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PATENT SPECIFICATION (11) 1 410 963

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(21) Application No. 54170/72 (22) Filed 23 Nov. 1972
(31) Convention Application No. 17225/71 (32) Filed 26 Nov. 1971 in
(33) Switzerland (CH)
(44) Complete Specification published 22 Oct. 1975
(51) INT CL² C07D 495/04; A61K 31/55 // (C07D 495/04, 223/00, 333/00)
(52) Index at acceptance
C2C 1510 151X 1626 213 214 215 21X 220 22Y 246 247 250 252 254 256 25Y 276 27X 280 281 28X 29X 29Y 305 30Y 313 316 31Y 321 32Y 337 338 339 342 349 34Y 351 352 355 35X 366 368 37X 385 386 40Y 43X 440 491 510 51X 534 535 579 604 620 622 625 628 62X 658 65X 660 665 675 699 69Y 707 714 761 762 790 79Y BC KF LL MH NJ SG TR ZB ZF



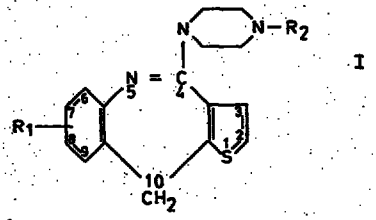
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(54) IMPROVEMENTS IN OR RELATING TO THIENOBENZAZEPINES

(71) We, WANDER LTD., of 115 Monbijoustrasse, Berne, 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 10H-thieno[3,2-c][1]benzazepine derivatives.

The present invention provides new compounds of formula I,



I

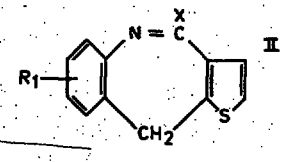
wherein

R_1 is hydrogen, fluorine, chlorine or bromine, or alkyl, alkoxy or alkylthio of 1 to 4 carbon atoms, and

R_2 is hydrogen, alkyl of 1 to 4 carbon atoms, hydroxyalkyl of 1 to 4 carbon atoms, acetoxyalkyl of 3 to 6 carbon atoms or alkoxyalkyl of 2 to 6 carbon atoms.

Further, in accordance with the invention a compound of formula I may be obtained by a process comprising

a) reacting a compound of formula II,

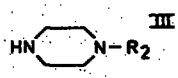


II

wherein R_1 is as defined above, and

X is a radical capable of being split off with the hydrogen atom on one of the nitrogen atoms of piperazine,

with a compound of formula III,

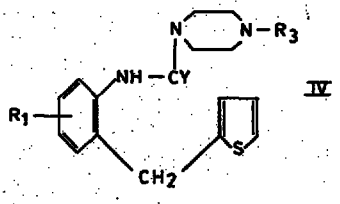


III

wherein R_2 is as defined above,

to produce a compound of formula I,

b) subjecting to a ring closure a compound of formula IV,



IV

wherein

R_1 is as defined above,

Y is an oxygen or sulphur atom, and

R_3 (i) is a protective radical capable of being split off,

and simultaneously or subsequently splitting off the protective radical to produce a compound of formula I wherein R_2 is hydrogen, or

(ii) has one of the significances of R_2,

to produce a compound of formula I,

c) alkylating a compound of formula I wherein R_2 is hydrogen, with an alkylating, hydroxyalkylating or alkoxyalkylating agent to produce a compound of formula I wherein R_2 is alkyl, hydroxyalkyl or alkoxyalkyl, respectively, or

d) acetylating a compound of formula I

wherein R_2 is hydroxyalkyl to produce a compound of formula I wherein R_2 is acetoxyalkyl.

Process variant a) may be effected as follows:

In a compound of formula II, the reactive radical X may be, for example, the sulfhydryl group, an alkoxy or alkylthio group contaning 1 to 5 carbon atoms, e.g. the methoxy or methylthio group, an aryloxy, aralkylthio or arylthio group which may be activated as a leaving group by substituents thereon conveniently in the aryl moiety thereof, e.g. the *p*-nitrobenzylthio group, an alkyl- or aryl-sulphonyloxy group, which preferably is activated as a leaving group by substituents on the hydrocarbon moiety thereof, e.g. a tosyloxy group.

The reactive radical X may alternatively be, for example, a halogen atom, conveniently the chlorine atom.

The reactive radical X may, alternatively, signify an amino group or a mono- or dialkyl-substituted amino group, the or each alkyl substituent thereof containing 1 to 5 carbon atoms (hereafter the term "amino group" with reference to a compound of formula II refers to any of these three afore-mentioned groups).

The compound of formula II, which may be used in crude form, may be reacted with a compound of formula III in an inert solvent, for example an aromatic hydrocarbon solvent, e.g. xylene, or a cyclic ether, e.g. dioxane. Alternatively if the compound of formula III is liquid at the reaction temperature, an excess of this compound may be used as the reaction medium, especially when the radical X in the compound of formula II is an amino group.

The temperature of the reaction is preferably from room temperature to the temperature of the reaction mixture boiling under reflux, preferably from 50 to 175°C. Suitable catalysts may be present in the reaction mixture, especially when the radical X in the compound of formula II is an amino group. A convenient catalyst is an acid, e.g. a toluenesulfonic acid or sulfuric acid, or an acid addition salt of an amine, e.g. a compound of formula II wherein X is an amino group in hydrochloride salt form, or ammonia, e.g. ammonium chloride.

Process variant b) may be effected as follows:

A compound of formula IV may be subjected to a ring closure, preferably at a temperature from 50°C to the temperature of the reaction mixture boiling under reflux, conveniently in the presence of a dehydration and ring closure agent, e.g. zinc chloride, aluminium chloride, tin tetrachloride, polyphosphoric acid, phosphorus pentasulfide, phosphorus oxychloride or phosphorus pentoxide.

A preferred method of effecting ring closure is by heating to the boil a compound of formula IV and phosphorus oxychloride, or a compound of formula IV and phosphorus oxychloride in the presence of phosphorus pentoxide, conveniently for from 10 to 20 hours.

If the reaction mixture is liquid, ring closure may be effected without additional solvent, otherwise an inert solvent such as benzene, xylene or toluene may be used.

When R_3 in the formula IV signifies a protective radical, this may be preferably a group capable of being split off hydrolytically or hydrogenolytically in known manner, e.g. a carbalkoxy group, preferably the carbethoxy group, or the carbobenzoxy group.

For example, depending on the reaction conditions used, a compound of formula IV having a carbethoxy group R_3 is cyclized as such to the corresponding 4-(1-piperazinyl) compound of formula I wherein R_2 is hydrogen, hydrolysis and removal of the R_3 group simultaneously taking place.

The carbobenzoxy group may be removed in known manner, e.g. hydrogenolytically, after ring closure to produce a compound of formula I wherein R_2 is hydrogen.

Process variant c) may be effected as follows:

Alkylation of a compound of formula I wherein R_2 is hydrogen, may be effected by reaction with an alkylation agent, for example an alkanol of the formula IX,

$$R_2OH \qquad IX$$

wherein R_2 is alkyl of 1 to 4 carbon atoms, in the form of a reactive ester, to produce the corresponding compound of formula I wherein R_2 is alkyl.

Representative reactive esters are esters of organic or inorganic acids, e.g. a toluenesulfonic acid or hydrohalic acid, particularly hydrogen iodide.

The reaction is conveniently effected by dissolving a compound of formula I wherein R_2 is hydrogen in an inert solvent, preferably an aromatic hydrocarbon, e.g. toluene, or a polar solvent, e.g. acetone or isopropanol. An acid-binding agent may be preferably present, e.g. potassium or sodium carbonate, or an excess of the compound of formula I wherein R_2 is hydrogen.

The temperature of the reaction may be, e.g., from room temperature (about 25°C) to the temperature of the reaction mixture boiling under reflux.

An alternative alkylation agent is a reductive alkylation agent, comprising the aldehyde corresponding to the alkanol of formula IX, in the presence of a reducing agent, for

example formic acid, conveniently 90% formic acid, or catalytically activated hydrogen, in the presence of an inert solvent, if necessary.

The reaction temperature may be, e.g., from room temperature to the temperature of the reaction mixture boiling under reflux.

The hydroxyalkylation of a compound of formula I wherein R_2 is hydrogen, may be effected by reacting this compound of formula I with a reactive monoester of a glycol of 1 to 4 carbon atoms, conveniently in a manner analogous to that described above for alkylation with a reactive ester, to produce the corresponding compound of formula I wherein R_2 is hydroxyalkyl. In an alternative method, this compound of formula I may be treated with a suitable alkylene oxide of 1 to 4 carbon atoms, conveniently in a pressure tube, and by heating to a temperature conveniently from 80 to 120°C to produce the corresponding compound of formula I wherein R_2 is hydroxyalkyl. An inert organic solvent, e.g. toluene, may be used.

The alkoxyalkylation of a compound of formula I wherein R_2 is hydrogen, may be effected by reaction of this compound of formula I with a reactive ester of an alcohol of formula IX, wherein R_2 is alkoxyalkyl of 2 to 6 carbon atoms, conveniently in a manner analogous to that described above for alkylation with a reactive ester, to produce the corresponding compound of formula I wherein R_2 is alkoxyalkyl.

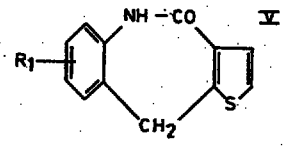
In accordance with process d) of the invention, compounds of formula I wherein R_2 is hydroxyalkyl, may be acetylated by, for example, treatment with a reactive derivative of acetic acid, e.g. acetic anhydride. An acid-binding agent, e.g. pyridine, or excess compound of formula I wherein R_2 is hydrogen, may be conveniently present.

The compounds of formula I obtained in accordance with the invention may be isolated in known manner, e.g. by precipitating from the reaction mixture, or concentrating the reaction mixture by evaporation, and may be purified in known manner, e.g. by recrystallization. The free base forms of the resulting compounds of formula I may be converted into acid addition salt forms in conventional manner and *vice versa*.

The maleate salt is a suitable acid addition salt form.

The compounds of formula II, used as starting materials in process variant a), may be obtained

a') by treating in known manner a compound of formula V,



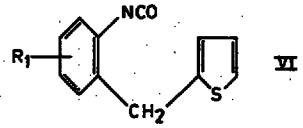
V

wherein R_1 is as defined above, with a halogenating agent, e.g. a chlorinating agent such as phosphorus oxychloride or phosphorus pentachloride, preferably in the presence of a catalytic amount of an amine such as N,N-dimethylaniline or dimethylformamide, to produce a compound of formula II wherein X is the corresponding halogen, e.g. chlorine,

b') by treating a compound of formula II, wherein X is halogen, with an alcoholate of 1 to 5 carbon atoms and preferably of an alkali metal, to produce a compound of formula II wherein X is alkoxy, or

c') by converting a compound of formula V in known manner into the thiolactam, thereby obtaining the corresponding tautomer of formula II wherein X is sulfhydryl.

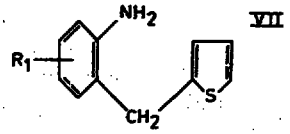
A compound of formula V may, for example, be obtained by ring closure of a compound of formula VI,



VI

wherein R_1 is as defined above, in the presence of, for example, phosphorus oxychloride and phosphorus pentoxide, or preferably polyphosphoric acid. This reaction may be conveniently carried out at an elevated temperature.

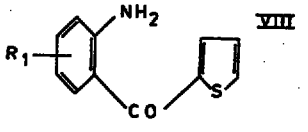
A compound of formula VI may, for example, be obtained by treating a compound of formula VII,



VII

wherein R_1 is as defined above, with an isocyanate-forming agent, for example, phosgene.

A compound of formula VII may, for example, be obtained by reducing, for example with hydrazine, a compound of formula VIII,



VIII

wherein R_1 is as defined above.

The compounds of formula VIII are known or may be produced in conventional manner.

The compounds of formula IV, used as starting materials in process variant b), may, for example, be obtained by treating a compound of formula VII with phosgene or thiophosgene, and reacting the resulting isocyanate or isothiocyanate, respectively, with

piperazine or a piperazine derivative of formula III, conveniently in an inert solvent, e.g. benzene.

The temperature of the reaction may be, e.g. from room temperature to the temperature of the reaction mixture boiling under reflux.

Insofar as the production of the starting materials is not particularly described, these are known or may be produced and purified in accordance with known processes, or in a manner analogous to processes described herein or to known processes.

The compounds of formula I exhibit interesting pharmacodynamic properties and are therefore indicated for use as medicaments.

The compounds of formula I exhibit neuroleptic activity as indicated by, for example, suppression of locomotor activity in mice, in accordance with the method of Caviezel and Baillod, described in Pharm. Acta Helv. *33*, 465—484 (1958).

The compounds of formula I are therefore indicated for use as neuroleptics. The indicated daily dosage is in the range of from 5 to 500 mg, conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing 1.25 to 250 mg of the compound of formula I, or in sustained release form.

The compounds of formula I may be administered in pharmaceutically acceptable acid addition salt form. A pharmaceutical composition may comprise a compound of formula I, in free base form or in pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent. Such compositions may be prepared by conventional techniques so as to be, for example, a tablet or solution.

4 - (4 - Methyl - 1 - piperazinyl) - 10H-thieno[3,2-c][1]benzazepine and the 7-chloro derivative thereof are the preferred compounds.

In the following Examples the temperatures are indicated in degrees Centigrade and are uncorrected, room temperature is between 20 and 30°C, and the vacuum usually employed is between 8 and 20 mm Hg, unless otherwise indicated.

EXAMPLE 1.

4 - (4 - Methyl - 1 - piperazinyl) - 10H-thieno[3,2-c][1]benzazepine

[process variant b)]

4.0 g of 2-[2-(4-methyl-1-piperazinyl)-carboxamidobenzyl]thiophene are boiled at reflux with 25 cc of phosphorus oxychloride for 18 hours. The two-phase reaction mixture is evaporated to dryness in a vacuum, ice-water and sufficient ammonia to render the mixture alkaline, residue and this is subsequently extracted with ether. After washing the ether phase twice with water, the basic components are separated by exhaustive extraction with 1N acetic acid, are liberated from the extracts with concentrated ammonia and taken up in ether. The ether solution is washed with water, dried with sodium sulphate, filtered through aluminium oxide and concentrated by evaporation. The residue is crystallized from ether/petroleum ether, whereby 4 - (4 - methyl - 1 - piperazinyl)-10H - thieno[3,2 - c][1]benzazepine is obtained in the form of colourless grains having a M.P. of 145—147°.

The 2 - [2 - (4 - methyl - 1 - piperazinyl)carboxamidobenzyl]thiophene, used as starting material in this Example, is obtained as follows:

14.8 g of 2-(2-aminophenyl)thienone, 23.8 g of solid potassium hydroxide and 19.6 g of hydrazine hydrate are heated to the boil at reflux in 180 cc of diethylene glycol for 3 hours. After diluting the reaction mixture with ice-water, extraction is effected with ether. The ether phase is washed thrice with water, is dried with sodium sulphate and concentrated. 2 - (2 - Aminobenzyl)thiophene is obtained in the form of a light yellow oil having a B.P. of 128—130°/0.1 mm Hg.

46 cc of a 20% solution of phosgene in toluene are added dropwise at −3° while stirring to a solution of 9.8 g of the product obtained above in 60 cc of toluene. The reaction mixture is subsequently allowed to warm to room temperature while passing a stream of phosgene through the same, and is subsequently heated to the boil at reflux for half an hour. After removing the excess phosgene with a stream of nitrogen, the reaction mixture is concentrated in a vacuum and the residue is distilled. 10.8 g of 2-(2-isocyanatobenzyl)thiophene, having a B.P. of 108°/0.05 mm Hg, are obtained.

A solution of 4.5 g of this product in 17 cc of absolute benzene is subsequently added dropwise within half an hour to a solution of 5 g of N-methyl-piperazine in 17 cc of absolute benzene. The reaction mixture is subsequently heated to the boil at reflux for 2 hours and is then completely concentrated in a vacuum. The residue is dissolved in dilute acetic acid, the solution is filtered through charcoal and is made alkaline with concentrated ammonia solution while cooling with ice. The precipitated base is extracted with chloroform, the extracts are washed with water, dried with sodium sulphate, filtered through aluminium oxide and concentrated by evaporation. Crystallization of the residue from acetone/petroleum ether yields 2-[2-(4-methyl - 1 - piperazinyl)carboxamidobenzyl]-thiophene in the form of white needles having a M.P. of 117—119°.

EXAMPLE 2.

4 - (4 - Methyl - 1 - piperazinyl) - 10H-thieno[3,2-c][1]benzazepine

[process variant a)]

5.1 g of 4,5-dihydro-10H-thieno[3,2-c]-[1]benzazepin-4-one are boiled at reflux with 40 cc of phosphorus oxychloride and 1.5 cc of N,N-dimethylaniline for 3 hours. The reaction mixture is evaporated to dryness in a vacuum and the residue is evaporated twice more with xylene. The residue, 4-chloro-10H-thieno[3,2-c][1]benzazepine, is subsequently taken up in 10 cc of absolute dioxane and 30 cc of N-methyl-piperazine are added. The reaction mixture is heated to the boil at reflux for 4 hours and is subsequently evaporated to dryness in a vacuum. Ice-water and ammonia are added to the residue and this is extracted with ether. After washing the ether phase twice with water, the basic components are separated by exhaustive extraction with 1N acetic acid, are liberated from the extracts with concentrated ammonia and are taken up in ether. The ether solution is washed with water, dried with sodium sulphate, filtered through aluminium oxide and concentrated by evaporation. Crystallization of the residue from ether/petroleum ether yields 4-(4-methyl-1-piperazinyl)-10H-thieno[3,2-c][1]benzazepine in the form of colourless grains having a M.P. of 145—147°.

The 4,5 - dihydro - 10H - thieno[3,2 - c]-[1]benzazepin-4-one, used as starting material in this Example, is obtained as follows:

10.5 g of 2-(2-isocyanatobenzyl)thiophene (B.P. 108°/0.05 mm Hg) are heated to 110° with 105 g of polyphosphoric acid for 1 hour while stirring. The reaction mixture is then made alkaline with concentrated ammonia solution with internal and external cooling with ice, and the resulting precipitate is filtered off. This precipitate is washed with water, treated in acetone with charcoal, filtered, dried and crystallized from acetone. 4,5 - Dihydro - 10H - thieno[3,2 - c][1]-benzazepin-4-one is obtained in the form of grains having a M.P. of 225—236°.

EXAMPLE 3.

8 - Chloro - 4 - (1 - piperazinyl) - 10H-thieno[3,2-c][1]benzazepine

[process variant a)]

A solution of 3.5 g of 4,8-dichloro-10H-thieno[3,2-c][1]benzazepine in 15 cc of toluene is added dropwise within 15 minutes to a mixture, boiling at reflux, of 11 g of anhydrous piperazine and 15 cc of dioxane. After boiling at reflux for a further 6 hours, the reaction mixture is evaporated to dryness in a vacuum and the residue is stirred at 60° for 15 minutes with a mixture of 20 cc of glacial acetic acid and 100 cc of water, whereby most of the material dissolves. The insoluble material is then separated by filtering with suction, the filtrate is treated with charcoal, filtered, and the base is liberated therefrom with concentrated ammonia solution. The liberated base is taken up in chloroform, the chloroform phase is washed with water, dried with sodium sulfate and concentrated by evaporation. After treating with charcoal and recrystallizing the residue from acetone/water, 8 - chloro - 4 - (1 - piperazinyl) - 10H - thieno[3,2 - c][1]benzazepine, having an indefinite M.P. of about 80—100°, is obtained.

The 4,8 - dichloro - 10H - thieno[3,2 - c]-[1]benzazepine, used as starting material in the above process, is produced as follows:

3.0 g of 8-chloro-4,5-dihydro-10H-thieno-[3,2-c][1]benzazepin-4-one, 18 cc of phosphorus oxychloride and 0.75 cc of N,N-dimethylaniline are heated to the boil at reflux for 3 hours. The reaction mixture is subsequently evaporated to dryness in a vacuum and is evaporated thrice more with xylene. The residue is divided between benzene and ice-water, the benzene phase is washed with water and aqueous potassium bicarbonate solution, is dried with sodium sulphate and concentrated. After recrystallizing the residue from benzene/petroleum ether, crystals having a M.P. of 135—140° are obtained.

EXAMPLE 4.

7 - Chloro - 4 - (1 - piperazinyl) - 10H-thieno[3,2-c][1]benzazepine

[process variant a)]

3.0 g of 7-chloro-4,5-dihydro-10H-thieno-[3,2-c][1]benzazepin-4-one, 18 cc of phosphorus oxychloride and 0.75 cc of N,N-dimethylaniline are heated to the boil at reflux for 3 hours. The reaction mixture is subsequently evaporated to dryness in a vacuum and is evaporated thrice more with xylene. The residue, consisting of 4,7-dichloro-10H-thieno[3,2-c][1]benzazepine, is taken up in 30 cc of toluene, and the resulting mixture is added dropwise to a boiling solution of 15 cc of anhydrous piperazine in 15 cc of dioxane; the mixture is subsequently heated to the boil at reflux for 6 hours. After working up in a manner analogous to that described in Example 3, 7 - chloro - 4 - (1 - piperazinyl) - 10H - thieno[3,2 - c][1]benzazepine is obtained as crystals having a M.P. of 155—157° (from acetone).

The 8 - chloro- (or 7 - chloro-) 4,5-dihydro - 10H - thieno[3,2 - c][1]benzazepin-4-one, used as starting material in Example 3 (or 4), may be obtained as follows:

6 g of N-*p*-toluenesulphonyl-5-chloro- (or 4-chloro-) anthranilic acid are heated to the boil at reflux for 1½ hours with 10 cc of thionyl chloride. After evaporating to dryness in a vacuum, the residue is recrystallized from methylene chloride/petroleum ether. The resulting N-*p*-toluenesulphonyl-5-chloro-

anthranilic acid chloride has a M.P. of 134—136° (or N-*p*-toluenesulphonyl-4-chloroanthranilic acid chloride has a M.P. of 135—140°).

A solution of 6 g of stannic chloride in 10 cc of carbon disulphide is slowly added dropwise to a mixture of 7 g of finely pulverized N - *p* - toluenesulphonyl - 5 - chloro- (or 4-chloro-) anthranilic acid chloride and 3.4 g of thiophene in 25 cc of carbon disulphide at the boil under reflux. After the addition is complete, stirring is effected at room temperature for 2 hours. The solvent is subsequently removed by evaporation in a vacuum, the residue is treated with ice-water and hydrochloric acid and extracted with ethyl acetate. The ethyl acetate extract is washed with 2N hydrochloric acid, water and a saturated aqueous potassium bicarbonate solution, is dried with sodium sulphate and concentrated. The evaporation residue is divided between ether and a 1N aqueous sodium hydroxide solution. The aqueous alkaline solution is acidified with concentrated hydrochloric acid, and the resulting precipitate is filtered off with suction. The suction filter residue is washed with water and recrystallized from ethyl acetate/petroleum ether. 2-(2-*p*-Toluenesulphonamido - 5 - chlorophenyl)thienone has a M.P. of 164—167° (or 2-(2-*p*-toluenesulphonamido - 4 - chlorophenyl)thienone has a M.P. of 140—141°).

8.4 g of 2 - (2 - *p* - toluenesulphonamido - 5 - chloro- (or 4 - chloro-) phenyl)thienone are stirred at room temperature with 100 cc of concentrated sulphuric acid for 4 hours. The reaction product is subsequently poured onto ice, and the resulting mixture is made alkaline with concentrated aqueous sodium hydroxide solution while cooling. A precipitate results, which is taken up in ether. The ether solution is washed with water, dried with sodium sulphate and concentrated, whereby a residue is obtained. After treatment with charcoal and aluminium oxide, and recrystallization from ether/petroleum ether, 2-(2-amino-5-chlorophenyl)thienone has a M.P. of 97—98° (or 2 - (2 - amino - 4 - chlorophenyl)-thienone has a M.P. of 66—72°).

15.5 g of 2-(2-amino-5-chloro- (or 4-chloro-) phenyl)thienone, 23.8 g of solid potassium hydroxide and 19.6 g of hydrazine hydrate are heated to the boil at reflux in 180 cc of diethylene glycol for 2 hours. After diluting the reaction mixture with ice-water, extraction is effected with ether. The ether phase is washed thrice with water, dried with sodium sulphate and concentrated. 2-(2-Amino-5-chlorobenzyl)thiophene, having a B.P. of 150—157°/0.1 mm Hg, (or 2-(2-amino-4-chlorobenzyl)thiophene, having a B.P. of 137—140°/0.05 mm Hg) is obtained as oil.

46 cc of a 20% solution of phosgene in toluene are added dropwise at −3° while stirring to a solution of 11 g of 2-(2-amino-5-chloro- (or 4-chloro-)benzyl)thiophene in 60 cc of toluene. The reaction mixture is subsequently allowed to warm to room temperature, while passing through a stream of phosgene, and is subsequently heated to the boil at reflux for half an hour. After expelling the excess phosgene with a stream of nitrogen, the reaction mixture is concentrated in a vacuum and the residue is distilled. 2 - (2 - Isocyanato - 5 - chlorobenzyl)thiophene, having a B.P. of 137—139°/0.1 mm Hg, (or 2-(2-isocyanato-4-chlorobenzyl)thiophene, having a B.P. of 124—125°/0.05 mm Hg) is obtained.

Ring closure of 2-(2-isocyanato-5-chloro- (or 4-chloro-) benzyl)thiophene, using the process described in Example 2, yields 2-chloro - 4,5 - dihydro - 10H - thieno[3,2 - c]-[1]benzazepin-4-one having a M.P. of 280—281° (after recrystallization from dioxane/acetone) (or 7-chloro-4,5-dihydro-10H - thieno[3,2 - c][1]benzazepin - 4 - one having a M.P. of 264—266° [after recrystallization from acetone]).

EXAMPLE 5.

4 - [4 - (2 - Acetoxyethyl) - 1 - piperazinyl] - 8 - chloro - 10H - thieno[3,2-c][1]benzazepine
[process variant d)]

0.1 g of 8-chloro-4-[4-(2-hydroxyethyl)-1 - piperazinyl] - 10H - thieno[3,2 - c][1]-benzazepine are heated in a steam bath for 15 minutes with 2 cc of acetic anhydride, and the mixture is subsequently allowed to stand at room temperature for 2½ days. The resulting crystalline product is stirred with 20 cc of water and after standing at room temperature again dissolved. The almost clear solution is filtered and made alkaline with concentrated ammonia solution. The resulting base is taken up in ether, and the ether solution is washed with water and dried with sodium sulphate. The evaporation residue which crystallizes spontaneously is clarified in a chloroform solution on basic aluminium oxide, and after concentrating again by evaporation is crystallized from ether/petroleum ether. The 4-[4-(2-acetoxyethyl)-1-piperazinyl] - 8 - chloro - 10H - thieno[3,2 - c]-[1]benzazepine, obtained in the form of colourless prisms, has a M.P. of 185—189°.

EXAMPLE 6.

8 - Chloro - 4 - (4 - methyl - 1 - piperazinyl) - 10H - thieno[3,2 - c][1]benzazepine
[process variant c)]

A solution of 3.1 g of methyl iodide in 20 cc of toluene is added dropwise at room

temperature, within 20 minutes, while stirring well, to a solution of 12.7 g of 8-chloro - 4 - (1 - piperazinyl) - 10H - thieno-[3,2-c] [1]benzazepine in 80 cc of toluene. After allowing to stand overnight at room temperature, the resulting salt precipitate is filtered with suction and washed with toluene. The fairly concentrated toluene solution is subsequently clarified on basic aluminium oxide and subsequently evaporated to dryness. The subsequently evaporated to dryness. The resulting residue is recrystallized from acetone/petroleum ether. The resulting 8-chloro - 4 - (4 - methyl - 1 - piperazinyl)-10H - thieno[3,2 - - c] [1]benzazepine has a M.P. of 193—195°.

EXAMPLE 7.

4 - (4 - Methyl - 1 - piperazinyl) - 10H-thieno[3,2-c] [1]benzazepine

[process variant a)]

5.4 g of 4-amino-10H-thieno[3,2-c] [1]-benzazepine are heated to 175° in a small stirring autoclave for 24 hours together with 1.5 g of ammonium chloride and 30 cc of N-methyl-piperazine. The reaction mixture is washed out with 120 cc of methanol and evaporated to dryness in a vacuum. The residue is taken up in dilute hydrochloric acid, the insoluble material is filtered off from the solution and the solution is made alkaline with concentrated ammonia solution while clarifying with coal. The resulting resin is taken up in ether, and the ether solution is washed with water, dried with sodium sulphate and concentrated. The residue is taken up in 1N acetic acid, and the solution is again clarified with coal and made alkaline with concentrated ammonia solution. After extracting with ether and working up as in the first cycle, a purer crude base is obtained, which is subsequently clarified in ether solution on basic aluminium oxide. After recrystallization from ether/petroleum ether, 4-(4 - methyl - 1 - piperazinyl) - 10H - thieno-[3,2-c] [1]benzazepine, having a M.P. of 144—147°, is obtained.

By using the processes described in the preceding Examples 1 to 4, 6 and 7, and the corresponding starting materials, compounds of formula I wherein R_1 and R_2 have the following significance, are obtained:

Example	R_1	R_2	M.P.
8	H	$-C(CH_3)_3$	147 - 176° (in maleate form)
9	7-CH_3	CH_3	180 - 181° from An/Pe
10	7-CH_3	$-CH_2-CH_2-OH$	169 - 171° fron An/Pe
11	7-Cl	CH_3	184 - 185° from An
12	7-Cl	$-CH_2-CH_2-OH$	192 - 194° from AcOEt
13	8-Cl	$-CH_2-CH_2-OH$	202 - 203° from AcOEt

In the above Table

An = acetone

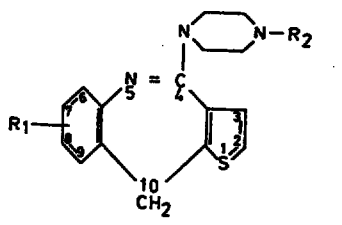
Pe = petroleum ether

AcOEt = ethyl acetate

M.P. = melting point of free base form except where otherwise stated

WHAT WE CLAIM IS:—

1. A process for the production of compounds of formula I,



I

wherein

R_1 is hydrogen, fluorine, chlorine or bromine, or alkyl, alkoxy or alkylthio of 1 to 4 carbon atoms, and

R_2 is hydrogen, alkyl of 1 to 4 carbon atoms, hydroxyalkyl of 1 to 4 carbon atoms, acetoxyalkyl of 3 to 6 carbon atoms or alkoxyalkyl of 2 to 6 carbon atoms,

which comprises

a) reacting a compound of formula II,

temperature, within 20 minutes, while stirring well, to a solution of 12.7 g of 8-chloro - 4 - (1 - piperazinyl) - 10H - thieno-[3,2-c] [1]benzazepine in 80 cc of toluene. After allowing to stand overnight at room temperature, the resulting salt precipitate is filtered with suction and washed with toluene. The fairly concentrated toluene solution is subsequently clarified on basic aluminium oxide and subsequently evaporated to dryness. The subsequently evaporated to dryness. The resulting residue is recrystallized from acetone/petroleum ether. The resulting 8-chloro - 4 - (4 - methyl - 1 - piperazinyl)-10H - thieno[3,2 - - c] [1]benzazepine has a M.P. of 193—195°.

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4 - (4 - Methyl - 1 - piperazinyl) - 10H-thieno[3,2-c] [1]benzazepine

[process variant a)]

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By using the processes described in the preceding Examples 1 to 4, 6 and 7, and the corresponding starting materials, compounds of formula I wherein R_1 and R_2 have the following significance, are obtained:

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10	7-CH_3	$-CH_2-CH_2-OH$	169-171° fron An/Pe
11	7-Cl	CH_3	184-185° from An
12	7-Cl	$-CH_2-CH_2-OH$	192-194° from AcOEt
13	8-Cl	$-CH_2-CH_2-OH$	202-203° from AcOEt

In the above Table An = acetone

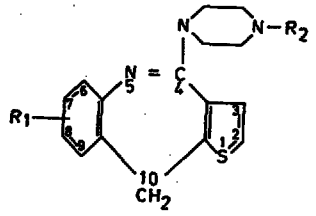
Pe = petroleum ether

AcOEt = ethyl acetate

M.P.= melting point of free base form except where otherwise stated

WHAT WE CLAIM IS:—

1. A process for the production of compounds of formula I,



I

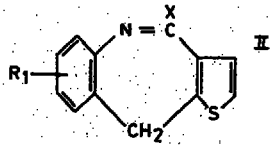
wherein

R_1 is hydrogen, fluorine, chlorine or bromine, or alkyl, alkoxy or alkylthio of 1 to 4 carbon atoms, and

R_2 is hydrogen, alkyl of 1 to 4 carbon atoms, hydroxyalkyl of 1 to 4 carbon atoms, acetoxyalkyl of 3 to 6 carbon atoms or alkoxyalkyl of 2 to 6 carbon atoms,

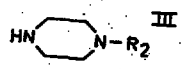
which comprises

a) reacting a compound of formula II,



II

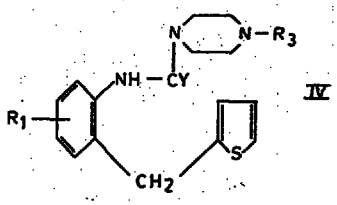
wherein R_1 is as defined above, and
X is a radical capable of being split off with the hydrogen atom on one of the nitrogen atoms of piperazine,
with a compound of formula III,



III

wherein R_2 is as defined above,
to produce a compound of formula I, or

b) subjecting to a ring closure a compound of formula IV,



IV

wherein
R_1 is as defined above,
Y is an oxygen or sulphur atom, and
R_3 (i) is a protective radical capable of being split off,
and simultaneously or subsequently splitting off the protective radical to produce a compound of formula I wherein R_2 is hydrogen, or

(ii) has one of the significances of R_2,
to produce a compound of formula I.

2. A process comprising
alkylating a compound of formula I as defined in claim 1 wherein R_2 is hydrogen, with an alkylating, hydroxyalkylating or alkoxyalkylating agent to produce a compound of formula I as defined in claim 1 wherein R_2 is alkyl, hydroxyalkyl or alkoxyalkyl, respectively, or
acetylating a compound of formula I as defined in claim 1 wherein R_2 is hydroxyalkyl to produce a compound of formula I as defined in claim 1 wherein R_2 is acetoxyalkyl.

3. A process for the production of a compound of formula I, as defined in Claim 1, substantially as hereinbefore described.

4. A compound of formula I, whenever produced by a process according to Claim 1, 2 or 3.

5. A compound of formula I, as defined in Claim 1.

6. A compound of formula I according to Claim 5, in which R_1 is hydrogen or chlorine.

7. 4 - (4 - methyl - 1 - piperazinyl) - 10H-thieno[3,2-c][1]benzazepine.

8. 8 - chloro - 4 - (1 - piperazinyl) - 10H-thieno[3,2-c][1]benzazepine.

9. 7 - chloro - 4 - (1 - piperazinyl) - 10H-thieno[3,2-c][1]benzazepine.

10. 4 - [4 - (2 - acetoxyethyl) - 1 - piperazinyl] - 8 - chloro - 10H - thieno[3,2 - c]-[1]benzazepine.

11. 8 - chloro - 4 - (4 - methyl - 1 - piperazinyl) - 10H - thieno[3,2 - c][1]benzazepine.

12. 4 - (4 - *tert* - butyl - 1 - piperazinyl)-10H-thieno[3,2-c][1]benzazepine.

13. 7 - methyl - 4 - (4 - methyl - 1-piperazinyl) - 10H - thieno[3,2 - c][1]-benzazepine.

14. 7 - methyl - 4 - [4 - (2 - hydroxyethyl) - 1 - piperazinyl] - 10H - thieno-[3,2-c][1]benzazepine.

15. 7 - chloro - 4 - (4 - methyl - 1 - piperazinyl) - 10H - thieno[3,2 - c][1]benzazepine.

16. 7 - chloro - 4 - [4 - (2 - hydroxyethyl) - 1 - piperazinyl] - 10H - thieno-[3,2-c][1]benzazepine.

17. 8 - chloro - 4 - [4 - (2 - hydroxyethyl) - 1 - piperazinyl] - 10H - thieno-[3,2-c][1]benzazepine.

18. A compound of formula I as defined in claim 1 wherein R_2 is hydrogen.

19. A compound of formula I as defined in claim 1 wherein R_2 is alkyl, hydroxyalkyl or alkoxyalkyl.

20. A compound of formula I as defined in claim 1 wherein R_2 is acetoxyalkyl.

21. A compound of formula I as defined in claim 1 wherein R_2 is hydroxyalkyl.

22. A compound according to any one of Claims 4 to 21, in acid addition salt form.

23. A pharmaceutical composition comprising a compound according to any one of Claims 4 to 22, in free base form or in pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical diluent or carrier.

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Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1975.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

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