

L120.735

PATENT SPECIFICATION

NO DRAWINGS

L120.735



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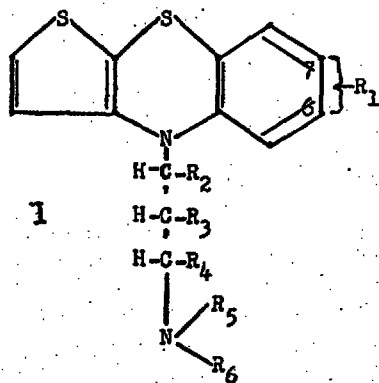
COMPLETE SPECIFICATION

Improvements in or relating to Thieno-benzothiazine Derivatives

We, SANDOZ LTD., of Lichtstrasse 35 Basle, Switzerland, a Swiss Body Corporate, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to new heterocyclic compounds and a process for their production.

The present invention provides thienobenzothiazine derivatives of formula I,



[Price 4s. 6d.]

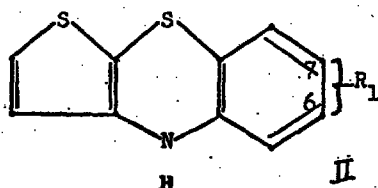
in which (i) R_1 signifies a hydrogen, chlorine or bromine atom, an alkoxy, alkylmercapto, alkylsulphonyl, or alkylsulphinyl radical, each having from 1 to 4 carbon atoms inclusive, an aliphatic acyl radical having from 2 to 4 carbon atoms inclusive, the trifluoromethyl or the cyano radical, 15
 R_2 signifies a hydrogen atom, each of R_3 and R_4 signifies a hydrogen atom or the methyl radical, and each of R_5 and R_6 signifies an alkyl radical having from 1—4 carbon atoms inclusive, or R_5 and R_6 together with the nitrogen atom form a piperidino radical which may be substituted in the 4-position by a hydroxy radical, or a piperazino radical which may be substituted on the second nitrogen atom by an alkyl radical having from 1—4 carbon atoms inclusive or by a 2-hydroxy-ethyl radical, or 20
(ii) R_7 signifies an alkyl radical having from 1—4 carbon atoms inclusive, R_8 together with R_9 signifies a trimethylene chain, and R_1 , R_2 and R_4 are as defined at (i) above, or 25
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35
40

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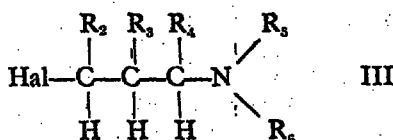
- (iii) R_1 together with R_2 signifies a trimethylene or tetramethylene chain, and R_1 , R_2 and R_3 are as defined at (i) above, and R_4 as in (ii) above,

5 and their acid addition salts.

- The present invention further provides a process for the production of compounds of formula I and their acid addition salts, characterized in that a compound of formula II,



in which R_1 has the above significance, is condensed with a compound of formula III,



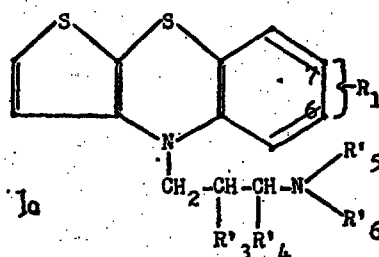
- 15 in which R_2 to R_6 have the above significance, and
Hal signifies a chlorine, bromine or iodine atom,

- 20 in the presence of an inert organic solvent and an acid binding agent and, when an acid addition salt is required, the resulting compound of formula I is reacted with an organic or inorganic acid.

- One method of producing the compounds of formula I is as follows:

- 25 A thieno-benzothiazine derivative of formula II is heated at reflux for several hours with an alkali metal amide or an alkali metal hydroxide in an inert organic solvent, e.g. an aromatic hydrocarbon. A basic halide of formula III, dissolved in a further amount of the same solvent or in another inert organic solvent, is added whilst boiling is continued, the reaction mixture is further heated for several hours, is subsequently cooled, washed with water and the resulting compound of formula I is extracted with an aqueous acid solution, e.g. an aqueous tartaric acid solution. The crude base is precipitated by making the acid extract alkaline and is purified in manner known *per se*, e.g. by distillation in a high vacuum, chromatography and/or recrystallization and, when required, the resulting compound of formula I is converted into its acid addition salts in manner known *per se*. The term "known" as used herein indicates methods in actual use or described in the literature on the subject.

- 50 Included in the present invention also is a method of producing compounds of formula Ia,

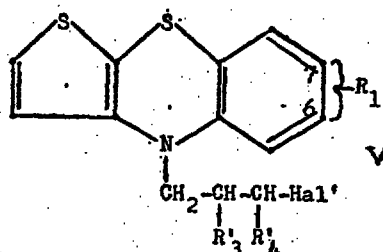


In which R_1 has the above significance, R_2 and R_3 signify hydrogen or methyl, and

each of R_4 and R_5 signifies an alkyl radical having from 1 to 4 carbon atoms inclusive, or

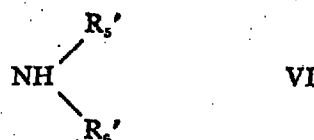
R_4 and R_5 together with the nitrogen atom form a piperidino radical which may be substituted in the 4-position by a hydroxy radical, or a piperazino radical which may be substituted on the second nitrogen atom by an alkyl radical having from 1 to 4 carbon atoms inclusive or by a 2-hydroxyethyl radical, and their acid addition salts, which method is as follows:

A compound of formula V,



wherein R_1 , R_2 and R_3 have the above significance, and

Hal' signifies a chlorine or bromine atom, is condensed with a compound of formula VI,



in which R_7 and R_8 have the above significance, advantageously in the presence of an alkaline condensation agent and in an inert organic solvent, e.g. a suspension of an alkali metal carbonate in an aromatic hydrocarbon, and, when an acid addition salt is required, the resulting compound of formula Ia is reacted with an organic or inorganic acid. The compounds of formula V may be produced by reacting a compound of formula II with 1-chloro-3-bromopropane or 1-bromo-3-iodopropane optionally substituted

ted by presence preferably in an aromatic

The formula crystalline or inorganic salts which are: fumaric, acid.

The compound produced amino-thiophene its alkali potassium thiophene of formula

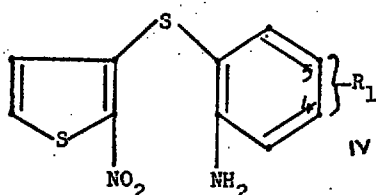
in which preferably amino group or sodium in the present ring is accomplished according hitherto or diphenyl compound it is called compound

Substituted for product some of obtained by 2-chloro-4- or 5-sulphide but sulphide a known per diphenyl substituted in the corresponding sulphide for holic solution and the required from manner known Compound

ted by one or two methyl radicals in the presence of an alkaline condensation agent, preferably sodium amide or sodium hydroxide, in an inert organic solvent, preferably an aromatic hydrocarbon.

The thieno-benzothiazine derivatives of formula I are bases which are viscous or crystalline at room temperature; with organic or inorganic acids they form relatively stable salts which are crystalline at room temperature. Examples of acids for acid addition salt formation with compounds of formula I are: hydrochloric, hydrobromic, sulphuric, fumaric, maleic, tartaric and methanesulphonic acid.

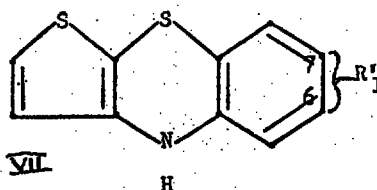
The compounds of formula II may be produced by condensing an appropriate 2-amino-thiophenol, preferably in the form of its alkaline metal salt, e.g. the sodium or potassium salt, with 3-bromo-2-nitrothiophene and heating the resulting compound of formula IV,



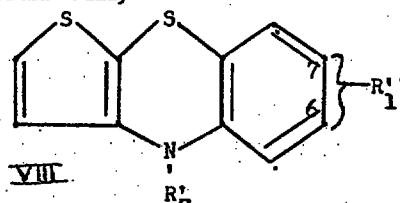
in which R_1 has the above significance, preferably after acylation of the primary amino group, in a suspension of potassium or sodium carbonate in dimethyl formamide in the presence of copper. The intramolecular ring closure produced by this reaction is accompanied by a rearrangement which, according to the literature on the subject, has hitherto only been observed in the case of diphenyl ethers and diphenyl sulphides when it is called Smiles' rearrangement, whereby a compound of formula II is obtained.

Substituted 2-amino-thiophenols used for producing the compounds of formula II, some of which are unknown, may be obtained by the following method: A 2-bromo-, 2-chloro- or 2-iodo-nitrobenzene, which may be correspondingly substituted in the 4- or 5-position, is converted to the disulphide by treatment with an alkali metal sulphide and powdered sulphur in manner known *per se*, the resulting 2,2'-dinitrodiphenyl-disulphide, which may be substituted in the 4,4'- or 5,5'-position, is reduced in manner known *per se* to the corresponding 2,2'-diamino compound, the disulphide linkage is subsequently split in alcoholic solution with a strong alkali metal base and the required thiophenol derivative is liberated from the resulting alkali metal salt in manner known *per se*.

Compounds of formula VII,

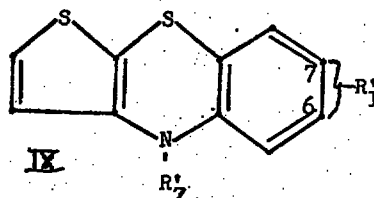


in which R_1' signifies an alkylsulphinyl radical of from 1 to 4 carbon atoms inclusive, may be obtained by oxidizing a compound of formula VIII,

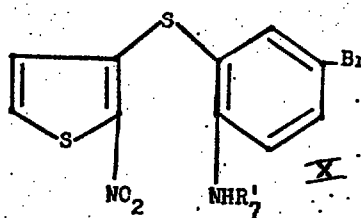


in which R_1'' signifies an alkylmercapto radical of from 1 to 4 carbon atoms inclusive, and

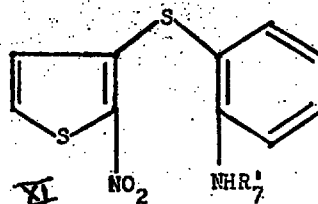
R_7' signifies an aliphatic acyl radical of from 1 to 4 carbon atoms inclusive or the benzoyl radical, with hydrogen peroxide in boiling alcoholic solution and saponifying the resulting compound of formula IX,



in which R_1' and R_7' have the above significance, by alkaline hydrolysis. Compounds of formula X,



in which R_7' has the above significance, may be produced by brominating a compound of formula XI



in which R_7' has the above significance,

with elementary bromine in manner known *per se*.

Compounds of formula I are of interest since they possess sedative and neuroleptic properties. In addition they possess antidepressant characteristics, as well as antihistaminic effects.

The antagonism to the Tetrabenazine syndrome indicates antidepressant properties.

The compounds of formula I are therefore indicated for use in clinical psychiatry in the treatment of psychoses, and depressive disorders, as well as psychosomatic illnesses. The compounds are also indicated for use in internal medicine in disorders where treatment with antihistamines is indicated.

A suitable daily dosage is 20—200 mg.

The compounds of formula I are indicated for use as pharmaceuticals on their own or in the form of appropriate medicinal preparations for administration, e.g. enterally or parenterally. In order to produce suitable medicinal preparations the compounds are worked up with inorganic or organic adjuvants which are inert and physiologically acceptable. Examples of such adjuvants are as follows:

For tablets and dragées:

lactose, starch, talc and stearic acid;

For syrups:

solution of cane sugar, invert sugar and glucose;

For injectable solutions:

water, alcohols, glycerin and vegetable oils;

For suppositories:

natural or hardened oils and waxes.

The preparations may furthermore contain suitable preserving, stabilizing and wetting agents, solubilizers, sweetening and colouring substances and flavourings.

The present invention thus further provides pharmaceutical compositions containing, in addition to a physiologically acceptable carrier, a compound of formula I and/or acid addition salt thereof which is physiologically acceptable.

In the following non-limitative Examples all temperature are indicated in degrees Centigrade. The melting points are corrected.

As may be seen from formulae I, Ia, II and V, the substituent R₁ may be in the 6- or 7-position of the thieno-benzothiazine nucleus and in the compounds of formula IV in the 4- or 5-position of the benzene ring.

The salts of naphthalene - 1,5 - disulphonic acid or of benzene-sulphonic acid are

called nadisylate or besylate in the following Examples.

EXAMPLE 1

4 - (3 - dimethylamino - propyl - 1)-
4H - thieno[2,3 - b][1,4]benzothiazine.

a) (2 - nitro - thienyl - 3) - 2 - amino-
phenyl - sulphide.

A total of 173 g of 3 - bromo - 2 - nitrothiophene (melting point 81—83°) is added portionwise at 60° to a solution of 104 g of *o*-aminothiophenol (boiling point 234°) and 30 g of sodium hydroxide in 500 cc of methanol and the mixture is kept at 60° for a further 1½ hours. Cooling, filtration and drying are effected. After recrystallizing twice, each time from 700 cc of ethanol, pure (2 - nitro - thienyl - 3) - 2 - aminophenyl - sulphide, having a melting point of 109—111°, is obtained.

b) (2 - nitro - thienyl - 3) - 2 - acetamido-
phenyl - sulphide.

50 g of acetic anhydride are added dropwise during the course of 5 minutes to a boiling mixture of 60.0 g of (2 - nitrothienyl - 3) - 2 - aminophenyl - sulphide in 180 cc of toluene and boiling is subsequently effected for a further 15 minutes. After cooling well, filtration and washing out with toluene are effected. After crystallizing from 650 cc of acetone, pure (2 - nitrothienyl - 3) - 2 - acetamidophenyl - sulphide, having a melting point of 159—161°, is obtained.

c) 4H - thieno[2,3 - b][1,4]benzothiazine.

A mixture of 80 g of (2 - nitro - thienyl - 3) - 2 - acetamidophenyl - sulphide, 80 g of finely pulverized potassium carbonate, 5 g of copper bronze and 600 cc of dimethyl formamide is heated in a nitrogen gas stream at an oil bath temperature of 150° for half an hour, i.e. until nitrogen monoxide evolution stops. The reaction mixture is poured on 2 litres of water whilst warm, is cooled, filtered and dried. The crude material is extracted in a Soxhlet apparatus with 500 cc of ether for 2½ hours. After evaporating the ether extract, the evaporation residue is crystallized twice, each time from 125 cc of chloroform. The resulting pure 4H - thieno[2,3 - b][1,4]benzothiazine has a melting point of 134—137°.

d) 4 - (3 - dimethylamino - propyl - 1)-
4H - thieno[2,3 - b][1,4]benzothiazine.

A mixture of 25.0 g of 4H - thieno[2,3-b][1,4]benzothiazine, 5.7 g of finely pulverized sodium amide and 125 cc of absolute xylene is heated to the boil at reflux at an oil bath temperature of 180° whilst stirring for 2 hours. A solution of 17.8 g of 3 - dimethylamino - 1 - chloropropane (boiling point

134—137° is added to the solution over a period of 1 hour with stirring. The mixture is then washed with benzene, concentrated, and 150 cc of water is added. The crude product is then washed with the mother liquor and 0.001 g of the product are dissolved in 10 ml of ethanol and recrystallized. The product is then washed with 4 - (3 - thienyl - 2 - amino)phenyl - sulphide, having a melting point of 109—111°.

4 - [1,4]benzothiazine

The product is then condensed and the condensation is effected in amounts of 25.0 g of thiazine, amide, 1 of 2 - (chloroethyl) Hg). The product is then distilled at a high vacuum and is collected further purified by dissolving in 30 cc of naphthalene and crystallizing from 4 - [2 - (1,4)benzothiazine] - 4H nadisylate 278°, is Besylate: 6.6 g of at the boiling point cooling is crystallizing from pure 4 - ethyl - 1 thiazine b 132—134°

134—135°) in 30 cc of absolute xylene is added dropwise during the course of half an hour whilst boiling is continued and boiling is effected for a further 3 hours. After cooling, washing out is effected three times, each time with 50 cc of water and extraction is then effected with 200 cc of 15% tartaric acid solution. The tartaric acid extract is washed out twice, each time with 50 cc of benzene, is made alkaline with 50 cc of concentrated sodium hydroxide solution and the precipitated base is taken up in a total of 150 cc of benzene. After washing the benzene solution twice, each time with 50 cc of water, evaporation is effected. The resulting crude base is distilled in a high vacuum and the main fraction which distils at 154—156° and 0.005 mm of Hg is collected. The fumarate is produced for further purification. 16.82 g of the distillate and 7.05 g of fumaric acid are dissolved at the boil in 85 cc of absolute ethanol and cooling is then effected. After recrystallizing from 190 cc of ethanol, pure 4 - (3 - dimethylamino - propyl - 1) - 4H-thieno[2,3 - b][1,4]benzothiazine fumarate, having a melting point of 160—162°, is obtained.

EXAMPLE 2

4 - [2 - (1 - methyl - piperidyl - 2) - ethyl - 1] - 4H - thieno[2,3 - b][1,4]benzothiazine

The production of the starting materials, the condensation reaction and working up are effected in a manner analogous to that described in Example 1, whereby the following amounts are used:

25.0 g of 4H - thieno[2,3 - b][1,4]benzothiazine, 5.7 g of finely pulverized sodium amide, 125 cc of absolute xylene and 23.6 g of 2 - (1 - methyl - piperidyl - 2) - 1-chloroethane (boiling point 84°/10 mm of Hg). The resulting crude base is distilled in a high vacuum and the main fraction which distils at 185—188° and 0.02 mm of Hg is collected. The nadisylate is produced for further purification. 5.0 g of the distillate are dissolved in 20 cc of absolute ethanol and are poured into a hot solution of 5.52 g of naphthalene - 1,5 - disulphonic acid (83%) in 30 cc of absolute ethanol. After recrystallizing from 2 litres of 80% methanol, pure 4 - [2 - (1 - methyl - piperidyl - 2) - ethyl - 1] - 4H - thieno[2,3 - b][1,4]benzothiazine nadisylate, having a melting point of 276—278°, is obtained.

Besylate: 13.15 g of the main fraction and 6.6 g of benzenesulphonic acid are dissolved at the boil in 75 cc of absolute ethanol and cooling is subsequently effected. After recrystallizing from 50 cc of absolute ethanol and drying above the boiling point of ethanol, pure 4 - [2 - (1 - methyl - piperidyl - 2) - ethyl - 1] - 4H - thieno[2,3 - b][1,4]benzothiazine besylate, having a melting point of 132—134°, is obtained.

EXAMPLE 3

4 - (1 - methyl - piperidyl - 3 - methyl) - 4H - thieno[2,3 - b][1,4]benzothiazine.

The production of the starting materials, the condensation reaction and working up are effected in a manner analogous to that described in Example 1, whereby the following amounts are used: 25.0 g of 4H - thieno[2,3 - b][1,4]benzothiazine, 5.7 g of finely pulverized sodium amide, 125 cc of absolute xylene and 21.6 g of 1 - methyl - 3 - chloromethyl - piperidine (boiling point 69°/11 mm of Hg). The resulting crude base is distilled in a high vacuum and the main fraction which distils at 173—175° and 0.02 mm of Hg is collected. The fumarate is produced for further purification. 3.79 g of the distilled base and 1.46 of fumaric acid are dissolved at the boil in 25 cc of absolute ethanol and cooling is then effected. After recrystallizing from 15 cc of 70% ethanol, pure 4 - (1 - methyl - piperidyl - 3 - methyl) - 4H-thieno[2,3 - b][1,4]benzothiazine fumarate, having a melting point of 216—218°, is obtained.

EXAMPLE 4

6 - chloro - 4 - (3 - dimethylamino - propyl - 1) - 4H - thieno[2,3 - b][1,4]benzothiazine.

a) (2 - nitro - thienyl - 3) - 2 - amino - 4 - chlorophenyl - sulphide.

A total of 250 g of 3 - bromo - 2 - nitrothiophene (melting point 81—83°) is added portionwise at 60° to a solution of 192 g of 2 - amino - 4 - chlorothiophenol (melting point 44—46°) and 48.2 g of sodium hydroxide in 900 cc of methanol and the mixture is then kept at 60° for half an hour. Cooling, filtration and drying are effected. After recrystallizing twice, each time from a 3-fold quantity of ethyl acetate, pure (2-nitrothienyl - 3) - 2 - amino - 4 - chlorophenyl-sulphide, having a melting point of 165—167°, is obtained.

b) (2 - nitro - thienyl - 3) - 2 - acetamido - 4 - chlorophenyl - sulphide.

192 g of acetic anhydride are added dropwise during the course of 5 minutes to a boiling mixture of 267 g of (2 - nitrothienyl - 3) - 2 - amino - 4 - chlorophenyl-sulphide in 800 cc of toluene and the mixture is subsequently boiled for one hour. After cooling well, filtration and washing out with toluene are effected. After crystallizing from a 10-fold quantity of acetone, pure (2 - nitrothienyl - 3) - 2 - acetamido - 4 - chlorophenyl - sulphide, having a melting point of 178—181°, is obtained.

c) 6 - chloro - 4H - thieno[2,3 - b][1,4]benzothiazine.

A mixture of 96.5 g of (2 - nitro - thienyl - 3) - 2 - acetamido - 4 - chlorophenyl - sul-

- phide, 85 g of finely pulverized potassium carbonate, 5 g of copper bronze and 650 cc of dimethyl formamide is heated in a nitrogen gas stream at an oil bath temperature of 150° for 40 minutes, i.e. until nitrogen monoxide evolution stops. The reaction mixture is poured on 2 litres of water whilst warm, is cooled, filtered and dried. The crude material is extracted in a Soxhlet apparatus with 350 cc of ether for 3½ hours. After evaporating the ether extract, the evaporating residue is recrystallized four times from chloroform and once from cyclohexane. The resulting, pure 6 - chloro - 4H - thieno[2,3 - b][1,4]benzothiazine has a melting point of 167—170°.
- d) 6 - chloro - 4 - (3 - dimethylamino - propyl - 1) - 4H - thieno[2,3 - b][1,4]benzothiazine.
- A mixture of 12.0 g of 6 - chloro - 4H - thieno[2,3 - b][1,4]benzothiazine, 2.35 g of finely pulverized sodium amide and 50 cc of absolute toluene is heated to the boil at reflux at an oil bath temperature of 150° whilst stirring for one hour. Cooling is subsequently effected to an internal temperature of 50° and a solution of 7.3 g of 3 - dimethylamino - 1 - chloropropane (boiling point 134—135°) in 10 cc of absolute toluene is added dropwise during the course of half an hour. Heating is then effected to an oil bath temperature of 110° for 3 hours, cooling is effected and the reaction mixture is washed out three times, each time with 20 cc of water.
- The toluene solution is extracted with 150 cc of 15% aqueous tartaric acid solution and the extract is washed out three times, each time with 50 cc of benzene. After making alkaline with 45 cc of concentrated sodium hydroxide solution, the precipitated base is extracted with 100 cc of benzene. The benzene solution is washed out with 50 cc of water and is evaporated. The evaporation residue is dissolved in 15 cc of benzene and the solution is adsorbed on a column of 75 g of aluminium oxide. The first 300 cc of benzene eluate are concentrated. 3.15 g of this evaporation residue and 1.18 g of fumaric acid are dissolved at the boil in 15 cc of absolute ethanol and the solution is subsequently cooled well. After recrystallizing from 15 cc of absolute ethanol, pure 6 - chloro - 4 - (3 - dimethylamino - propyl - 1) - 4H - thieno[2,3 - b][1,4]benzothiazine fumarate, having a melting point of 146—148°, is obtained.

EXAMPLE 5

- 6 - methylmercapto - 4 - (3 - dimethylamino - propyl - 1) - 4H - thieno[2,3 - b][1,4]benzothiazine.
- a) (2 - nitro - thienyl - 3) - 2 - amino - 4 - methylmercapto - phenylsulphide.
- A total of 416 g of 3 - bromo - 2 -

nitrothiophene (melting point 81—83°) is added portionwise at 60° to a solution of 342 g of 2 - amino - 4 - methylmercapto - thiophenol (melting point 49—51°) and 80 g of sodium hydroxide in 1.5 litres of methanol and the mixture is then kept at 60° for half an hour. Cooling, filtration and drying are effected. After recrystallizing twice, each time from a 4-fold quantity of ethyl acetate, pure (2 - nitro - thienyl - 3) - 2 - amino - 4 - methylmercapto - phenyl - sulphide, having a melting point of 136—138°, is obtained.

- b) (2 - nitro - thienyl - 3) - 2 - acetamido - 4 - methylmercapto - phenyl - sulphide.
- 315 g of acetic anhydride are added dropwise during the course of 15 minutes to a boiling mixture of 457 g of (2 - nitro - thienyl - 3) - 2 - amino - 4 - methylmercapto - phenyl - sulphide in 1370 cc of toluene and boiling is subsequently effected for a further 15 minutes. After cooling well, filtration and washing out with toluene are effected. After crystallizing from a 25-fold quantity of acetone, pure (2 - nitro - thienyl - 3) - 2 - acetamido - 4 - methylmercapto - phenyl - sulphide, having a melting point of 177—179°, is obtained.

- c) 6 - methylmercapto - 4H - [2,3 - b][1,4]benzothiazine.

A mixture of 100 g of (2 - nitro - thienyl - 3) - 2 - acetamido - 4 - methylmercapto - phenyl - sulphide, 85 g of finely pulverized potassium carbonate, 5 g of copper bronze and 650 cc of dimethyl formamide is heated in a nitrogen gas stream at an oil bath temperature of 150° for one hour, i.e. until nitrogen monoxide evolution stops. The reaction mixture is poured on 2 litres of water whilst warm, is cooled, filtered off and dried. The crude material is extracted in a Soxhlet apparatus with 350 cc of ether for 3 hours. After evaporating the ether extract, the evaporation residue is recrystallized four times from chloroform. The resulting, pure 6 - methylmercapto - 4H - thieno[2,3 - b][1,4]benzothiazine has a melting point of 123—125°.

- d) 6 - methylmercapto - 4 - (3 - dimethylamino - propyl - 1) - 4H - thieno[2,3 - b][1,4]benzothiazine.

A mixture of 12.0 g of 6 - methylmercapto - 4H - thieno[2,3 - b][1,4]benzothiazine, 2.25 g of finely pulverized sodium amide and 50 cc of absolute xylene is heated to the boil at reflux for one hour at an oil bath temperature of 180° whilst stirring. A solution of 7.0 g of 3 - dimethylamino - 1 - chloropropane (boiling point 134—135°) in 10 cc of absolute xylene is added dropwise during the course of half an hour whilst boiling is continued and boiling is effected for a further 3 hours. After cooling, washing out is effected three times, each time with 30 cc

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of water and extraction is then effected with 150 cc of 15% aqueous tartaric acid solution. The tartaric acid extract is washed out three times, each time with 30 cc of benzene, is made alkaline with 45 cc of concentrated sodium hydroxide solution and the precipitated base is taken up in a total of 100 cc of benzene. After washing the benzene solution twice, each time with 30 cc of water, evaporation is effected and the crude base obtained as evaporation residue is distilled in a high vacuum. The main fraction which distils at 186—188° and 0.01 mm of Hg is collected and converted into the fumarate for further purification. 4.0 g of the evaporation residue and 1.45 g of fumaric acid are dissolved at the boil in 25 cc of absolute ethanol and the solution is cooled well. After recrystallizing from 20 cc of absolute ethanol, pure 6 - methylmercapto - 4 - (3 - dimethylamino - propyl - 1) - 4H - thieno[2,3-b][1,4]benzothiazine fumarate, having a melting point of 127—129°, is obtained.

EXAMPLE 6

6 - methylmercapto - 4 - [2 - (1 - methylpiperidyl - 2 - ethyl - 1) - 4H - thieno[2,3 - b][1,4]benzothiazine.

A mixture of 12.0 g of 6 - methylmercapto - 4H - thieno[2,3 - b][1,4]benzothiazine, [produced in a manner analogous to that indicated in Examples 5 a), b) and c)], 2.25 g of finely pulverized sodium amide and 50 cc of absolute xylene is heated to the boil at reflux at an oil bath temperature of 180° whilst stirring for one hour. A solution of 9.3 g of 2 - [1 - methyl - piperidyl - 2) - 1 - chloroethane (boiling point 84°/10 mm of Hg) in 10 cc of absolute xylene is added dropwise during the course of half an hour whilst boiling is continued and boiling is then continued for a further 3 hours. After cooling, washing out is effected three times, each time with 30 cc of water and extraction is then effected with 150 cc of 15% aqueous tartaric acid solution. The tartaric acid extract is washed out three times, each time with 30 cc of benzene, is made alkaline with 45 cc of concentrated sodium hydroxide solution and the precipitated base is taken up in a total of 100 cc of benzene. After washing the benzene solution twice, each time with 30 cc of water, evaporation is effected, whereby the crude base is obtained. The resulting crude base is purified by chromatography on a column of silica gel. 8.4 g of the crude base are dissolved in 50 cc of benzene and adsorbed on a column of 84 g of silica gel. The first 950 cc of benzene eluate and the following 850 cc of benzene + 1% methanol eluate are discarded. The following 600 cc of benzene + 1% methanol eluate are reduced in volume and converted into the benzenesulphonate. 5.89 g of the chromatogram evaporation residue and 2.60 g of

benzene-sulphonic acid are dissolved at the boil in 55 cc of absolute ethanol and the solution is subsequently cooled well. After recrystallizing from 75 cc of absolute ethanol, pure 6 - methylmercapto - 4 - [2 - (1 - methylpiperidyl - 2) - ethyl - 1] - 4H - thieno[2,3 - b][1,4]benzothiazine besylate, having a melting point of 143—145°, is obtained.

EXAMPLE 7

6 - chloro - 4 - [2 - (1 - methylpiperidyl - 2) - ethyl - 1] - 4H - thieno[2,3 - b][1,4]benzothiazine.

A mixture of 15.0 g of 6 - chloro - 4H - thieno[2,3 - b][1,4]benzothiazine, 2.93 g of finely pulverized sodium amide and 80 cc of absolute toluene is heated to the boil at reflux at an oil bath temperature of 150° whilst stirring for one hour. Cooling is subsequently effected to an internal temperature of 50° and a solution of 12.1 g of 2 - (1 - methylpiperidyl - 2) - 1 - chloroethane (boiling point 84°/10 mm of Hg) in 15 cc of absolute toluene is added dropwise during the course of half an hour. Heating is then effected to an oil bath temperature of 110° for 3 hours, cooling is effected and the reaction mixture is washed out three times, each time with 25 cc of water. The toluene solution is extracted with 200 cc of 15% aqueous tartaric acid solution and the extract is washed out thrice, each time with 50 cc of benzene. After making alkaline with 50 cc of concentrated sodium hydroxide solution the precipitated base is extracted with 150 cc of benzene. The benzene solution is washed out with 60 cc of water, is evaporated and the residue is distilled in a high vacuum. The main fraction which distils at 218—221° and 0.02 mm of Hg is collected. The besylate is produced in that 16.4 g of the distillate and 7.45 g of benzenesulphonic acid are dissolved at the boil in 100 cc of absolute ethanol, filtration and cooling are effected. After crystallizing from 80 cc of absolute ethanol, pure 6 - chloro - 4 - [2 - (1 - methyl - piperidyl - 2) - ethyl - 1] - 4H - thieno[2,3 - b][1,4]benzothiazine besylate, having a melting point of 133—135°, is obtained.

EXAMPLE 8

7 - bromo - 4 - (3 - dimethylamino - propyl - 1) - 4H - thieno[2,3 - b][1,4]benzothiazine.

a) (2 - nitro - thienyl - 3) - 2 - acetamido - 5 - bromo - phenyl - sulphide.

100 cc of bromine are added dropwise at an internal temperature of 15—25° whilst stirring during the course of 45 minutes to a solution of 193 g of (2 - nitro - thienyl - 3) - 2 - acetamido - phenyl - sulphide in 800 cc of dimethyl formamide and stirring is subsequently effected for a further 1½ hours at the same temperature. The reaction mix-

ture is added whilst stirring well to a solution of 250 g of sodium pyrosulphite in 4 litres of water. The precipitated material is filtered off, washed out well with water and dried. After recrystallizing from 6-fold quantity by volume of acetone, pure (2 - nitrothienyl - 3) - 2 - acetamido - 5 - bromophenyl - sulphide, having a melting point of 178—180°, is obtained.

10 b) 7 - bromo - 4H - thieno[2,3 - b][1,4]benzothiazine.

A mixture of 60 g of (2 - nitro - thienyl - 3) - 2 - acetamido - 5 - bromo - phenyl - sulphide, 60.0 g of finely pulverized potassium carbonate, 3 g of copper bronze and 450 cc of dimethyl formamide is heated in a nitrogen gas stream at an oil bath temperature of 160° for 25 minutes, i.e. until nitrogen monoxide evolution stops. The reaction mixture is poured on 1.6 litres of water whilst warm, is cooled, filtered off and dried. The crude material is extracted in a Soxhlet apparatus with 350 cc of ether for 3 hours. After evaporating the ether extract, the evaporation residue is recrystallized once from chloroform and then from methanol. The resulting, pure 7 - bromo - 4H - thieno[2,3 - b][1,4]benzothiazine has an indefinite melting point: above 163° slow decomposition.

30 c) 7 - bromo - 4 - (3 - dimethylamino - propyl - 1) - 4H - thieno[2,3 - b][1,4]benzothiazine.

The condensation reaction and working up are effected in a manner analogous to that described in Example 7, whereby the following amounts are used: 9.0 g of 7 - bromo - 4H - thieno[2,3 - b][1,4]benzothiazine, 1.48 g of finely pulverized sodium amide, 55 cc of absolute toluene and 4.62 g of 3 - dimethylamino - 1 - chloropropane (boiling point 134—135°). The resulting crude base is distilled in a high vacuum and the main fraction which distils at 183—188° and 0.01 mm of Hg is collected. The maleate is produced in that 1.77 g of the distillate and 0.59 g of maleic acid are dissolved at the boil in 9 cc of absolute ethanol and the solution is cooled well. After recrystallizing from 6 cc of absolute ethanol, pure 7 - bromo - 4 - (3 - dimethylamino - propyl - 1) - 4H - thieno[2,3 - b][1,4]benzothiazine maleate, having a melting point of 115—117°, is obtained.

EXAMPLE 9

55 7 - bromo - 4 - [2 - (1 - methyl - piperidyl - 2) - ethyl - 1] - 4H - thieno[2,3 - b][1,4]benzothiazine.

The condensation reaction and working up are effected in a manner analogous to that described in Example 7, whereby the following amounts are used: 20.0 g of 7 - bromo - 4H - thieno[2,3 - b][1,4]benzothiazine (melting

point above 163°, slow decomposition), 3.3 g of finely pulverized sodium amide, 115 cc of absolute toluene and 13.7 g of 2 - (1 - methyl - piperidyl - 2) - 1 - chloroethane. The resulting crude base is distilled in a high vacuum and the main fraction which distils at 200—218° and 0.04 mm of Hg is collected. The production of the fumarate is effected in that 5.7 g of the distillate and 1.69 g of fumaric acid are dissolved at the boil in 30 cc of absolute ethanol and the solution is cooled well. After recrystallizing from 25 cc of 80% ethanol, pure 7 - bromo - 4 - [2 - (1 - methyl - piperidyl - 2) - ethyl - 1] 4H - thieno[2,3 - b][1,4]benzothiazine fumarate, having a melting point of 176—178°, is obtained.

EXAMPLE 10

4 - {3 - [1 - (2 - hydroxyethyl) - piperazinyl - 4] - propyl - 1} - 4H - thieno[2,3 - b][1,4]benzothiazine.

a) 3 - [1 - (2 - hydroxyethyl) - piperazinyl - 4] - 1 - chloropropane.

A mixture of 75 g of 1 - (2 - hydroxyethyl) - piperazine, 45.5 g of 1 - chloro - 3 - bromo - propane and 250 cc of benzene is heated to 40° whilst stirring for 24 hours. After cooling, the precipitated hydrobromide is filtered off and the filtrate is concentrated in a vacuum at a bath temperature of 40°, whereby the compound mentioned in the heading is obtained. 3 - [1 - (2 - hydroxyethyl) - piperazinyl - 4] - 1 - chloropropane dihydrochloride has a decomposition point of 218—222°.

b) 4 - {3 - [1 - (2 - hydroxyethyl) - piperazinyl - 4] - propyl - 1} - 4H - thieno[2,3 - b][1,4]benzothiazine.

A mixture of 30.0 g of 4H - thieno[2,3 - b][1,4]benzothiazine, 23.4 g of finely pulverized sodium hydroxide and 150 cc of toluene is boiled for half an hour whilst stirring at a bath temperature of 150° with a water separator and a solution of 36.2 g of 3 - [1 - (2 - hydroxyethyl) - piperazinyl - 4] - 1 - chloropropane in 25 cc of toluene is added dropwise during the course of half an hour. After boiling for a further 3 hours, cooling is effected, washing out is effected twice, each time with 50 cc of water and subsequently extraction is effected with 250 cc of 15% aqueous tartaric acid solution. The tartaric acid extract is washed out twice, each time with 50 cc of benzene, is made alkaline with 65 cc of concentrated sodium hydroxide solution and the precipitated base is extracted with 150 cc of benzene. After washing out the benzene extract with 50 cc of water, drying over potassium carbonate and evaporation are effected. The evaporation residue is distilled in a high vacuum and the main fraction which distils at 235—240° and 0.01 mm of Hg is collected. The

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fumarate is produced in that 16.28 g of the distillate and 10.85 g of fumaric acid are dissolved at the boil in 500 cc of absolute ethanol and the solution is then cooled well. After recrystallizing twice, each time from 500 cc of absolute ethanol, pure 4-{3-[1-(2-hydroxyethyl) - piperazinyl - 4] - propyl - 1} - 4H - thieno[2,3 - b][1,4]benzothiazine fumarate, having a melting point of 157—159°, results.

EXAMPLE 11

6 - chloro - 4 - {3 - [1 - (2 - hydroxyethyl) - piperazinyl - 4] - propyl} - 4H - thieno[2,3 - b][1,4]benzothiazine.

The condensation reaction and working up are effected in a manner analogous to that described in Example 10 b), whereby the following amounts are used: 20.0 g of 6-chloro - 4H - thieno[2,3 - b][1,4]benzothiazine, 13.4 g of finely pulverized sodium hydroxide, 150 cc of toluene and 20.7 g of 3 - [1 - (2 - hydroxyethyl) - piperazinyl - 4] - 1 - chloropropane. The resulting crude base is crystallized thrice, each time from 60 cc of acetone. Pure 6 - chloro - 4 - {3 - [1 - (2 - hydroxyethyl) - piperazinyl - 4] - propyl - 1} - 4H - thieno[2,3 - b][1,4]benzothiazine has a melting point of 105—107°.

EXAMPLE 12

7 - chloro - 4 - {3 - [1 - (2 - hydroxyethyl) - piperazinyl - 4] - propyl - 1} - 4H - thieno[2,3 - b][1,4]benzothiazine.

a) (2 - nitro - thienyl - 3) - 2 - amino - 5 - chlorophenyl - sulphide.

A total of 36.5 g of 3 - bromo - 2 - nitrothiophene is added portionwise at 60° to a solution of 28 g of 5,5' - dichloro - 2,2'-diamino - diphenyl - disulphide (melting point 109—111°) [production see Farrington and Warburton, Austral. Journ. of Chemistry, 8, 549 (1955), wherein, however, the compound is described as 2 - amino - 5 - chlorothiophenol] and 7.04 g of sodium hydroxide in 130 cc of methanol and the mixture is then kept at 60° for half an hour. Cooling, filtration and drying are effected. After recrystallizing twice, each time from a 4-fold quantity of ethylene chloride, pure (2 - nitrothienyl - 3) - 2 - amino - 5 - chlorophenylsulphide, having a melting point of 158—160°, is obtained.

b) (2 - nitro - thienyl - 3) - 2 - acetamido - 5 - chlorophenyl - sulphide.

10.8 g of acetic anhydride are added dropwise during the course of 5 minutes to a boiling mixture of 15.0 g of (2 - nitrothienyl - 3) - 2 - amino - 5 - chlorophenylsulphide in 45 cc of toluene and boiling is subsequently effected for one hour. After cooling well, filtration and washing out with

toluene are effected. After crystallizing from an 85-fold quantity of 80% ethanol, pure (2 - nitro - thienyl - 3) - 2 - acetamido - 5 - chlorophenyl - sulphide, having a melting point of 183—185°, is obtained.

c) 7 - chloro - 4H - thieno[2,3 - b][1,4]benzothiazine.

A mixture of 15.0 g of (2 - nitro - thienyl - 3) - 2 - acetamido - 5 - chloro - phenylsulphide, 15.0 g of finely pulverized potassium carbonate, 1 g of copper bronze and 120 cc of dimethyl formamide is heated in a nitrogen gas stream at an oil bath temperature of 150° for 15 minutes, i.e. until nitrogen monoxide evolution stops. The reaction mixture is poured on 500 cc of water whilst warm, is cooled, filtered off and dried. The crude material is extracted in a Soxhlet apparatus for 3½ hours with 600 cc of ether. After evaporating the ether extract, the residue is recrystallized once from chloroform and twice from methanol. The resulting, pure 7 - chloro - 4H - thieno[2,3 - b][1,4]benzothiazine has a melting point above 167° with slow decomposition (indefinite).

d) 7 - chloro - 4 - {3 - [1 - (2 - hydroxyethyl) - piperazinyl - 4] - propyl - 1} - 4H - thieno[2,3 - b][1,4]benzothiazine.

The condensation reaction and working up are effected in a manner analogous to that described in Example 10 b), whereby the following amounts are used; 20.0 g of 7 - chloro - 4H - thieno[2,3 - b][1,4]benzothiazine, 13.4 g of finely pulverized sodium hydroxide, 150 cc of toluene and 20.7 g of 3 - [1 - (2 - hydroxyethyl) - piperazinyl - 4] - 1 - chloropropane. The resulting crude base is chromatographed on a column of silica gel. 20 g of the base are dissolved in 100 cc of benzene and adsorbed on 400 g of silica gel. The first eluates, i.e. 900 cc of benzene eluate and 2000 cc of benzene + 5% methanol eluate, are discarded and the following 2000 cc of benzene + 5% methanol eluate are evaporated. The dimaleate is produced in that 6.35 g of the evaporation residue and 3.78 g of maleic acid are dissolved at the boil in 80 cc of absolute ethanol and the solution is subsequently cooled. After recrystallizing twice, each time from 80 cc of 90% ethanol, pure 7 - chloro - 4 - {3 - [1 - (2 - hydroxyethyl) - piperazinyl - 4] - propyl - 1} - 4H - thieno[2,3 - b][1,4]benzothiazine dimaleate, having a decomposition point of 162—164°, is obtained.

EXAMPLE 13

6 - methylmercapto - 4 - {3 - [1 - methylpiperazinyl - 4] - propyl - 1} - 4H - thieno[2,3 - b][1,4]benzothiazine.

A mixture of 17.5 g of 6 - methylmercapto - 4H - thieno[2,3 - b][1,4]benzothiazine, 3.26 g of finely pulverized sodium

amide and 100 cc of absolute xylene is heated to the boil at reflux at an oil bath temperature of 180° whilst stirring for one hour.

- 5 A solution of 13.8 g of 3 - (1 - methylpiperazinyl - 4) - 1 - chloropropane in 20 cc of absolute xylene is added dropwise during the course of half an hour whilst boiling is continued. Boiling at reflux is then effected for a further 3 hours. After cooling the reaction mixture is washed out twice, each time with 25 cc of water and is then extracted with 150 cc of 15% aqueous tartaric acid solution. The tartaric acid extract is washed out twice, each time with 15 25 cc of benzene, is made alkaline with 40 cc of concentrated sodium hydroxide solution and the precipitated base is extracted with 125 cc of benzene. After washing out the benzene solution with 50 cc of water, 20 the solution is evaporated and the residue distilled in a high vacuum. The main fraction which distils at 240—250° and 0.04 mm of Hg is collected. The dimaleate is produced in that 11.05 g of the distillate and 6.88 g of maleic acid are dissolved at the boil in 25 250 cc of absolute ethanol and the solution is then cooled. After crystallizing twice, each time from 350 cc of 90% ethanol, pure 6-methylmercapto - 4 - [3 - (1 - methylpiperazinyl - 4) - propyl - 1] - 4H - thieno[2,3 - b][1,4]benzothiazine dimaleate, having a decomposition point of 174—176°, is obtained.

EXAMPLE 14

- 35 6 - methoxy - 4 - (3 - dimethylamino - propyl - 1) - 4H - thieno[2,3-b][1,4]benzothiazine.
- a) (2 - nitro - thienyl - 3) - 2 - amino - 4 - methoxyphenyl - sulphide.
- 40 A total of 46.4 g of 3 - bromo - 2 - nitrothiophene (melting point 81—83°) is added portionwise at 60° to a mixture of 42.7 g of 3 - amino - 4 - mercapto - anisole hydrochloride and 17.93 g of sodium hydroxide in 330 cc of methanol and the mixture is 45 then kept at 60° for half an hour. Cooling, filtration and drying are effected. After recrystallizing twice, each time from a 4-fold quantity of chlorobenzene, pure (2 - nitrothienyl - 3) - 2 - amino - 4 - methoxyphenylsulphide, having a melting point of 164—165°, is obtained.
- b) (2 - nitro - thienyl - 3) - 2 - formamido - 4 - methoxyphenyl - sulphide.
- 55 A mixture of 61.2 g of (2 - nitro - thienyl - 3) - 2 - amino - 4 - methoxy - phenylsulphide and 350 cc of approximately 98% concentrated formic acid is boiled at reflux for half an hour. Cooling, filtration and drying are effected. After recrystallizing thrice, 60 each time from a 35-fold quantity of methyl-ethyl ketone, pure (2 - nitro - thienyl - 3) - 2 - formamido - 4 - methoxyphenyl - sul-

phide, having a decomposition point of 204°, is obtained.

- c) 6 - methoxy - 4H - thieno[2,3 - b][1,4]benzothiazine.

A mixture of 46.0 g of (2 - nitro - thienyl - 3) - 2 - formamido - 4 - methoxyphenylsulphide, 90.0 g of finely pulverized potassium carbonate, 2.5 g of copper bronze and 400 cc of dimethyl formamide is heated at an oil bath temperature of 130° for 35 minutes. The reaction mixture is poured on 2.0 litres of water whilst warm, is cooled, filtered off and dried. The crude material is boiled at reflux with 1.0 litre of chloroform for one hour, is filtered off and the filtrate is evaporated. 9 g of the evaporation residue are dissolved in 50 cc of chloroform and adsorbed on a column of 250 g of silica gel. The first 1000 cc of chloroform eluate are discarded and the following 1000 cc of chloroform eluate are evaporated. After crystallizing thrice from benzene, pure 6 - methoxy-4H - thieno[2,3 - b][1,4]benzothiazine, having a melting point of 131—133°, is obtained.

- d) 6 - methoxy - 4 - (3 - dimethylamino - propyl - 1) - 4H - thieno[2,3 - b][1,4]benzothiazine.

A mixture of 6.5 g of 6 - methoxy - 4H-thieno[2,3 - b][1,4]benzothiazine, 1.3 g of finely pulverized sodium amide and 65 cc of absolute toluene is heated to the boil at reflux at an oil bath temperature of 150° whilst stirring for one hour. A solution of 4.03 g of 3 - dimethylamino - 1 - chloropropane in 10 cc of absolute toluene is added dropwise during the course of half an hour whilst boiling is continued. Boiling at reflux is then effected for a further 3 hours. After cooling, the reaction mixture is washed out twice, each time with 15 cc of water, and is then extracted with 75 cc of 15% aqueous tartaric acid solution. The tartaric acid extract is washed out twice, each time with 15 cc of benzene, is made alkaline with 20 cc of concentrated sodium hydroxide solution and the precipitated base is extracted with 75 cc of benzene. After washing out the benzene layer with 25 cc of water, evaporation is effected and the residue is distilled in a high vacuum. The main fraction which distils at 185—188° and 0.02 mm of Hg is collected. The fumarate is produced in that 4.13 g of the distillate and 1.57 g of fumaric acid are dissolved at the boil in 20 cc of absolute ethanol and cooling is subsequently effected. After crystallizing from 60 cc of absolute ethanol, pure 6 - methoxy - 4 - (3 - dimethylamino - propyl - 1) - 4H-thieno[2,3 - b][1,4]benzothiazine fumarate, having a melting point of 143—147°, is obtained.

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EXAMPLE 15

6 - methylsulphinyl - 4 - (3 - dimethylamino - propyl - 1) - 4H - thieno[2,3 - b][1,4]benzothiazine.

- 5 a) 6 - methylsulphinyl - 4 - acetyl - 4H - thieno[2,3 - b][1,4]benzothiazine.

3.9 cc of hydrogen peroxide (35.6% by volume) are added dropwise whilst stirring for half an hour to a boiling solution of 10.0 g of 6 - methylmercapto - 4 - acetyl - 4H - thieno[2,3 - b][1,4]benzothiazine in 120 cc of ethanol and boiling is subsequently effected in a reflux condenser for a further 5 hours. 50 cc of water are added to the reaction mixture and evaporation in a vacuum is effected until ethanol no longer distils off. The evaporation residue is extracted with 100 cc of benzene, the benzene solution is washed out with 25 cc of water and concentrated in a vacuum. The 6 - methylsulphinyl - 4 - acetyl - 4H - thieno[2,3 - b][1,4]benzothiazine obtained as evaporation residue is further worked up without isolation.

- 25 b) 6 - methylsulphinyl - 4H - thieno[2,3 - b][1,4]benzothiazine.

A solution of 12.1 g of crude 6 - methylsulphinyl - 4 - acetyl - 4H - thieno[2,3 - b][1,4]benzothiazine and 8.03 g of potassium carbonate in 150 cc of 90% aqueous methanol is boiled at reflux at an oil bath temperature of 120° for 2 hours. After the addition of 50 cc of water, evaporation is effected in a vacuum until all the methanol has been distilled off. The precipitated material is filtered off, dried and crystallized twice, each time from 600 cc of ethanol. The resulting, pure 6 - methylsulphinyl - 4H - thieno[2,3 - b][1,4]benzothiazine has a melting point of 239—241°.

- 40 c) 6 - methylsulphinyl - 4 - (3 - dimethylamino - propyl - 1) - 4H - thieno[2,3 - b][1,4]benzothiazine.

The condensation reaction and working up are effected in a manner analogous to that described in Example 1, whereby the following amounts are used: 50.0 g of 6 - methylsulphinyl - 4H - thieno[2,3 - b][1,4]benzothiazine, 8.76 g of finely pulverized sodium amide, 500 cc of absolute toluene and 27.3 g of 3 - dimethylamino - 1 - chloropropane. The resulting crude base is chromatographed on a column of silica gel. 54.5 g of the base are dissolved in 250 cc of benzene and adsorbed on 760 g of silica gel. The first eluates, i.e. 1.8 litres of benzene and 14 litres of benzene+2% of methanol, are discarded and the following 6.6 litres of benzene+2% of methanol eluate are evaporated. The nadisylate is produced in that 8.5 g of the evaporation residue and 8.8 g of naphthalene - 1,5-disulphonic acid are dissolved at the boil in 50 cc of absolute ethanol and cooling is sub-

sequently effected. After crystallizing from 45 cc of ethanol, pure 6 - methylsulphinyl - 4 - (3 - dimethylamino - propyl - 1) - 4H - thieno[2,3 - b][1,4]benzothiazine nadisylate hydrate, having a melting point of 158—160°, is obtained.

EXAMPLE 16

6 - methylsulphonyl - 4 - (3 - dimethylamino - propyl - 1) - 4H - thieno[2,3 - b][1,4]benzothiazine.

- a) 2,2' - dinitro - 4,4' - dimethylsulphonyl - diphenyl - disulphide.

A mixture of 13.1 g of sodium sulphide, 3.21 g of sulphur powder and 95 cc of absolute ethanol is boiled at reflux for 2 hours. After cooling to 30° this solution is slowly added dropwise at approximately 80° to a solution of 47.13 g of 5 - methylsulphonyl - 2 - chloro - nitro - benzene in 800 cc of absolute ethanol. Subsequently boiling is effected for a further 2 hours. Cooling and filtration are effected and the moist residue is suspended in 800 cc of water. Filtration, washing and drying are effected. After recrystallizing thrice, each time from a 20-fold quantity of diethylene - glycol - monomethyl ether, pure 2,2' - dinitro - 4,4' - dimethylsulphonyl - diphenyl - disulphide, having a decomposition point of 274°, is obtained.

- b) 2,2' - diamino - 4,4' - dimethylsulphonyl - diphenyl - disulphide.

356 g of hydrazine hydrate are slowly added dropwise at reflux temperature to a mixture of 563 g of 2,2' - dinitro - 4,4' - dimethylsulphonyl - diphenyl - disulphide and 2420 cc of absolute ethanol. Boiling is subsequently effected for a further 5 hours. Cooling is effected, the pH value of the mixture is adjusted to 5.1 with approximately 625 cc of 10% hydrochloric acid solution, filtration and drying are effected. After recrystallizing four times from 80% aqueous ethanol (60—100-fold quantity), pure 2,2' - diamino - 4,4' - dimethylsulphonyl - diphenyl - disulphide, having a melting point of 196—197°, is obtained.

- c) (2 - nitro - thienyl - 3) - 2 - amino - 4 - methylsulphonyl - phenyl - sulphide.

A total of 173 g of 3 - bromo - 2 - nitrothiophene (melting point 81—83°) is added portionwise at 60° to a mixture of 168 g of 2,2' - diamino - 4,4' - dimethylsulphonyl - diphenyl - disulphide and 33.6 g of sodium hydroxide in 615 cc of methanol and the mixture is kept at 60° for a further half hour. Cooling, filtration and drying are effected. After recrystallizing four times, each time from a 25-fold quantity of chloro-benzene, pure (2 - nitro - thienyl - 3) - 2 - amino - 4 - methylsulphonyl - phenyl - sulphide, having a decomposition point of 182°, is obtained.

d) (2 - nitro - thienyl - 3) - 2 - formamido - 4 - methylsulphonyl - phenylsulphide.

A mixture of 165.2 g of (2 - nitro - thienyl - 3) - 2 - amino - 4 - methylsulphonyl - phenylsulphide and 250 cc of approximately 98% concentrated formic acid is boiled at reflux for half an hour. Cooling, filtration and drying are effected. After recrystallizing twice, each time from a 6-fold quantity of diethylene-glycol-monomethylether, pure (2 - nitro - thienyl - 3) - 2 - formamido - 4 - methylsulphonyl - phenyl - sulphide, having a decomposition point of 217°, is obtained.

e) 6 - methylsulphonyl - 4H - thieno[2,3-b][1,4]benzothiazine.

A mixture of 20.0 g of (2 - nitro - thienyl - 3) - 2 - formamido - 4 - methylsulphonyl - phenyl - sulphide, 60.0 g of finely pulverized potassium carbonate, 1.5 g of copper bronze and 200 cc of dimethyl formamide is heated in a nitrogen gas stream in an oil bath to 100° for 20 minutes, to 120° for 15 minutes and to 140° for half an hour. The reaction mixture is poured on 1 litre of water whilst warm, is cooled, filtered off and dried. The crude material is boiled at reflux with 300 cc of chloroform for one hour, is filtered off and the filtrate is evaporated. Crystallization is effected twice from chloroform and once from isopropanol. The resulting, pure 6 - methylsulphonyl - 4H - thieno[2,3 - b][1,4]benzothiazine has a melting point of 203—205°.

f) 6 - methylsulphonyl - 4 - (3 - dimethylamino - propyl - 1) - 4H - thieno[2,3-b][1,4]benzothiazine.

The condensation reaction and working up are effected in a manner analogous to that described in Example 1, whereby the following amounts are used: 10.0 g of 6 - methylsulphonyl - 4H - thieno[2,3 - b][1,4]benzothiazine, 1.65 g of finely pulverized sodium amide, 100 cc of absolute toluene and 5.15 g of 3 - dimethylamino - 1 - chloropropane. The resulting crude base is chromatographed on a column of silica gel. 5.89 g of the crude base are dissolved in 40 cc of benzene and adsorbed on 120 g of silica gel. The first eluates, i.e. 375 cc of benzene and 1600 cc of benzene + 2.5% of methanol are discarded and the following 1750 cc of benzene + 2.5% of methanol and 375 cc of benzene + 5% of methanol eluates are evaporated.

The maleate is produced in that 2.64 g of the evaporation residue and 0.87 g of maleic acid are dissolved at the boil in 20 cc of absolute ethanol. After crystallizing from 20 cc of absolute ethanol, pure 6 - methylsulphonyl - 4 - (3 - dimethylamino - propyl - 1) - 4H - thieno[2,3 - b][1,4]benzothiazine maleate, having a melting point of 126—128°, is obtained.

EXAMPLE 17

6 - trifluoromethyl - 4 - [2 - (1 - methylpiperidyl - 2) - ethyl - 1] - 4H - thieno[2,3 - b][1,4]benzothiazine.

a) 2,2' - diamino - 4,4' - ditrifluoromethyl - diphenyl - disulphide.

323 g of hydrazine hydrate are slowly added dropwise at reflux temperature to a mixture of 488.76 g of 2,2' - dinitro - 4,4' - ditrifluoromethyl - diphenyl - disulphide and 900 cc of absolute ethanol. Boiling is subsequently effected for a further 5 hours. The reaction solution is evaporated in a water jet vacuum at a bath temperature of 80°, 900 cc of water are added to the residue and extraction is effected with a total of 1500 cc of chloroform. After washing out the chloroform solution with 200 cc of water, the solution is evaporated and the evaporation residue is distilled in a high vacuum. The main fraction which distils at 140—156° and 0.02 mm of Hg is collected. After recrystallizing 4 times, each time from a 15-fold quantity of n-hexane, pure 2,2' - diamino - 4,4' - ditrifluoromethyl - diphenyl - disulphide, having a melting point of 77—78°, is obtained.

b) (2 - nitro - thienyl - 3) - 2 - amino - 4 - trifluoromethylphenyl - sulphide.

A total of 235 g of 3 - bromo - 2 - nitrothiophene (melting point 81—83°) is added portionwise at 60° to a solution of 217.7 g of 2,2' - diamino - 4,4' - ditrifluoromethyl - diphenyl - disulphide and 45.2 g of sodium hydroxide in 1100 cc of methanol and the mixture is then kept at 60° for half an hour. Cooling, filtration and drying are effected. After recrystallizing thrice, each time from a 10-fold quantity of 80% aqueous ethanol, pure (2 - nitro - thienyl - 3) - 2 - amino - 4 - trifluoromethyl - phenyl - sulphide, having a melting point of 146—147°, is obtained.

c) (2 - nitro - thienyl - 3) - 2 - formamido - 4 - trifluoromethyl - phenylsulphide.

A mixture of 200 g of (2 - nitro - thienyl - 3) - 2 - amino - 4 - trifluoromethyl - phenylsulphide and 267 cc of approximately 98% concentrated formic acid is boiled at reflux for 2 hours. Cooling, filtration and drying are effected. After recrystallizing thrice, each time from a 10-fold quantity of 4 - methylpentanol - (2), pure (2 - nitro - thienyl - 3) - 2 - formamido - 4 - trifluoromethyl - phenyl - sulphide, having a decomposition point of 192°, is obtained.

d) 6 - trifluoromethyl - 4H - thieno[2,3-b][1,4]benzothiazine.

A solution of 35.0 g of (2 - nitro - thienyl - 3) - 2 - formamido - 4 - trifluoromethyl -

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phenyl - sulphide in 100 cc of dimethyl formamide is added dropwise at an internal temperature of 140° to a mixture of 90.0 g of finely pulverized potassium carbonate, 2.0 g of copper bronze and 150 cc of dimethyl formamide whilst stirring for 20 minutes and the mixture is immediately poured on 1.0 litre of water whilst warm. Cooling, filtration and drying are effected. The crude material is boiled at reflux with 500 cc of chloroform for half an hour, is filtered off and the filtrate is evaporated. After recrystallizing thrice from chloroform, pure 6 - trifluoromethyl - 4H - thieno[2,3 - b][1,4]benzothiazine, having a melting point of 162—164°, is obtained.

e) 6 - trifluoromethyl - 4 - [2 - (1 - methylpiperidyl - 2) - ethyl - 1] - 4H - thieno[2,3 - b][1,4]benzothiazine.

The condensation reaction and working up are effected in a manner analogous to that described in Example 1, whereby the following amounts are used: 12.0 g of 6 - trifluoromethyl - 4H - thieno[2,3 - b][1,4]benzothiazine, 2.06 g of finely pulverized sodium amide, 100 cc of absolute toluene and 8.52 g of 2 - (1 - methyl - piperidyl - 2) - 1 - chloroethane. The resulting crude base is distilled in a high vacuum. The main fraction which distils at 140—150° and 0.02 mm of Hg is collected. The besylate is produced in that 2.07 g of the distillate and 0.86 g of benzenesulphonic acid are dissolved at the boil in 15 cc of absolute ethanol and cooling is then effected. After crystallizing from 10 cc of absolute ethanol, pure 6 - trifluoromethyl - 4 - [2 - (1 - methylpiperidyl - 2) - ethyl - 1] - 4H - thieno[2,3 - b][1,4]benzothiazine besylate, having a melting point of 148—150°, is obtained.

EXAMPLE 18

6 - cyano - 4 - [2 - methyl - piperidyl - 2) - ethyl - 1] - 4H - thieno[2,3 - b][1,4]benzothiazine.

a) (2 - nitro - thienyl - 3) - 2 - amino - 4 - cyanophenyl - sulphide.

150 cc of concentrated hydrochloric acid are added to 16.9 g of the zinc salt of 2,2'-diamino - 4,4' - dicyano - diphenyl - disulphide at room temperature. After filtering off, washing out and drying are effected. A total of 16.9 g of 3 - bromo - 2 - nitrothiophene (melting point 81—83°) is added portionwise at 60° to a mixture of 15.19 g of the resulting 3 - amino - 4 - mercaptobenzonitrile hydrochloride (melting point above 350°), 6.55 g of sodium hydroxide and 120 cc of methanol. The mixture is kept at 60° for a further half hour. Cooling, filtration and drying are effected. After recrystallizing four times, each time from a 17-fold quantity of chlorobenzene, pure (2 -

nitro - thienyl - 3) - 2 - amino - 4 - cyanophenyl - sulphide, having a decomposition point of 214°, is obtained.

b) (2 - nitro - thienyl - 3) - 2 - formamido - 4 - cyanophenyl - sulphide.

A mixture of 138.7 g of (2 - nitro - thienyl - 3) - 2 - amino - 4 - cyanophenyl - sulphide and 950 cc of approximately 98% concentrated formic acid is boiled at reflux for half an hour. Cooling, filtration and drying are effected. After recrystallizing twice, each time from a 40-fold quantity of methylisobutyl ketone, pure (2 - nitro - thienyl - 3) - 2 - formamido - 4 - cyanophenyl - sulphide, having a decomposition point of 213°, is obtained.

c) 6 - cyano - 4H - thieno[2,3 - b][1,4]benzothiazine.

A mixture of 30.0 g of (2 - nitro - thienyl - 3) - 2 - formamido - 4 - cyanophenyl - sulphide, 90.0 g of finely pulverized potassium carbonate, 2.0 g of copper bronze and 250 cc of dimethyl formamide is kept in a nitrogen gas stream at an oil bath temperature of 60° for 1 hour 45 minutes and then at an oil bath temperature of 130° for 45 minutes. The reaction mixture is poured on 1.5 litres of water whilst warm. Cooling, filtration and drying are effected. The crude material is boiled at reflux with 500 cc of chloroform for 2 hours, is filtered off and the filtrate is evaporated. After crystallizing thrice from chloroform, recrystallization is effected once more from benzene, whereby the pure 6 - cyano - 4H - thieno[2,3 - b][1,4]benzothiazine, having a melting point of 160—162°, is obtained.

d) 6 - cyano - 4 - [2 - (1 - methylpiperidyl - 2) - ethyl - 1] - 4H - thieno[2,3 - b][1,4]benzothiazine.

The condensation reaction and working up are effected in a manner analogous to that described in Example 1, whereby the following amounts are used: 15.0 g of 6 - cyano - 4H - thieno[2,3 - b][1,4]benzothiazine, 3.05 g of finely pulverized sodium amide, 150 cc of absolute toluene and 12.62 g of 2 - (1 - methyl - piperidyl - 2) - 1 - chloroethane, 18.9 g of the resulting crude base are crystallized from 90 cc of acetone with the addition of 1 g of charcoal. After crystallizing twice more, each time from 80 cc of acetone, pure 6 - cyano - 4 - [2 - (1 - methyl - piperidyl - 2) - ethyl - 1] - 4H - thieno[2,3 - b][1,4]benzothiazine, having a melting point of 121—123°, is obtained.

EXAMPLE 19

6 - methylsulphonyl - 4 - [2 - (1 - methylpiperidyl - 2) - ethyl - 1] - 4H - thieno[2,3 - b][1,4]benzothiazine.

The condensation reaction and working up

are effected in a manner analogous to that described in Example 14, whereby the following amounts are used: 25.0 g of 6-methylsulphinyl - 4H - thieno[2,3 - b][1,4] benzothiazine, 4.38 g of finely pulverized sodium amide, 350 cc of absolute toluene and 18.1 g of 2 - (1 - methylpiperidyl - 2) - 1 - chloroethane. The resulting crude base is chromatographed on a column of silica gel. 35.4 g of the base are dissolved in 150 cc of benzene and adsorbed on 700 g of silica gel. The first eluates, i.e. 2.8 litres of benzene, 10.4 litres of benzene+2% of methanol and 3.6 litres of benzene+5% of methanol, are discarded and the following 5.2 litres of benzene+5% of methanol eluate are evaporated.

The besylate is produced in that 13.46 g of the evaporation residue and 5.7 g of benzenesulphonic acid are dissolved at the boil in 75 cc of absolute ethanol and cooling is then effected. After crystallizing from 100 cc of absolute ethanol, pure 6 - methylsulphinyl - 4 - [2 - (1 - methyl - piperidyl - 2) - ethyl - 1] - 4H - thieno[2,3 - b][1,4]benzothiazine besylate, having a melting point of 158—160°, is obtained.

EXAMPLE 20

6 - chloro - 4 - [2 - methyl - 3 - (4-hydroxy - piperidyl - 1) - propyl - 1] - 4H - thieno[2,3 - b][1,4] benzothiazine.

a) 6 - chloro - 4 - (2 - methyl - 3 - chloropropyl - 1) - 4H - thieno[2,3 - b][1,4] benzothiazine.

100 g of 6 - chloro - 4H - thieno[2,3 - b][1,4]benzothiazine, 19.6 g of finely pulverized sodium amide and 500 cc of absolute toluene are heated to the boil at reflux at an oil bath temperature of 150° whilst stirring for one hour. Cooling is then effected to an internal temperature of 50° and a solution of 89.5 g of 2 - methyl - 1 - chloro - 3-bromopropane in 100 cc of absolute toluene is added dropwise during the course of one hour. After the dropwise addition, the reaction mixture is heated for half an hour in an oil bath at 120° and for half an hour in an oil bath at 145° and is then cooled. After washing out thrice, each time with 100 cc of water, concentration is effected in a water jet vacuum at a final bath temperature of 90°. The crude 6 - chloro - 4 - (2 - methyl - 3 - chloropropyl - 1) - 4H - thieno[2,3 - b][1,4]benzothiazine obtained as evaporation residue is worked up further as such.

b) 6 - chloro - 4 - [2 - methyl - 3 - (4-hydroxy - piperidyl - 1) - propyl - 1] - 4H - thieno[2,3 - b][1,4]benzothiazine. A mixture of 103 g of crude 6 - chloro -

4 - (2 - methyl - 3 - chloropropyl - 1) - 4H - thieno[2,3 - b][1,4]benzothiazine, 63.0 g of 4-hydroxypiperidine, 64.7 g of finely pulverized potassium carbonate and 500 cc of xylene is heated to the boil at reflux at an oil bath temperature of 180° whilst stirring for 20 hours. After cooling, washing out is effected with 400 cc of water and then extraction is effected with 700 cc of 15% aqueous tartaric acid solution. The tartaric acid extract is washed out twice, each time with 100 cc of benzene, and is made alkaline with 175 cc of concentrated sodium hydroxide solution. The precipitated oily base is taken up in 400 cc of benzene, the benzene layer is washed out twice, each time with 75 cc of water, is evaporated and the evaporation residue is distilled in a high vacuum. The main fraction which distils at 225—232° and 0.04 mm of Hg is collected. The maleate is produced in that 10.7 g of the distillate and 3.3 g of maleic acid are dissolved at the boil in 65 cc of absolute ethanol and cooling is then effected. After crystallizing from 50 cc of absolute ethanol, pure 6 - chloro - 4 - [2 - methyl - 3 - (4-hydroxy - piperidyl - 1) - propyl - 1] - 4H - thieno[2,3 - b][1,4]benzothiazine maleate, having a melting point of 137—140°, is obtained.

EXAMPLE 21

6 - bromo - 4 - {3 - [1 - (2 - hydroxyethyl) - piperazinyl - 4] - propyl - 1} - 4H - thieno[2,3 - b][1,4]benzothiazine.

a) 2,2' - diamino - 4,4' - dibromo - diphenyl - disulphide.

133.1 g of hydrazine hydrate are slowly added dropwise at reflux temperature to a mixture of 195.8 g of 2,2' - dinitro - 4,4' - dibromo - diphenyl - disulphide and 1960 cc of absolute ethanol. Boiling is subsequently effected for a further 5 hours and the reaction solution is then evaporated in a water jet vacuum at a bath temperature of 60°. The residue is recrystallized once from a 90-fold quantity of 80% aqueous ethanol and then thrice, each time from an 8-fold quantity of isopropyl alcohol. Pure 2,2' - diamino - 4,4' - dibromo - diphenyl - disulphide has a melting point of 136—138°.

b) (2 - nitro - thienyl - 3) - 2 - amino - 4 - bromophenyl - sulphide.

A total of 62.4 g of 3 - bromo - 2 - nitrothiophene (melting point 81—83°) are added portionwise at 60° to a mixture of 60.9 g of 2,2' - diamino - 4,4' - dibromo - diphenyl - disulphide and 12.9 g of sodium hydroxide in 220 cc of methanol and the mixture is then kept at 60° for half an hour. Cooling, filtration and drying are effected. After recrystallizing thrice, each time

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from a 9-fold quantity of trichloroethylene, pure (2 - nitro - thienyl - 3) - 2 - amino - 4 - bromophenyl - sulphide, having a melting point of 163—165°, is obtained.

- 5 c) (2 - nitro - thienyl - 3) - 2 - formamido - 4 - bromophenyl - sulphide.

A mixture of 106 g of (2 - nitro - thienyl - 3) - 2 - amino - 4 - bromophenyl - sulphide and 550 cc of approximately 98% concentrated formic acid is boiled at reflux for half an hour. Cooling, filtration and drying are effected. After recrystallizing twice, each time from a 45-fold quantity of chlorobenzene, pure (2 - nitro - thienyl - 3) - 2 - formamido - 4 - bromophenyl - sulphide, having a decomposition point of 238°, is obtained.

- d) 6 - bromo - 4H - thieno[2,3 - b][1,4] benzothiazine.

A mixture of 7.5 g of (2 - nitro - thienyl - 3) - 2 - formamido - 4 - bromophenyl - sulphide, 13.0 g of finely pulverized potassium carbonate, 0.5 g of copper bronze and 80 cc of dimethyl formamide is heated in a nitrogen gas stream at an oil bath temperature of 120° for 10 minutes. The reaction mixture is poured on 0.5 litres of water whilst warm, is cooled, filtered off and dried. The crude material is boiled at reflux with 150 cc of chloroform for one hour, is filtered off and the filtrate is evaporated. After crystallizing from chloroform and then twice from isopropanol, pure 6 - bromo - 4H - thieno[2,3 - b][1,4]benzothiazine, having a melting point of 170—172°, is obtained.

- e) 6 - bromo - 4 - {3 - [1 - (2 - hydroxyethyl - piperazinyl - 4) - propyl - 1] - 4H - thieno[2,3 - b][1,4]benzothiazine.

7.0 g of 6 - bromo - 4H - thieno[2,3 - b][1,4]benzothiazine, 3.94 g of finely pulverized sodium hydroxide and 50 cc of toluene are heated to the boil at reflux with a water separator at an oil bath temperature of 150° whilst stirring for half an hour. A solution of 6.1 g of 3 - [1 - (2 - hydroxyethyl) - piperazinyl - 4] - 1 - chloropropane in 10 cc of toluene is then added dropwise during the course of half an hour and heating is effected for a further 3 hours. After cooling, washing out is effected twice, each time with 10 cc of water, and extraction is subsequently effected with 50 cc of 15% aqueous tartaric acid solution. After washing the tartaric acid extract twice, each time with 10 cc of benzene, it is made alkaline with 15 cc of concentrated sodium hydroxide solution and the precipitated oily base is taken up in a total of 100 cc of benzene. The

benzene solution is washed twice, each time with 15 cc of water, is evaporated and the evaporation residue is chromatographed on a column of silica gel. 1.78 g of the evaporation residue are dissolved in 10 cc of benzene and adsorbed on 35 g of silica gel. The first eluates, i.e. 250 cc of benzene, 600 cc of benzene+2% of methanol and 150 cc of benzene+5% of methanol, are discarded and the following 250 cc of benzene+5% methanol and 325 cc of benzene+10% of methanol eluates are evaporated.

The dimaleate is produced in that 0.32 g of the evaporation residue and 0.172 g of maleic acid are dissolved at the boil in 10 cc of absolute ethanol and cooling is then effected. After crystallizing from 13 cc of absolute ethanol, pure 6 - bromo - 4 - {3 - [1 - (2 - hydroxyethyl) - piperazinyl - 4] - propyl - 1} - 4H - thieno[2,3 - b][1,4]benzothiazine dimaleate, having a decomposition point of 157—159°, is obtained.

EXAMPLE 22

- 6 - trifluoromethyl - 4 - {3 - [1 - (2 - hydroxyethyl) - piperazinyl - 4] - propyl - 1} - 4H - thieno[2,3 - b][1,4]benzothiazine.

The condensation reaction and working up are effected in a manner analogous to that described in Example 21, whereby the following amounts are used: 20.0 g of 6 - trifluoromethyl - 4H - thieno[2,3 - b][1,4]benzothiazine, 11.7 g of finely pulverized sodium hydroxide, 120 cc of toluene and 18.2 g of 3 - [1 - (2 - hydroxyethyl) - piperazinyl - 4] - 1 - chloropropane. The crude material is chromatographed on a column of silica gel. 16.8 g of the base are dissolved in 100 cc of benzene and adsorbed on 325 g of silica gel. The first eluates, i.e. 750 cc of benzene and 4250 cc of benzene+2% of methanol, are discarded and the following 3.2 litres of benzene+2% methanol and 2.7 litres of benzene+4% methanol eluates are evaporated.

The dimaleate is produced in that 12.36 g of the evaporation residue and 6.77 g of maleic acid are dissolved at the boil in 120 cc of absolute ethanol and cooling is then effected. After crystallizing from 500 cc of absolute ethanol, pure 6 - trifluoromethyl - 4 - {3 - [1 - (2 - hydroxyethyl) - piperazinyl - 4] - propyl - 1} - 4H - thieno[2,3 - b][1,4]benzothiazine dimaleate, having a decomposition point of 163—165°, is obtained.

WHAT WE CLAIM IS:—

1. A process for the production of thienobenzothiazine derivatives of formula I,

from a 9-fold quantity of trichloroethylene, pure (2 - nitro - thienyl - 3) - 2 - amino - 4 - bromophenyl - sulphide, having a melting point of 163—165°, is obtained.

- 5 c) (2 - nitro - thienyl - 3) - 2 - formamido - 4 - bromophenyl - sulphide.

A mixture of 106 g of (2 - nitro - thienyl - 3) - 2 - amino - 4 - bromophenyl - sulphide and 550 cc of approximately 98% concentrated formic acid is boiled at reflux for half an hour. Cooling, filtration and drying are effected. After recrystallizing twice, each time from a 45-fold quantity of chlorobenzene, pure (2 - nitro - thienyl - 3) - 2 - formamido - 4 - bromophenyl - sulphide, having a decomposition point of 238°, is obtained.

- 20 d) 6 - bromo - 4H - thieno[2,3 - b][1,4] benzothiazine.

A mixture of 7.5 g of (2 - nitro - thienyl - 3) - 2 - formamido - 4 - bromophenyl - sulphide, 13.0 g of finely pulverized potassium carbonate, 0.5 g of copper bronze and 80 cc of dimethyl formamide is heated in a nitrogen gas stream at an oil bath temperature of 120° for 10 minutes. The reaction mixture is poured on 0.5 litres of water whilst warm, is cooled, filtered off and dried. The crude material is boiled at reflux with 150 cc of chloroform for one hour, is filtered off and the filtrate is evaporated. After crystallizing from chloroform and then twice from isopropanol, pure 6 - bromo - 4H - thieno[2,3 - b][1,4]benzothiazine, having a melting point of 170—172°, is obtained.

- 40 e) 6 - bromo - 4 - {3 - [1 - (2 - hydroxyethyl - piperazinyl - 4) - propyl - 1] - 4H - thieno[2,3 - b][1,4]benzothiazine.

7.0 g of 6 - bromo - 4H - thieno[2,3-b][1,4]benzothiazine, 3.94 g of finely pulverized sodium hydroxide and 50 cc of toluene are heated to the boil at reflux with a water separator at an oil bath temperature of 150° whilst stirring for half an hour. A solution of 6.1 g of 3 - [1 - (2 - hydroxyethyl) - piperazinyl - 4] - 1 - chloropropane in 10 cc of toluene is then added dropwise during the course of half an hour and heating is effected for a further 3 hours. After cooling, washing out is effected twice, each time with 10 cc of water, and extraction is subsequently effected with 50 cc of 15% aqueous tartaric acid solution. After washing the tartaric acid extract twice, each time with 10 cc of benzene, it is made alkaline with 15 cc of concentrated sodium hydroxide solution and the precipitated oily base is taken up in a total of 100 cc of benzene. The

benzene solution is washed twice, each time with 15 cc of water, is evaporated and the evaporation residue is chromatographed on a column of silica gel. 1.78 g of the evaporation residue are dissolved in 10 cc of benzene and adsorbed on 35 g of silica gel. The first eluates, i.e. 250 cc of benzene, 600 cc of benzene+2% of methanol and 150 cc of benzene+5% of methanol, are discarded and the following 250 cc of benzene+5% methanol and 325 cc of benzene+10% of methanol eluates are evaporated.

The dimaleate is produced in that 0.32 g of the evaporation residue and 0.172 g of maleic acid are dissolved at the boil in 10 cc of absolute ethanol and cooling is then effected. After crystallizing from 13 cc of absolute ethanol, pure 6 - bromo - 4 - {3 - [1 - (2 - hydroxyethyl) - piperazinyl - 4] - propyl - 1} - 4H - thieno[2,3 - b][1,4]benzothiazine dimaleate, having a decomposition point of 157—159°, is obtained.

EXAMPLE 22

6 - trifluoromethyl - 4 - {3 - [1 - (2 - hydroxyethyl) - piperazinyl - 4] - propyl - 1} - 4H - thieno[2,3-b][1,4]benzothiazine.

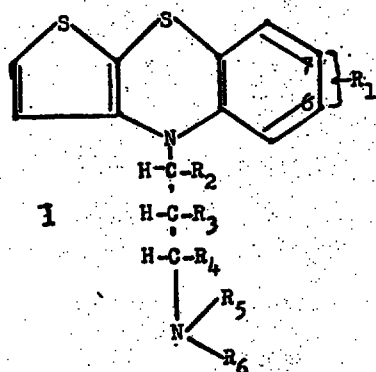
The condensation reaction and working up are effected in a manner analogous to that described in Example 21, whereby the following amounts are used: 20.0 g of 6 - trifluoromethyl - 4H - thieno[2,3 - b][1,4]benzothiazine, 11.7 g of finely pulverized sodium hydroxide, 120 cc of toluene and 18.2 g of 3 - [1 - (2 - hydroxyethyl) - piperazinyl - 4] - 1 - chloropropane. The crude material is chromatographed on a column of silica gel. 16.8 g of the base are dissolved in 100 cc of benzene and adsorbed on 325 g of silica gel. The first eluates, i.e. 750 cc of benzene and 4250 cc of benzene+2% of methanol, are discarded and the following 3.2 litres of benzene+2% methanol and 2.7 litres of benzene+4% methanol eluates are evaporated.

The dimaleate is produced in that 12.36 g of the evaporation residue and 6.77 g of maleic acid are dissolved at the boil in 120 cc of absolute ethanol and cooling is then effected. After crystallizing from 500 cc of absolute ethanol, pure 6 - trifluoromethyl - 4 - {3 - [1 - (2 - hydroxyethyl) - piperazinyl - 4] - propyl - 1} - 4H - thieno[2,3 - b][1,4]benzothiazine dimaleate, having a decomposition point of 163—165°, is obtained.

WHAT WE CLAIM IS:—

1. A process for the production of thienobenzothiazine derivatives of formula I,





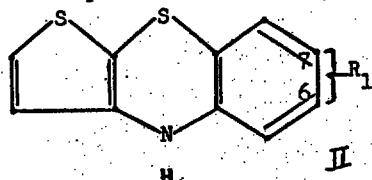
in which (i) R_1 signifies a hydrogen, chlorine or bromine atom, an alkoxy, alkylmercapto, alkylsulphonyl, or alkylsulphanyl radical, each having from 1 to 4 carbon atoms inclusive, an aliphatic acyl radical having from 2 to 4 carbon atoms inclusive, the trifluoromethyl or the cyano radical,

R_2 signifies a hydrogen atom, each of R_3 and R_4 signifies a hydrogen atom or the methyl radical, and each of R_5 and R_6 signifies an alkyl radical having from 1 to 4 carbon atoms inclusive, or R_5 and R_6 together with the nitrogen atom form a piperidino radical which may be substituted in the 4-position by a hydroxy radical, or a piperazino radical which may be substituted on the second nitrogen atom by an alkyl radical having from 1 to 4 carbon atoms inclusive or by a 2-hydroxyethyl radical, or

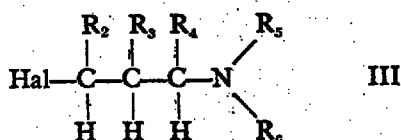
(ii) R_5 signifies an alkyl radical having from 1 to 4 carbon atoms inclusive, R_5 together with R_6 signifies a trimethylene chain, and R_1 , R_2 and R_4 are as defined at (i) above,

(iii) R_4 together with R_6 signifies a trimethylene or tetramethylene chain, and R_1 , R_2 and R_3 are as defined at (i) above, and

and their acid addition salts, characterized in that a compound of formula II,



in which R_1 has the above significance, is condensed with a compound of formula III,

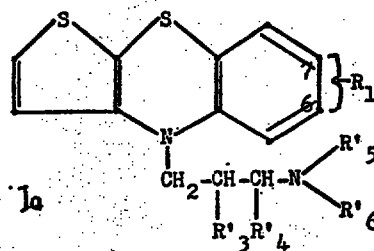


in which R_2 to R_6 have the above significance, and

Hal signifies a chlorine, bromine or iodine atom,

in the presence of an inert organic solvent and an acid binding agent and, when an acid addition salt is required, the resulting compound of formula I is reacted with an organic or inorganic acid.

2. A process for the production of compounds of formula Ia,

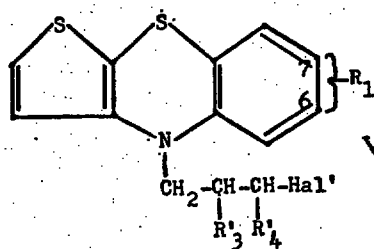


in which R_1 has the significance stated in Claim 1,

R_5 and R_6 signify hydrogen or methyl, and

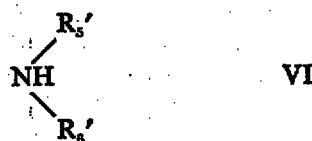
each of R_5 and R_6 signifies an alkyl radical having from 1 to 4 carbon atoms inclusive, or R_5 and R_6 together with the nitrogen atom form a piperidino radical which may be substituted in the 4-position by a hydroxy radical, or a piperazino radical which may be substituted on the second nitrogen atom by an alkyl radical having from 1 to 4 carbon atoms inclusive or by a 2-hydroxyethyl radical,

and their acid addition salts, characterized in that a compound of formula V,



in which R_1 , R_5 and R_6 have the above significance, and

Hal signifies a chlorine or bromine atom, is condensed with a compound of formula VI,



in which R_5 and R_6 have the above significance, advantageously in the presence of an alkaline



* C L M S *

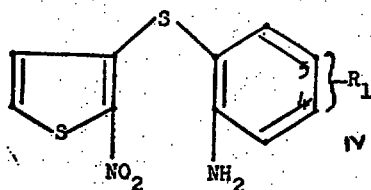
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condensation agent and in an inert organic solvent, e.g. a suspension of an alkali metal carbonate in an aromatic hydrocarbon, and, when an acid addition salt is required, the resulting compound of formula Ia is reacted with an organic or inorganic acid.

3. A process according to Claim 2, in which the compound of formula V is produced by reacting a compound of formula II as stated in Claim 1 with 1 - chloro-3 - bromo - propane or 1 - bromo - 3-iodopropane optionally substituted by one or two methyl radicals in the presence of an alkaline condensation agent is an inert organic solvent.

4. A process according to Claim 1 and 3 in which the compound of formula II is produced by condensing an appropriate 2-amino - thiophenol or its alkali metal salt with 3 - bromo - 2 - nitro - thiophene and heating the resulting compound of formula IV,



in which R₁ has the significance stated in Claim 1,

preferably after acylation of the primary amino group, in a suspension of potassium or sodium carbonate in dimethyl formamide in the presence of copper.

5. A process for the production of the compounds of formula I stated in Claim 1 substantially as herein described with reference to any one of Examples 1 to 19, 21 and 22.

6. A process for the production of the compounds of formula Ia stated in Claim 2, substantially as herein described with reference to Example 20.

7. The compounds of formula I stated in Claim 1 and their acid addition salts whenever produced by the process claimed in any one of Claims 1 to 6.

8. 4 - (3 - Dimethylamino - propyl - 1)-4H - thieno[2,3 - b][1,4]benzothiazine.

9. 4 - [2 - (1 - Methyl - piperidyl - 2)-ethyl - 1] - 4H - thieno[2,3 - b][1,4]benzothiazine.

10. 4 - (1 - Methyl - piperidyl - 3-methyl) - 4H - thieno[2,3 - b][1,4]benzothiazine.

11. 6 - Chloro - 4 - (3 - dimethylamino-propyl - 1) - 4H - thieno[2,3 - b][1,4]benzothiazine.

12. 6 - Methylmercapto - 4 - (3 - dimethyl-amino - propyl - 1) - 4H - thieno[2,3-b][1,4]benzothiazine.

13. 6 - Methylmercapto - 4 - [2 - (1-methyl - piperidyl - 2) - ethyl - 1] - 4H-thieno[2,3 - b][1,4]benzothiazine.

14. 6 - Chloro - 4 - [2 - (1 - methyl-piperidyl - 2) - ethyl - 1] - 4H - thieno[2,3 - b][1,4]benzothiazine.

15. 7 - Bromo - 4 - (3 - dimethylamino-propyl - 1) - 4H - thieno[2,3 - b][1,4]benzothiazine.

16. 7 - Bromo - 4 - [2 - (1 - methyl-piperidyl - 2) - ethyl - 1] - 4H - thieno[2,3 - b][1,4]benzothiazine.

17. 4 - {3 - [1 - (2 - Hydroxyethyl)-piperazinyl - 4] - propyl - 1} - 4H - thieno[2,3 - b][1,4]benzothiazine.

18. 6 - Chloro - 4 - {3 - [1 - (2 - hydroxy-ethyl) - piperazinyl - 4] - propyl - 1} - 4H - thieno[2,3 - b][1,4]benzothiazine.

19. 7 - Chloro - 4 - {3 - [1 - (2 - hydroxy-ethyl) - piperazinyl - 4] - propyl - 1} - 4H - thieno[2,3 - b][1,4]benzothiazine.

20. 6 - Methylmercapto - 4 - [3 - (1-methyl - piperazinyl - 4) - propyl - 1] - 4H-thieno[2,3 - b][1,4]benzothiazine.

21. 6 - Methoxy - 4 - (3 - dimethyl-amino - propyl - 1) - 4H - thieno[2,3 - b][1,4]benzothiazine.

22. 6 - Methylsulphonyl - 4 - (3 - di-methylamino - propyl - 1) - 4H - thieno[2,3 - b][1,4]benzothiazine.

23. 6 - Methylsulphonyl - 4 - (3 - di-methylamino - propyl - 1) - 4H - thieno[2,3 - b][1,4]benzothiazine.

24. 6 - Trifluoromethyl - 4 - [2 - (1-methyl - piperidyl - 2) - ethyl - 1] - 4H-thieno[2,3 - b][1,4]benzothiazine.

25. 6 - Cyano - 4 - [2 - (1 - methyl-piperidyl - 2) - ethyl - 1] - 4H - thieno[2,3 - b][1,4]benzothiazine.

26. 6 - Methylsulphonyl - 4 - [2 - (1-methyl - piperidyl - 2) - ethyl - 1] - 4H-thieno[2,3 - b][1,4]benzothiazine.

27. 6 - Chloro - 4 - [2 - methyl - 3-(4 - hydroxy - piperidyl - 1) - propyl - 1] - 4H - thieno[2,3 - b][1,4]benzothiazine.

28. 6 - Bromo - 4 - {3 - [1 - (2 - hydroxy-ethyl) - piperazinyl - 4] - propyl - 1} - 4H-thieno[2,3 - b][1,4]benzothiazine.

29. 6 - Trifluoromethyl - 4 - {3 - [1-(2 - hydroxyethyl) - piperazinyl - 4] - propyl - 1} - 4H - thieno[2,3 - b][1,4]benzothiazine.

30. The acid addition salts of the compounds claimed in any one of Claims 8 to 29.

31. The compounds of formula I stated in Claim 1 and their acid addition salts.

32. Pharmaceutical compositions containing, in addition to a physiologically acceptable carrier, a compound of formula I stated



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in Claim 1 or claimed in any one of Claims 8 to 29 and/or a physiologically acceptable acid addition salt thereof.

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ERRATA

SPECIFICATION No. 1,120,735

- Page 3, line 19, for "alkaline" read "alkali"
- Page 4, line 31, for "solution" read "solutions"
- Page 6, lines 11 and 12, for "evaporating" read "evaporation"
- Page 6, line 47, for "3.15g" read "3.14g"
- Page 8, line 5, after "from" insert "a"
- Page 8, line 12, for "60g" read "60.0g"
- Page 9, line 2, for "10.85g" read "10.58g"
- Page 9, line 13, for "propyl-4T" read "propyl-1-4H"
- Page 13, line 42, after "[2-" insert "(1-"
- Page 14, line 107, for "90-fold" read "9-fold"
- Page 15, lines 36 and 37, for "(2-hydroxyethyl" read "(2-hydroxyethyl)"
- Page 16, line 28, after "above," insert "or"
- Page 16, line 33, delete whole line and substitute "R_n as in (ii) above"
- Page 17, line 14, for "is" read "in"
- Page 17, lines 21 and 22, for "ormula" read "formula"

THE PATENT OFFICE
26th August 1968