipitated by adding ether. After recrystallization from methanol, the oxalate melted at 159.5°—160° C.

EXAMPLE 23

A mixture of 15.2 g of 8 - chloro - 1 - (3 - chloro - propyl) - 3 - methyl - 3,5 - dihydro - benzthiaz[4,1]epinone - (2), 7.5 g of sodium iodide and 23.4 g of 1 - methyl - piperazine in 150 ml dioxan was heated at reflux for 25 hours. After cooling to room temperature, the mixture was filtered and the filtrate evaporated to dryness. The residue was dissolved in methylene chloride and the solution was washed with water and extracted several times with 2-N hydrochloric acid. The combined acid extracts were made alkaline with 3-N sodium hydroxide solution, then extracted three times with methylene chloride. The last-mentioned methylene chloride extracts were washed with water, dried over anhydrous sodium sulphate and evaporated to dryness to give a residue containing crude 8 - chloro - 1 - (3 - (4 - methyl - piperazino) propyl) - 3 - methyl - 3,5 - dihydro - benzthiaz[4,1]epinone - (2). The residue was dissolved in methanol and to the solution was added an excess of isopropanolic hydrochloric

acid. Upon addition of ether, crystalline 8-chloro - 1 - [3 - (4-methyl - piperazino) - propyl] - 3 - methyl - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) dihydrochloride was obtained. After drying *in vacuo* and several recrystallizations from methanol, the salt melted at 244°—246° C.

EXAMPLE 24

A mixture of 15.2 g of 8-chloro - 1 - (3-chloro - propyl) - 3 - methyl - 3,5 - dihydro - benzthiaz[4,1]epinone - (2), 7.5 g of sodium iodide and 26 g of 1 - (2-hydroxy - ethyl) - piperazine in 150 ml of dioxan was stirred and heated at reflux for 24 hours. The mixture was then diluted with methylene chloride, washed with water and extracted several times with 1-N hydrochloric acid. The acidic extracts were combined, made alkaline with 6-N sodium hydroxide solution and extracted with methylene chloride. The last-mentioned methylene chloride extract was washed with water, dried over anhydrous sodium sulphate and evaporated to dryness to yield 8-chloro - 1 - [3 - [4 - (2-hydroxy - ethyl) - piperazino] - propyl] - 3 - methyl - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) as an oil. The oily base was dissolved in 1-N methanolic hydrochloric acid and, after the addition of ether, crystalline 8-chloro - 1 - [3 - [4 - (2-hydroxy - ethyl) - piperazino] - propyl] - 3 - methyl - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) dihydrochloride was collected. After three recrystallizations from methanol, the dihydrochloride had a melting point of 171°—174° C.

EXAMPLE 25

A) The preparation of the starting material:

A stirred solution of 32 g (0.24 mol) of α -mercapto isovaleric acid and 19.2 g (0.48 mol) of sodium hydroxide in 150 ml of water was carefully added at 0° C to a solution of 59.7 g (0.24 mol) of 4-chloro - 2-nitro - benzyl bromide in 200 ml of acetone. The resulting mixture was stirred at room temperature for 3 days, then diluted with water and extracted with methylene chloride. The alkaline aqueous layer was acidified with acetic acid and extracted with methylene chloride. The last-mentioned methylene chloride extract was washed with water, dried over anhydrous sodium sulphate and evaporated to dryness to give crude oily 2 - (4-chloro - 2-nitro - benzylmercapto) - isovaleric acid.

The acid thus obtained was dissolved in 600 ml of methanol and, after the addition of 10 g of 10% palladium-on-carbon catalyst, hydrogenated under 50—100 pounds per square inch at room temperature until the theoretical amount of hydrogen was absorbed. The catalyst was then separated by filtration and the filtrate evaporated to dryness to give crude 2 - (2-amino - 4-chloro - benzylmercapto) - isovaleric acid.

The crude 2 - (2-amino - 4-chloro - benzylmercapto) - isovaleric acid was dissolved in 1000 ml of xylene and the solution was heated at reflux over a period of 48 hours, with removal of the water formed while refluxing. The solution was then filtered and evaporated. The residue was crystallized from ether to give 8-chloro - 3-isopropyl - 3,5-dihydro - benzthiaz[4,1]epinone - (2) of melting point 237°—242° C. After two recrystallizations from methanol, the product melted at 239.5°—240.5° C.

B) The process:

To a suspension of 2.56 g of 8-chloro - 3-isopropyl - 3,5-dihydro - benzthiaz[4,1]epinone - (2) in 20 ml of N,N-dimethyl-formamide stirred at 0° C there were added 0.65 g of sodium methoxide in 2.6 ml of methanol, the temperature being maintained at 0° C and stirring being continued for 0.25 hours after complete addition. 2.44 g of 3-dimethylamino-propyl chloride were then added and the mixture obtained was heated at 50° C for 2 hours, then left at room temperature overnight. After concentration of the mixture *in vacuo*, the residue was taken up in methylene chloride and the solution was washed with water and extracted with 3-N hydrochloric acid. The combined acidic layers were washed with ether, made alkaline with 6-N sodium hydroxide solution and extracted with methylene chloride. The last-mentioned extract was washed with water, dried over anhydrous sodium sulphate and evaporated to dryness *in vacuo* to give 8-chloro - 1 - (3-dimethylamino - propyl) - 3 - isopropyl - 3,5-dihydro - benzthiaz[4,1]epinone - (2) as an oil. The oily residue was dissolved in methanol and, after the addition of oxalic acid and ether, 8-chloro - 1 - (3-dimethylamino - propyl) - 3 - isopropyl - 3,5-dihydro - benzthiaz[4,1]epinone - (2) oxalate was obtained, melting point=167°—168° C. After two recrystallizations from methanol/ether, the oxalate melted at 167.5°—169° C.

EXAMPLE 26

A mixture of 2.56 g (0.01 mol) of 8-chloro - 3-isopropyl - 3,5-dihydro - benzthiaz[4,1]epinone - (2) and 0.487 g (0.0125 mol) of sodium hydride in 20 ml of dioxan was stirred and heated at reflux for 20 hours. After cooling to 60° C, 1.46 g of 3-dimethylamino - propyl chloride in 30 ml of dioxan were carefully added over a period of 10—15 minutes. The resulting mixture was heated at reflux for 4 hours, filtered and the filtrate evaporated to dryness. The residue was dissolved in ether and the solution was extracted with 3-N hydrochloric acid. The acidic extract was made alkaline with 6-N sodium hydroxide solution and extracted with chloroform. The chloroform extract was washed with

water, dried and evaporated. The oily residue was purified by chromatography on a silica-gel column with a methanol/benzene (1:1) system. The oily product obtained in this way was converted to an oily hydrochloride when treated with isopropanolic hydrochloric acid and ether. The aqueous solution of this hydrochloride was made alkaline with 6-N sodium hydroxide solution and extracted with chloroform. The chloroform solution was washed with water, dried over anhydrous sodium sulphate and evaporated to dryness to give 8-chloro-1-(3-dimethylamino-propyl)-3-isopropyl-3,5-dihydro-benzthiaz[4,1]epinone (2) as a colourless oil. To the solution of the base in methanol were added 0.18 g of oxalic acid to give 8-chloro-1-(3-dimethylamino-propyl)-3-isopropyl-3,5-dihydro-benzthiaz[4,1]epinone (2) oxalate. After two recrystallizations from methanol/ether and drying at 60° C in high vacuum for 24 hours, it melted at 165°—169° C (with decomposition).

EXAMPLE 27

25 A) The preparation of the starting material

A stirred solution of 24 g (0.2 mol) of α -mercapto-butyric acid and 16 g (0.4 mol) of sodium hydroxide in 150 ml of water was carefully added at 10° C to a solution of 49.8 g (0.2 mol) of 4-chloro-2-nitro-benzyl bromide in 150 ml of acetone. The resulting mixture was stirred at room temperature for 3 days, then diluted with water and extracted with methylene chloride. The alkaline aqueous layer was acidified with acetic acid and extracted with methylene chloride. The last-mentioned methylene chloride extract was washed with water, dried over anhydrous sodium sulphate and evaporated to dryness to yield crude oily 2-(4-chloro-2-nitro-benzylmercapto)-butyric acid. The thus formed acid was dissolved in 600 ml of methanol and, after addition of 10 g of a 10% palladium-on-carbon catalyst, hydrogenated under 5—100 pounds per square inch pressure at room temperature, until the theoretical amount of hydrogen had been absorbed. The catalyst was then separated by filtration and the filtrate was evaporated to dryness to yield crude 2-(2-amino-4-chloro-benzylmercapto)-butyric acid.

The crude 2-(2-amino-4-chloro-benzylmercapto)-butyric acid was dissolved in 1000 ml of xylene and the solution was heated at reflux for 72 hours, with removal of the water formed when refluxing. The resulting mixture was filtered and evaporated to dryness. The residue was crystallized from methanol to give 8-chloro-3-ethyl-3,5-dihydro-benzthiaz[4,1]epinone (2) of melting point 205°—208° C. After two recrystallizations from methanol, the product melted at 210°—211° C.

B) The process:

A mixture of 2.42 g (0.01 mol) of 8-chloro-3-ethyl-3,5-dihydro-benzthiaz[4,1]epinone (2) and 0.487 g (0.0125 mol) of sodium hydride in 20 ml of dry dioxan was heated at reflux with stirring for 20 hours. After cooling to 60° C, 1.46 g of 3-dimethylamino-propyl chloride in 3 ml of dioxan was carefully added over a period of 10—15 minutes. The mixture was then heated at reflux for 4 hours and thereafter filtered. The filtrate was evaporated to dryness and the oily residue was dissolved in ether. The solution obtained was extracted twice with 3-N hydrochloric acid. The acidic extract was made alkaline with 6-N sodium hydroxide solution and extracted with methylene chloride. The organic extract was dried over anhydrous sodium sulphate and evaporated to dryness to give 8-chloro-1-(3-dimethylamino-propyl)-3-ethyl-3,5-dihydro-benzthiaz[4,1]epinone (2) as an oil. The oily residue was dissolved in methanol and, upon addition of isopropanolic hydrochloric acid, crystalline 8-chloro-1-(3-dimethylamino-propyl)-3-ethyl-3,5-dihydro-benzthiaz[4,1]epinone (2) hydrochloride was obtained. After recrystallization from methanol/ether and drying in vacuum, the hydrochloride melted at 192°—194° C.

45 ml of a 1-N toluene solution of diisobutyl aluminium hydroxide were added to a solution of 4.8 g (0.015 mol) of 8-chloro-1-(3-dimethylamino-propyl)-3-ethyl-3,5-dihydro-benzthiaz[4,1]epinone (2) in 1000 ml of anhydrous toluene. The resulting mixture was heated at reflux overnight in a nitrogen atmosphere. After cooling, a mixture of 20 ml of methanol and 10 ml of water was carefully added. The mixture was then filtered and the filtrate evaporated to dryness to give a crude residue containing 8-chloro-1-(3-dimethylamino-propyl)-3-ethyl-1,2,3,5-tetrahydrobenzthiaz[4,1]epine. 4.36 g of the crude residue were dissolved in methanol and one molar equivalent of oxalic acid was added. 8-Chloro-1-(3-dimethylamino-propyl)-3-ethyl-1,2,3,5-tetrahydro-benzthiaz[4,1]epine oxalate crystallized upon addition of ether. After two recrystallizations from a mixture of methanol and ether, the oxalate melted at 151°—153° C.

EXAMPLE 28

A) The preparation of the starting

material:
A stirred solution of 24 g (0.18 mol) of α -mercapto-valeric acid and 14.4 g (0.36 mol) of sodium hydroxide in 100 ml of water was carefully added at 0° C to a solution of 44.8 g (0.18 mol) of 4-chloro-2-nitro-benzyl bromide in 200 ml of acetone. The resulting mixture was stirred at room temperature for 3 days, then dilu-

ted with water and extracted with methylene chloride. The alkaline aqueous layer was acidified with acetic acid and extracted with methylene chloride. The last-mentioned methylene chloride extract was washed with water, dried over anhydrous sodium sulphate and evaporated to dryness to yield crude oily 2 - (4 - chloro - 2 - nitro - benzylmercapto) - valeric acid.

The acid thus obtained was dissolved in 600 ml of methanol and, after the addition of 10 g of 10% palladium-on-carbon catalyst, hydrogenated under 50—100 pounds per square inch at room temperature, until the theoretical amount of hydrogen had been absorbed. The catalyst was then removed by filtration and the filtrate evaporated to dryness to give crude 2 - (2 - amino - 4 - chloro - benzylmercapto) - valeric acid.

The crude material thus obtained was dissolved in 1500 ml of xylene and the solution was heated at reflux for 48 hours, with removal of the water formed when refluxing. The solution was then filtered and evaporated to give 8 - chloro - 3 - propyl - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) of melting point 163°—165°C. Three recrystallizations from methanol raised the melting point to 165°—166°C.

B) The process:

To a stirred solution of 2.56 g (0.01 mol) of 8 - chloro - 3 - propyl - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) in 20 ml of N,N-dimethyl - formamide at 0°C, there was added a solution of 0.65 g (0.012 mol) of sodium methoxide in 2.6 ml of methanol; the temperature and the stirring were maintained for 0.25 hour. 2.44 g of 3 - dimethylamino - propyl chloride were then added and the resulting mixture was heated at 50°C for 2 hours, then left at room temperature overnight. The reaction mixture was subsequently diluted with 100 ml of methylene chloride, washed twice with water and extracted with 3-N hydrochloric acid. The acidic extract was washed with ether, made alkaline with 6-N sodium hydroxide and extracted twice with methylene chloride. The last-mentioned methylene chloride extract was washed with water, dried over anhydrous sodium sulphate and evaporated to dryness to yield a crude residue containing 8 - chloro - 1 - (3 - dimethylamino - propyl) - 3 - propyl - 3,5 - dihydro - benzthiaz[4,1]epinone - (2). 0.45 g of the said crude residue were dissolved in methanol, one molar equivalent of oxalic acid was added and 8 - chloro - 1 - (3 - dimethylamino - propyl) - 3 - propyl - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) oxalate was precipitated by addition of ether; melting point=159°—160°C. After recrystallization from methanol/ether, the oxalate melted at 162—163.5°C.

EXAMPLE 29

36 ml of a 1-N toluene solution of diisobutyl aluminium hydride were added to a solution of 4.1 g (0.012 mol) of 8 - chloro - 1 - (3 - dimethylamino - propyl) - 3 - propyl - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) in 1000 ml of anhydrous toluene. The resulting mixture was heated at reflux overnight. After cooling in an ice-bath, a mixture of 20 ml of methanol and 10 ml of water was carefully added and the mixture filtered. The filtrate was dried over anhydrous sodium sulphate and evaporated to dryness to yield a crude residue containing 8 - chloro - 1 - (3 - dimethylamino - propyl) - 3 - propyl - 1,2,3,5 - tetrahydro - benzthiaz[4,1]epine. 3.42 g of the crude residue were dissolved in methanol and, after addition of one molar equivalent of oxalic acid, 8 - chloro - 1 - (3 - dimethylamino - propyl) - 3 - propyl - 1,2,3,5 - tetrahydro - benzthiaz[4,1]epine oxalate was crystallized by the addition of ether. After recrystallization from methanol, the oxalate melted at 161°—162°C.

EXAMPLE 30

A) The preparation of the starting material:

A stirred solution of 22 g (0.13 mol) of α - mercapto - phenylacetic acid and 10.4 g (0.26 mol) of sodium hydroxide in 100 ml of water was carefully added at 0°C to a solution of 32.4 g (0.13 mol) of 4 - chloro - 2 - nitro - benzyl bromide in 100 ml of acetone. The resulting mixture was stirred at room temperature for 3 days, then diluted with water and extracted with methylene chloride. The alkaline aqueous layer was acidified with acetic acid and extracted with methylene chloride. The last-mentioned methylene chloride extract was washed with water, dried over anhydrous sodium sulphate and evaporated to dryness to give crude oily 2 - (4 - chloro - 2 - nitro - benzylmercapto) - 2 - phenyl - acetic acid.

The crude acid thus obtained was dissolved in 600 ml of methanol and, after the addition of 10 g of 10% palladium-on-carbon catalyst, hydrogenated under 50—100 pounds per square inch at room temperature, until the theoretical amount of hydrogen had been absorbed. The catalyst was then removed by filtration and the filtrate evaporated to dryness to give crude 2 - (2 - amino - 4 - chloro - benzylmercapto) - 2 - phenyl - acetic acid.

The crude material thus obtained was dissolved in 1200 ml of xylene and the solution was heated at reflux for 24 hours, with removal of the water formed when refluxing. The solution was then filtered and the filtrate evaporated. The residue was crystallized from methanol to yield 8 - chloro - 3 - phenyl - 3,5 - dihydro - benzthiaz[4,1] -

epinone - (2) of melting point 262°—271°C. After two recrystallizations from methanol, the product melted at 267°—269°C.

B) The process:

- 5 To a stirred solution of 5.8 g (0.02 mol) of 8 - chloro - 3 - phenyl - 3,5 - dihydro-benzthiaz[4,1]epinone - (2) in 160 ml of N,N-dimethyl - formamide at 0°C, there was added a solution of 1.35 g (0.025 mol) of sodium methoxide in 16 ml of methanol; the stirring was continued for 0.25 hour while maintaining the temperature at 0°C. 4.8 g of 3 - dimethylamino - propyl chloride in 20 ml of toluene were then added and the resulting mixture was heated at 50°C for 2 hours, then left at room temperature overnight and subsequently diluted with 200 ml of methylene chloride. The resulting solution was washed with water and extracted with 3-N hydrochloric acid. The acidic extract was washed with ether, made alkaline with 6-N sodium hydroxide and extracted twice with methylene chloride. The last-mentioned methylene chloride extract was washed with water, dried over anhydrous sodium sulphate and evaporated to dryness to yield a crude residue containing 8 - chloro - 1-(3 - dimethylamino - propyl) - 3 - phenyl-3,5 - dihydro - benzthiaz[4,1]epinone - (2). 30 0.76 g of this residue were dissolved in a minimal amount of methanol and to the solution were added 0.232 g of maleic acid. Upon dilution with ether, crystalline 8-chloro-1 - (3 - dimethylamino - propyl) - 3 - phenyl-3,5 - dihydro - benzthiaz[4,1]epinone - (2) maleate was obtained. After recrystallization from methanol/ether, the maleate melted at 159°—162°C.

EXAMPLE 31

- 40 A) The preparation of the starting material:

A solution of 125 g (0.5 mol) of 4-chloro-2 - nitro - benzyl bromide in 200 ml of acetone was carefully added to a stirred solution of 53 g (0.5 mol) of β - mercapto - propionic acid and 40 g (1 mol) of sodium hydroxide in 300 ml of water. The resulting mixture was stirred at room temperature for 3 days, after which time it was 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. 55 The last-mentioned methylene chloride extract was washed with water, dried over anhydrous sodium sulphate and evaporated to dryness to give a dark oil. On purification with charcoal in methanol solution, the dark oil gave crystalline 3 - (4 - chloro - 2-nitro - benzylmercapto) - propionic acid (melting point=87°—89°C after recrystallization from benzene).

The thus formed acid was dissolved in 1200 ml of methanol and, after the addition of 30 g of 10% palladium-on-carbon catalyst, hydrogenated at 185—225 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 evaporated to dryness to give crude 3 - (2 - amino - 4-chloro - benzylmercapto) - propionic acid. The crude material was dissolved in 1000 ml of anhydrous xylene and the solution heated at reflux for 24 hours, with removal of water formed when refluxing. After evaporation to dryness, the residue was chromatographed on a silica gel column with a benzene/(ethyl acetate) solvent system to give crystalline 9 - chloro - 1,3,4,6 - tetrahydro - benzthiaz[5,1]ocinone - (2). After two recrystallizations from ethyl acetate, the product melted at 215°—216°C.

B) The process:

In the manner described in Example 30B, 9 - chloro - 1,3,4,6 - tetrahydro - benzthiaz[5,1]ocinone - (2) was reacted with sodium methoxide and 3 - dimethylamino-propyl chloride to give 9 - chloro - 1 - (3-dimethylamino - propyl) - 1,3,4,6 - tetrahydro-benzthiaz[5,1]ocinone - (2) and the maleate thereof.

9 - Chloro - 1 - (3 - dimethylamino-propyl) - 1,3,4,6 - tetrahydro - benzthiaz[5,1]ocinone - (2) was converted into 9-chloro-1 - (3 - dimethylamino - propyl) - 2,3,4,6-tetrahydro - 1H - benzthiaz[5,1]ocine and its hydrochloride utilizing diisobutyl aluminium hydride as reducing agent.

EXAMPLE 32

Other thiaza-heterocyclics suitable for use in the process provided by the invention may be prepared as follows:

- i) To a suspension of 2.4 g (0.01 mol) of 8 - chloro - 3 - ethyl - 3,5 - dihydro-benzthiaz[4,1]epinone - (2) in 1500 ml of anhydrous toluene there were added 21 ml of a 1-N toluene solution of diisobutyl aluminium hydride. The resulting mixture was heated at reflux overnight in a nitrogen atmosphere; shortly after refluxing began, a clear solution was obtained. 10 ml of 1-N diisobutyl aluminium hydride were then added and the reaction mixture was heated at reflux for 24 hours. A further 10 ml of 1-N diisobutyl aluminium hydride were subsequently added and the resulting mixture was heated at reflux for 6 more hours. After cooling in an ice-bath, a mixture of 40 ml of methanol and 20 ml of water was added dropwise and the precipitated salts were removed by filtration. The filtrate was dried over anhydrous sodium sulphate and evaporated. The residue was crystallized from methanol to give 8 - chloro - 3 - ethyl-

1,2,3,5 - tetrahydro - benzthiaz[4,1]epine of melting point 207.5°—210°C. The hydrochloride was prepared by conventional techniques and was found to have a melting point of 162°—166°C after two recrystallizations from ethanol.

In a manner similar to that described in the preceding paragraph, 8 - chloro - 3 - methyl - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) was converted into 8 - chloro - 3 - methyl - 1,2,3,5 - tetrahydro - benzthiaz[4,1]epine of melting point 73°—74°C (after recrystallization from methanol).

ii) To a suspension of 7.6 g (0.03 mol) of 8 - chloro - 3 - propyl - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) in 1500 ml of anhydrous toluene there were added 63 ml of 1-N diisobutyl aluminium hydride in toluene. The resulting mixture was heated at reflux for 24 hours in a nitrogen atmosphere; shortly after refluxing began, a clear solution was obtained. After 24 hours, 10 ml of 1-N diisobutyl aluminium hydride were added and the mixture was heated at reflux for a further 12 hours. After cooling in an ice-bath, a mixture of 40 ml of methanol and 20 ml of water was added dropwise and the precipitated salts were removed by filtration. The filtrate was dried over anhydrous sodium sulphate and evaporated to give a crude residue containing 8 - chloro - 3 - propyl - 1,2,3,5 - tetrahydro - benzthiaz[4,1]epine. The crude residue was dissolved in ethanolic hydrochloric acid and from the solution, on standing, there crystallized 8 - chloro - 3 - propyl - 1,2,3,5 - tetrahydro - benzthiaz[4,1]epine hydrochloride of melting point 143°—153°C. After two recrystallizations from ethanol the melting point was 143°—145°C.

iii) To a suspension of 3.1 g (0.012 mol) of 8 - chloro - 3 - isopropyl - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) in 1000 ml of anhydrous toluene there were added 63 ml of 1-N diisobutyl aluminium hydride in toluene. The resulting mixture was heated at reflux in a nitrogen atmosphere for 24 hours. After cooling in an ice-bath, a mixture of 40 ml of methanol and 20 ml of water was added dropwise and the precipitated salts were removed by filtration. The filtrate was dried over anhydrous sodium sulphate and evaporated to give a crude residue containing 8 - chloro - 3 - isopropyl - 1,2,3,5 - tetrahydro - benzthiaz[4,1]epine. The crude residue was treated with ethanolic hydrochloric acid and then evaporated to dryness. Crystallization from ethyl acetate gave 8 - chloro - 3 - isopropyl - 1,2,3,5 - tetrahydro - benzthiaz[4,1]epine hydrochloride. After two recrystallizations from ethyl acetate the salt melted at 113°—115°C.

iv) To a stirred suspension of 5 g of lithium aluminium hydride in 600 ml of anhydrous tetrahydro - furan at 0°C there

was added dropwise a solution of 9 - chloro - 1,3,4,6 - tetrahydro - benzthiaz[5,1]ocinone - (2) in 150 ml of anhydrous tetrahydrofuran. The resulting mixture was stirred overnight at room temperature. After cooling in an ice-bath, the excess of lithium aluminium hydride was destroyed by dropwise addition of a saturated solution of sodium sulphate. The resulting suspension was dried over anhydrous sodium sulphate and filtered and the filtrate was evaporated. Unreduced starting material was removed by crystallization from methanol. After evaporation, the mother liquors which contained the base were treated with ethanolic hydrochloric acid to give crystalline 9 - chloro - 2,3,4,6 - tetrahydro - 1H - benzthiaz[5,1]ocine hydrochloride of melting point 216°—221°C (after recrystallization from ethanol).

The following Examples illustrate how the novel thiaza-heterocyclics provided by the invention may be made up into pharmaceutical preparations:

EXAMPLE A

Tablets each containing 25.0 mg of 8 - chloro - 1 - (3 - dimethylamino - propyl) - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) hydrochloride, 72.0 mg of lactose (spray dried), 2.0 mg of corn starch and 1.0 mg of calcium stearate and each having a total weight of 100.0 mg were prepared by blending the active substance, the lactose, the corn starch and the calcium stearate in a suitable mixer, compressing the resulting powder on a heavy-duty tablet compressing machine to yield tablet slugs, passing the slugs through a suitable comminuting machine and recompressing the granulation obtained on a tablet compressing machine to tablets of 100 mg.

Tablets each containing 25 mg of 8 - chloro - 1 - (3 - dimethylamino - propyl) - 3 - methyl - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) hydrochloride as the active substance were prepared in exactly the same way.

EXAMPLE B

Capsules each containing 25 mg of 8 - chloro - 1 - (3 - dimethylamino - propyl) - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) hydrochloride (or the 3 - methyl derivative thereof), 158 mg of lactose, 37 mg of corn starch and 5 mg of talc and each having a total weight of 225 mg were prepared by mixing the active substance with the lactose and the corn starch in a suitable mixer, further blending the resulting mixture by passing it through a comminuting machine, returning the blended powder to the mixer, adding the talc, thoroughly mixing the resulting blend and filling it into hard shell gelatin capsules on a capsulating machine.

EXAMPLE C

Suppositories each containing 0.025 mg of 8 - chloro - 1 - (3 - dimethylamino-propyl) - 3,5 - dihydro - benzthiaz[4,1] epinone - (2) hydrochloride (or the 3-methyl derivative thereof), 1.230 g of hydrogenated coconut oil and 0.045 g of carnauba wax and each having a total weight of 1.3 g were prepared by melting the hydrogenated coconut oil and the carnauba wax in a suitable size glass-lined container, mixing them well, cooling to 45°C, adding the active substance (reduced to a fine powder with no lumps), stirring until complete and uniform dispersion is obtained, pouring the mixture into suppository moulds to yield suppositories having an individual weight of 1.3 g, cooling the suppositories, removing them from the moulds and individually wrapping them in wax paper for packaging.

EXAMPLE D

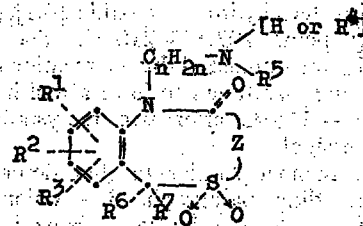
A parenteral dosage formulation was prepared by filling 25 mg of dry 8 - chloro - 1 - (3 - dimethylamino - propyl) - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) hydrochloride (fibre free) into a 5 ml ampoule, sealing the ampoule and sterilizing it at 124°C for 2 hours; immediately before use, the powder was solubilized with 5 ml of water for injection.

EXAMPLE E

A parenteral dosage formulation containing in each ml 5.1 mg of 8 - chloro - 1 - (3 - dimethylamino - propyl) - 3 - methyl - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) hydrochloride, 0.4 ml of propylene glycol, 0.015 ml of benzyl alcohol (benzaldehyde free); 0.10 ml of ethanol, 48.8 mg of sodium benzoate, 1.2 mg of benzoic acid and water for injection q.s. to 1.0 ml was prepared by dissolving 51 g of 8 - chloro - 1 - (3 - dimethylamino - propyl) - 3 - methyl - 3,5 - dihydro - benzthiaz[4,1] epinone - (2) hydrochloride in 150 ml of benzyl alcohol, adding 4,000 ml of propylene glycol and 1,000 ml of ethanol, dissolving 12 g of benzoic acid in the solution obtained, then adding 488 g of sodium benzoate dissolved in 3,000 ml of water for injection, bringing the solution up to the final volume of 10,000 ml with water for injection, filtering the solution through a filter candle, filling it into suitable size ampoules, gassing with nitrogen, sealing the ampoules and autoclaving them at 0.7 atmospheres excess pressure for 0.5 hour.

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, R¹, R² and R³ each stand for a halogen atom or a lower-alkyl or lower-alkoxy group, R⁴ and R⁵ each stand for a lower-alkyl or benzyl group or jointly, together with the nitrogen atom to which they are attached, form a 5- or 6-membered heteromonocyclic ring which may contain one further nitrogen or oxygen atom and which may contain one substituent, R⁶ represents a lower-alkyl group, R⁷ represents a lower-alkyl, phenyl or halo-phenyl group and n stands for 2,3,4,5,6 or 7 and wherein the broken lines denote that the groups or atoms attached thereby are optional, and acid addition salts thereof.

2) 3,5 - Dihydro - benzthiaz[4,1] epinone - (2)s as set forth in claim 1, wherein R² and R³ are absent, and acid addition salts thereof.

3) Thiaza-heterocyclics as set forth in claim 2, wherein R¹ (when present) is in the 8-position, R⁴ (when present) represents a lower-alkyl group and R⁵ represents a lower-alkyl group.

4) An 8 - halo - 1 - [di(lower alkyl)amino-alkyl] - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) as set forth in claim 1, and acid addition salts thereof.

5) An 8 - halo - 1 - (lower alkylamino-alkyl) - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) as set forth in claim 1, and acid addition salts thereof.

6) 8 - Chloro - 1 - (3 - dimethylamino-propyl) - 3,5 - dihydro - benzthiaz[4,1] epinone - (2) and acid addition salts thereof.

7) 8 - Chloro - 1 - (3 - methylamino-propyl) - 3,5 - dihydro - benzthiaz[4,1] epinone - (2) and acid addition salts thereof.

8) An 8 - halo - 1 - [N - (lower alkyl)-N - benzyl - amino - alkyl] - 3,5 - dihydro-benzthiaz[4,1]epinone - (2) as set forth in claim 1, and acid addition salts thereof.

9) An 8 - (lower alkoxy) - 1 - [di(lower

EXAMPLE C

Suppositories each containing 0.025 mg of 8 - chloro - 1 - (3 - dimethylamino-propyl) - 3,5 - dihydro - benzthiaz[4,1] epinone - (2) hydrochloride (or the 3-methyl derivative thereof), 1.230 g of hydrogenated coconut oil and 0.045 g of carnauba wax and each having a total weight of 1.3 g were prepared by melting the hydrogenated coconut oil and the carnauba wax in a suitable size glass-lined container, mixing them well, cooling to 45°C, adding the active substance (reduced to a fine powder with no lumps), stirring until complete and uniform dispersion is obtained, pouring the mixture into suppository moulds to yield suppositories having an individual weight of 1.3 g, cooling the suppositories, removing them from the moulds and individually wrapping them in wax paper for packaging.

EXAMPLE D

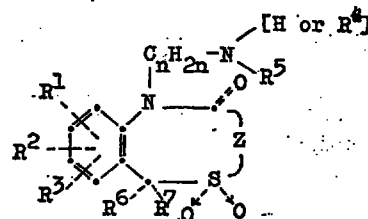
A parenteral dosage formulation was prepared by filling 25 mg of dry 8 - chloro - 1 - (3 - dimethylamino - propyl) - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) hydrochloride (fibre free) into a 5 ml ampoule, sealing the ampoule and sterilizing it at 124°C for 2 hours; immediately before use, the powder was solubilized with 5 ml of water for injection.

EXAMPLE E

A parenteral dosage formulation containing in each ml 5.1 mg of 8 - chloro - 1 - (3 - dimethylamino - propyl) - 3 - methyl - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) hydrochloride, 0.4 ml of propylene glycol, 0.015 ml of benzyl alcohol (benzaldehyde free); 0.10 ml of ethanol, 48.8 mg of sodium benzoate, 1.2 mg of benzoic acid and water for injection q.s. to 1.0 ml was prepared by dissolving 51 g of 8 - chloro - 1 - (3 - dimethylamino - propyl) - 3 - methyl - 3,5 - dihydro - benzthiaz[4,1] epinone - (2) hydrochloride in 150 ml of benzyl alcohol, adding 4,000 ml of propylene glycol and 1,000 ml of ethanol, dissolving 12 g of benzoic acid in the solution obtained, then adding 488 g of sodium benzoate dissolved in 3,000 ml of water for injection, bringing the solution up to the final volume of 10,000 ml with water for injection, filtering the solution through a filter candle, filling it into suitable size ampoules, gassing with nitrogen, sealing the ampoules and autoclaving them at 0.7 atmospheres excess pressure for 0.5 hour.

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, R¹, R² and R³ each stand for a halogen atom or a lower-alkyl or lower-alkoxy group, R⁴ and R⁵ each stand for a lower-alkyl or benzyl group or jointly, together with the nitrogen atom to which they are attached, form a 5- or 6-membered heteromonocyclic ring which may contain one further nitrogen or oxygen atom and which may contain one substituent, R⁶ represents a lower-alkyl group, R⁷ represents a lower-alkyl, phenyl or halo-phenyl group and n stands for 2,3,4,5,6 or 7 and wherein the broken lines denote that the groups or atoms attached thereby are optional, and acid addition salts thereof.

2) 3,5 - Dihydro - benzthiaz[4,1] epinone - (2)s as set forth in claim 1, wherein R² and R³ are absent, and acid addition salts thereof.

3) Thiaza heterocyclics as set forth in claim 2, wherein R¹ (when present) is in the 8-position, R⁴ (when present) represents a lower-alkyl group and R⁵ represents a lower-alkyl group.

4) An 8 - halo - 1 - [di(lower alkyl)amino-alkyl] - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) as set forth in claim 1, and acid addition salts thereof.

5) An 8 - halo - 1 - (lower alkylamino-alkyl) - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) as set forth in claim 1, and acid addition salts thereof.

6) 8 - Chloro - 1 - (3 - dimethylamino-propyl) - 3,5 - dihydro - benzthiaz[4,1] epinone - (2) and acid addition salts thereof.

7) 8 - Chloro - 1 - (3 - methylamino-propyl) - 3,5 - dihydro - benzthiaz[4,1] epinone - (2) and acid addition salts thereof.

8) An 8 - halo - 1 - [N - (lower alkyl)-N - benzyl - amino - alkyl] - 3,5 - dihydro-benzthiaz[4,1]epinone - (2) as set forth in claim 1, and acid addition salts thereof.

9) An 8 - (lower alkoxy) - 1 - [di(lower



alkyl)amino - alkyl] - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) as set forth in claim 1, and acid addition salts thereof.

10) 8 - Methoxy - 1 - (3 - dimethylamino-propyl) - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) and acid addition salts thereof.

11) A 6 - halo - 1 - [di(lower alkyl)amino-alkyl] - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) as set forth in claim 1, and acid addition salts thereof.

12) A 9 - halo - 1 - [di(lower alkyl)amino-alkyl] - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) as set forth in claim 1, and acid addition salts thereof.

13) A 7 - halo - 1 - [di(lower alkyl)amino-alkyl] - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) as set forth in claim 1, and acid addition salts thereof.

14) 1,2,3,5 - Tetrahydro - benzthiaz[4,1]epines as set forth in claim 1, wherein R^2 and R^3 are absent, R^1 (when present) is in the 8-position and R^4 and R^5 each represent a lower-alkyl group, and acid addition salts thereof.

15) An 8 - halo - 1 - [di(lower alkyl)amino-alkyl] - 1,2,3,5 - tetrahydro - benzthiaz[4,1]epine as set forth in claim 1, and acid addition salts thereof.

16) 8 - Chloro - 1 - (3 - dimethylamino-propyl) - 1,2,3,5 - tetrahydro - benzthiaz[4,1]epine and acid addition salts thereof.

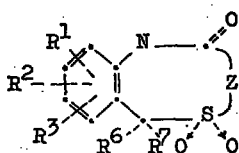
17) 3,5 - Dihydro - benzthiaz[4,1]epinone - (2) 4-oxides as set forth in claim 1, wherein R^2 and R^3 are absent, R^1 (when present) is in the 8-position and R^4 and R^5 each represent a lower-alkyl group, and acid addition salts thereof.

18) An 8 - halo - 1 - [di(lower alkyl)amino-alkyl] - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) 4-oxide as set forth in claim 1, and acid addition salts thereof.

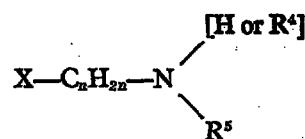
19) 8 - Chloro - 1 - (3 - dimethylamino-propyl) - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) 4-oxide and acid addition salts thereof.

20) A pharmaceutical preparation comprising a compound or salt as set forth in claim 1 in admixture with a compatible pharmaceutical carrier.

21) A process for the manufacture of the thiazia heterocyclics claimed in claim 1, which process comprises reacting a compound of the general formula



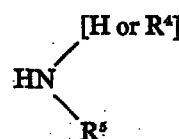
either with a compound of the general formula



or with a compound of the general formula



and treating the reaction product with an amine of the general formula



and, in either case, converting any carbonyl group present into a methylene group if desired, oxidising any thio group present to a sulphinyl or sulphonyl group if desired, introducing a lower-alkanoyloxy group on to the carbon atom adjacent to the thia atom if required and, also if desired, converting the product into an acid addition salt; in which formulae n , Z , $R^1, R^2, R^3, R^4, R^5, R^6, R^7$ and the broken lines have the significance given in claim 1, X stands for a halogen atom or a sulphonyloxy group and Hal stands for a chlorine, bromine or iodine atom.

22) A process as set forth in claim 21, wherein a compound of the first formula written in that claim is converted into a 1-(alkali metal) derivative prior to the reaction with a compound of the second or third formula written in that claim.

23) A process as set forth in claim 22, wherein said alkali-metal derivative is the sodio derivative.

24) A process as set forth in claim 21, claim 22 or claim 23, wherein a compound of the third formula written in claim 21 in which X stands for a bromine atom and Hal stands for a chlorine atom is used.

25) A process as set forth in any one of claims 21 to 24 inclusive, wherein a 3,5-dihydro - benzthiaz[4,1]epinone - (2) in which R^2 and R^3 are absent is used as the starting material.

26) A process as set forth in claim 25, wherein a 3,5 - dihydro - benzthiaz[4,1]epinone - (2) in which R^1 (when present) is in the 8-position is reacted either with a lower alkylamino - alkyl halide or a di-(lower alkyl) amino-alkyl halide or with an ω - halo - alkyl halide and the reaction product treated with a lower-alkyl amine or a di(lower alkyl) amine.

27) A process as set forth in claim 26, wherein a 8 - halo - 3,5 - dihydro - benzthiaz[4,1]epinone - (2) is used as the starting material.





28) A process as set forth in claim 27, wherein the 8-chloro compound is used.

29) A process as set forth in claim 27 or claim 28, wherein the starting material is reacted *either* with a dimethylamino-propyl halide *or* with 1-bromo-3-chloro-propane and the reaction product treated with dimethyl amine.

30) A process as set forth in claim 27 or claim 28, wherein said starting material is reacted *either* with a methylamino-propyl halide *or* with 1-bromo-3-chloro-propane and the reaction product treated with methyl amine.

31) A process as set forth in claim 25, wherein a 8-halo-3,5-dihydro-benzthiaz[4,1]epinone-(2) is reacted *either* with an N-(lower alkyl)-N-benzyl-amino-alkyl halide *or* with an ω -halo-alkyl halide and the reaction product treated with an N-(lower alkyl)-N-benzyl amine.

32) A process as set forth in claim 31, wherein the 8-chloro compound is used.

33) A process as set forth in claim 31 or claim 32, wherein the starting material is reacted *either* with an N-methyl-N-benzyl-amino-propyl halide *or* with 1-bromo-3-chloro-propane and the reaction product treated with N-methyl-N-benzyl amine.

34) A process as set forth in claim 26, wherein a 8-(lower alkoxy)-3,5-dihydro-benzthiaz[4,1]epinone-(2) is reacted *either* with a di(lower alkyl)amino-alkyl halide *or* with an ω -halo-alkyl halide and the product treated with a di(lower alkyl) amine.

35) A process as set forth in claim 34, wherein the 8-methoxy compound is used.

36) A process as set forth in claim 34 or claim 35, wherein the starting material is reacted *either* with a dimethylamino-propyl halide *or* with 1-bromo-3-chloro-propane and the reaction product treated with dimethyl amine.

37) A process as set forth in claim 25, wherein a 6-halo-3,5-dihydro-benzthiaz[4,1]epinone-(2) is reacted *either* with a di(lower alkyl)amino-alkyl halide *or* with an ω -halo-alkyl halide and the reaction product treated with a di(lower alkyl) amine.

38) A process as set forth in claim 37, wherein the 6-chloro compound is used.

39) A process as set forth in claim 37 or claim 38, wherein the starting material is reacted *either* with a dimethylamino-propyl halide *or* with 1-bromo-3-chloro-propane and the reaction product treated with dimethyl amine.

40) A process as set forth in claim 25, wherein a 9-halo-3,5-dihydro-benzthiaz[4,1]epinone-(2) is reacted *either* with a di(lower alkyl)amino-alkyl halide *or* with an ω -halo-alkyl halide and the reaction product treated with a di(lower alkyl) amine.

41) A process as set forth in claim 40, wherein the 9-chloro compound is used.

42) A process as set forth in claim 40 or claim 41, wherein the starting material is reacted *either* with a dimethyl-amino halide *or* with 1-bromo-3-chloro-propane and the reaction product treated with dimethyl amine.

43) A process as set forth in claim 25, wherein a 7-halo-3,5-dihydro-benzthiaz[4,1]epinone-(2) is reacted *either* with a di(lower alkyl)amino-alkyl halide *or* with an ω -halo-alkyl halide and the reaction product treated with the di(lower alkyl) amine.

44) A process as set forth in claim 43, wherein the 7-chloro compound is used.

45) A process as set forth in claim 43 or claim 44, wherein the starting material is reacted *either* with a dimethylamino-propyl halide *or* with 1-bromo-3-chloro-propane and the reaction product treated with dimethyl amine.

46) A process as set forth in any one of claims 21 to 24 inclusive, wherein a 1,2,3,5-tetrahydro-benzthiaz[4,1]epine in which R^2 and R^3 are absent and R^1 (when present) is in the 8-position is reacted *either* with a di(lower alkyl)amino-alkyl halide *or* with an ω -halo-alkyl halide and the reaction product treated with a di(lower alkyl) amine.

47) A process as set forth in claim 46, wherein a 8-halo-1,2,3,5-tetrahydro-benzthiaz[4,1]epine is used as the starting material.

48) A process as set forth in claim 47, wherein the 8-chloro compound is used.

49) A process as set forth in claim 47 or claim 48, wherein the starting material is reacted *either* with a dimethyl-propyl halide *or* with 1-bromo-3-chloro-propane and the reaction product treated with dimethyl amine.

50) A process as set forth in any one of claims 21 to 24 inclusive, wherein a 3,5-dihydro-benzthiaz[4,1]epinone-(2) 4-oxide in which R^2 and R^3 are absent and R^1 (when present) is in the 8-position is reacted *either* with a di(lower alkyl)amino-alkyl halide *or* with an ω -halo-alkyl halide and the reaction product treated with a di(lower alkyl) amine.

51) A process as set forth in claim 50, wherein a 8-halo-3,5-dihydro-benzthiaz[4,1]epinone-(2) 4-oxide is used as the starting material.

52) A process as set forth in claim 51, wherein the 8-chloro compound is used.

53) A process as set forth in claim 51 or claim 52, wherein the starting material is reacted *either* with a dimethylamino-propyl halide *or* with 1-bromo-3-chloro-propane and the reaction product treated with dimethyl amine.

54) A process for the manufacture of the thiaza heterocyclics set forth in claim 1, sub-

70

75

80

85

90

95

100

105

110

115

120

125

130

stantially as described with reference to the Examples.

- 5 55) Thiaza heterocyclics as set forth in claim 1, when manufactured by the process claimed in any one of claims 21 to 54 inclusive.

W. D. WHITAKER
—Patent Agent—
for F. Hoffmann-La Roche & Co.,
Aktiengesellschaft.

Leamington Spa: Printed for Her Majesty's Stationery Office by the Courier Press.—1967.
Published at The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.



* C L M S *