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PATENT SPECIFICATION

(11) 1415591

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- (52) Index at acceptance



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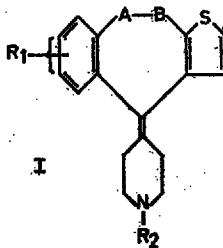
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(54) BENZOCYCLOHEPTATHIOPHENE DERIVATIVES

(71) We, SANDOZ LTD., of 35 Lichtstrasse, 4002 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:—

This invention relates to heterocyclic compounds and more specifically to benzocycloheptathiophene derivatives.

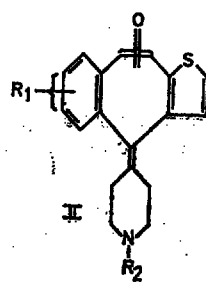
In accordance with the invention, there are provided new compounds of formula I,



It is to be understood that reference to substituted benzyl or substituted diphenylmethyl is intended to be limited to substitution only on the phenyl ring or rings thereof.

Further, the invention provides a process for producing a compound of formula I, which comprises

- a) reducing a compound of formula II,



wherein

R_1 is hydrogen, chlorine, bromine or alkoxy of 1 to 4 carbon atoms and is in the 6 or 7 position of the benzocycloheptathiophene nucleus,

R_2 is alkyl of 1 to 4 carbon atoms; benzyl; fluoro, chloro or bromo substituted benzyl; diphenylmethyl; or fluoro, chloro or bromo substituted diphenylmethyl, and either one of

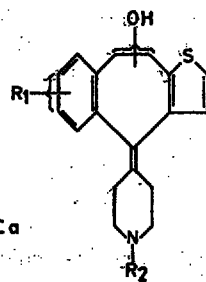
A and B is hydroxymethylene or hydroxyiminomethylene and the other is methylene, or each of

A and B is carbonyl, or, when R_2 is benzyl; fluoro, chloro or bromo substituted benzyl; diphenylmethyl; or fluoro, chloro or bromo substituted diphenylmethyl, then one of

A and B is carbonyl the other is methylene.

wherein

R_1 and R_2 are as defined above, and the oxo group is in the 9 or 10 position of the benzocycloheptathiophene nucleus, to produce a compound of formula Ia,



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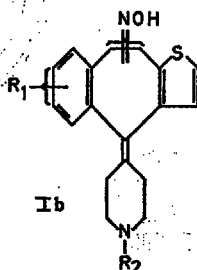
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wherein

R_1 and R_2 are as defined above, and the hydroxy group is in the 9 or 10 position of the benzocycloheptathiophene nucleus,

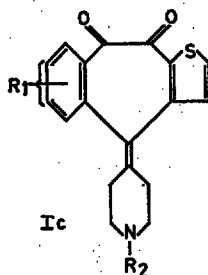
- 5 b) reacting a compound of formula II with hydroxylamine, to produce a compound of formula Ib,



wherein

- 10 R_1 and R_2 are as defined above, and the hydroxyimino group is in the 9 or 10 position of the benzocycloheptathiophene nucleus,

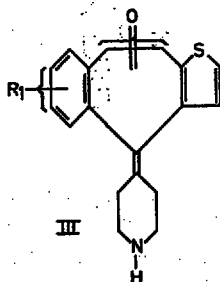
c) oxidizing a compound of formula II to produce a compound of formula Ic,



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wherein

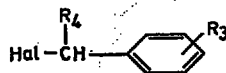
R_1 and R_2 are as defined above, or d) reacting a compound of formula III,



20 wherein

R_1 is as defined above, and the oxo group is in the 9 or 10 position of the benzocycloheptathiophene nucleus, with a compound of formula IV:

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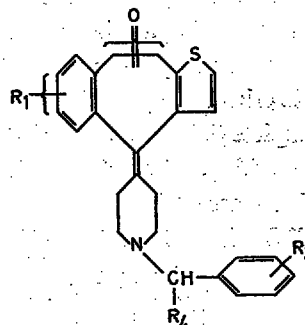


wherein

R_3 is hydrogen, fluorine, chlorine or bromine,

R_4 is hydrogen, phenyl, or fluoro, chloro, or bromo substituted phenyl, and

Hal is chlorine or bromine, to produce a compound of formula Id,



Id

wherein

R_1 , R_2 and R_4 are as defined above, and the oxo group is in the 9 or 10 position of the benzocycloheptathiophene nucleus.

The compounds of formula I may exist either in free base or acid addition salt forms. Acid addition salt forms may be produced from free base forms and *vice versa* in manner known *per se*. Examples of suitable reagents for acid addition salt formation are inorganic acids, e.g. hydrochloric acid or sulphuric acid, and organic acids, e.g. fumaric acid or maleic acid.

The processes a), b), c) and d) of the invention may be effected as follows:

a) The reduction of the keto group is conveniently effected with a complex borohydride, for example sodium borohydride, and in an inert organic solvent (suspension agent), e.g. a lower alkanol such as ethanol.

It is generally convenient to effect the reduction at a moderate temperature, e.g. room temperature.

b) In accordance with a process for the production of oximes of formula Ib a compound of formula II is conveniently reacted with an acid addition salt form of hydroxylamine, e.g. with hydroxylamine hydrochloride.

The reaction may, for example, be effected in an inert solvent, e.g. an alkanol such as ethanol, or in water. When an acid addition salt form of hydroxylamine is used, then the resulting compound of formula Ib precipitates out from the reaction mixture in acid addition salt form.

The reaction temperature may range between room temperature and reflux temperature. The reaction time is dependent on the reaction temperature.

c) The use of selenium dioxide has been found to be specially convenient for the oxidation of a compound of formula II to a compound of formula Ic.

This oxidation may, for example, be effected by adding an oxidizing agent such as selenium dioxide to a solution of a com-

ound of formula II in an inert organic solvent, preferably glacial acetic acid.

The reaction temperature may vary between room and reflux temperature.

The oxidation proceeds smoothly and, when effected at reflux temperature, is completed within about half an hour.

d) The reaction of a compound of formula III with a compound of formula IV may, for example, be effected in an inert organic solvent and preferably in the presence of a condensation agent, e.g. an alkali metal carbonate such as sodium or potassium carbonate. It is advantageous to use a strong polar solvent such as hexamethylphosphoric acid triamide, dimethyl sulphoxide or dimethyl formamide.

The reaction temperature is preferably kept low, between room temperature and approximately 60°C.

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

The compounds of formula I possess pharmacological activity. In particular, the compounds of formula I possess histaminolytic activity as indicated by standard tests, e.g. in the histamine toxicity test in guinea pigs.

From the serotonin and acetylcholine toxicity tests, it may be seen that in general the 10 hydroxy compounds, the 10-keto compounds, and the specific 9-hydroxy compound of Example 2 mentioned hereinafter have less anti-serotonin and anticholinergic activity than other compounds of formula I.

The 10 hydroxy, and 9-keto compounds of formula I and the Example 2 compound are therefore indicated for use as specific histaminolytics, and the remaining compounds as antaminics, e.g. in the treatment of allergic conditions of various origins. An indicated suitable daily dosage for the abovementioned specific histaminolytic, or, as the case may be, antaminic, use, is from 0.5 to 200 mg, preferably given in divided doses two or three times daily or in sustained release form. An indicated suitable unit dosage is from about 0.15 to 100 mg of the compound which may be administered with a solid or liquid pharmaceutical carrier or diluent.

The compounds of formula I may be employed in pharmaceutically acceptable acid addition salt form. Such acid addition salt forms possess the same order of activity as the free base forms.

The compounds in free base or pharmaceutically acceptable acid addition salt form may be employed on their own, or as a pharmaceutical composition, in association with conventional pharmaceutical carriers or diluents. Indicated suitable forms of composition for oral administration include a tablet and a capsule.

In the following non-limitative Examples all temperatures are indicated in degrees Centigrade and are uncorrected.

"soda" as used hereinafter is sodium carbonate.

EXAMPLE 1:

9,10 - Dihydro - 4 - (1 - methyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2-b]thiophene - 9 - ol

48.5 g of 4 - (1 - methyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2-b]thiophen - 9(10H) - one base are dissolved in 1000 cc of 95% ethanol, and 6 g of sodium borohydride are added at 20°. After stirring at 20° for 3 hours the solution is concentrated. 400 cc of water are added to the evaporation residue, this is rendered alkaline with concentrated caustic soda solution, and the base is extracted with 1000 cc of chloroform. The chloroform solution is concentrated and the evaporation residue is recrystallized from absolute ethanol. The pure 9,10 - dihydro - 4 - (1 - methyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2-b]thiophen - 9 - ol base, having a M.P. of 244—247°, is obtained in this manner. Microanalysis agrees with the formula $C_{19}H_{21}NOS$. The structure was ascertained from the infrared, ultraviolet, nuclear magnetic resonance and mass spectrograph spectra.

EXAMPLE 2:

4 - (1 - Ethyl - 4 - piperidylidene) - 9,10 - dihydro - 4H - benzo[4,5]cyclohepta[1,2-b]thiophen - 9 - ol

The process is effected as described in Example 1, except that the 4 - (1 - ethyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2-b]thiophen - 9(10H) - one base is used in place of the 4 - (1 - methyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2-b]thiophen - 9(10H) - one base. The product 4 - (1 - ethyl - 4 - piperidylidene) - 9,10 - dihydro - 4H - benzo[4,5]cyclohepta[1,2-b]thiophen - 9 - ol is isolated as base. M.P. 200—214° (crystallization from absolute ethanol).

EXAMPLE 3:

9,10 - Dihydro - 4 - (1 - methyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2-b]thiophen - 10 - ol

25 g of 4 - (1 - methyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2-b]thiophen - 10(9H) - one base are suspended in 500 cc of 95% ethanol, and 3.06 g of sodium borohydride are added at 20°. After stirring at room temperature for 40 hours the reaction mixture is concentrated. 500 cc of water are added to the evaporation residue, this is made alkaline with concentrated caustic soda solution, and the free base is extracted with 2500 cc of chloroform. The chloroform solution is concentrated, and the evaporation residue is recrystallized from toluene. The pure 9,10 - dihydro - 4 - (1 - methyl - 4 -

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piperidylidene) - 4H - benzo[4,5]cyclohepta [1,2-b]thiophen - 10 - ol base, having a M.P. of 236—241°, is obtained in this manner. Microanalysis agrees with the formula $C_{19}H_{21}NOS$. The structure was ascertained from the infrared, ultraviolet, nuclear magnetic resonance and mass spectrograph spectra.

EXAMPLE 4:

9,10 - Dihydro - 9 - hydroxyimino - 4 - (1 - methyl - 4 - piperidylidene) - 4H - benzo [4,5]cyclohepta[1,2-b]thiophene

A mixture of 13.5 g of hydroxylamine hydrochloride, 200 cc of absolute ethanol and 20 g of 4 - (1 - methyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2-b]thiophen - 9,10 - dione base is boiled at reflux for 1 hour. The mixture is then cooled to 0—5°, and the precipitated crystalline material is filtered off. After recrystallization from methanol, pure 9,10 - dihydro - 9 - hydroxyimino - 4 - (1 - methyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2-b]thiophene hydrochloride, having a decomposition point of 290—300°, is obtained. Microanalysis agrees with the formula $C_{19}H_{20}N_2OS \cdot HCl$. The structure was ascertained from the infrared and nuclear magnetic resonance spectra.

EXAMPLE 5:

9,10 - Dihydro - 10 - hydroxyimino - 4 - (1 - methyl - 4 - piperidylidene) - 4H - benzo [4,5]cyclohepta[1,2-b]thiophene

A mixture of 15 g of 4 - (1 - methyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta [1,2-b]thiophen - 10(9H) - one base, 10.1 g of hydroxylamine hydrochloride and 120 cc of water is stirred at an internal temperature of 90° for 1 hour. The hot reaction solution is subsequently made alkaline with 3N caustic soda solution, and the base which crystallizes is filtered off. The crude base is purified by dissolving the same in 25 cc of glacial acetic acid and 50 cc of water, filtering with a small amount of charcoal and pouring the filtrate into a solution of 80 cc of concentrated ammonia and 500 cc of water. The precipitated base is filtered off, washed with water and dried in a vacuum. The pure 9,10 - dihydro - 10 - hydroxyimino - 4 - (1 - methyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2-b]thiophene base, having a M.P. of 239—241° (decomp.), is obtained in this manner. Microanalysis agrees with the formula $C_{19}H_{20}N_2OS$. In accordance with the nuclear magnetic resonance spectrum the product is a mixture of isomers of the syn/anti oxime at a ratio of 6:4.

EXAMPLE 6:

4 - (1 - Methyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2-b]thiophene - 9,10 - dione

50 g of 4 - (1 - methyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2-b]

thiophen - 10(9H) - one base are dissolved in 500 cc of glacial acetic acid, and 19.7 g of selenium dioxide are subsequently added. The reaction mixture is subsequently boiled at reflux for half an hour, is then poured on 1300 g of ice, and the pH is adjusted to 10 with 850 cc of concentrated caustic soda solution at 20° while cooling. The free base is extracted with 700 cc of chloroform. The chloroform solution is concentrated, and the evaporation residue is recrystallized from chloroform/petroleum ether (1:2). The pure 4 - (1 - methyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2-b]thiophene - 9,10 - dione base, having a M.P. of 200—201° (decomp.), is obtained in this manner. Microanalysis agrees with the formula $C_{19}H_{17}NO_2S$. The structure was ascertained from the infrared, ultraviolet, nuclear magnetic resonance and mass spectrograph spectra.

EXAMPLE 7:

4 - (1 - Benzyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2-b]thiophen - 10(9H) - one

11.6 g of 4 - (4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2-b]thiophen - 10(9H) - one base and 12.5 g of anhydrous soda are added to 120 cc of hexamethylphosphoric acid triamide, and 6 g of benzyl chloride are added at 25°. After stirring at room temperature for 18 hours, stirring is continued at 50° for 1 hour. The reaction mixture is subsequently diluted with 1000 cc of water, and the base is extracted with 500 cc of benzene. The benzene solution is concentrated and the residue is recrystallized from isopropanol. The pure 4 - (1 - benzyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta [1,2-b]thiophen - 10(9H) - one base, having a M.P. of 136—138°, is obtained in this manner. Microanalysis agrees with the formula $C_{25}H_{28}NOS$.

EXAMPLE 8:

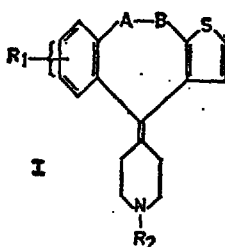
4 - (1 - p - Chlorobenzyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2-b]thiophen - 10(9H) - one

5.17 g of 4 - (4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2-b]thiophene - 10(9H) - one base and 5.56 g of anhydrous soda are added to 60 cc of hexamethylphosphoric acid triamide, and 3.38 g of p-chlorobenzyl chloride are added at 20—25°. After stirring at room temperature for 18 hours the reaction mixture is diluted with 500 cc of water, and the base is extracted with 350 cc of benzene. The benzene solution is concentrated and the residue is dissolved in 30 cc of absolute ethanol. This solution is made weakly acid with hydrochloric acid in ethanol, and after allowing to stand over night, the hydrochloride which crystallizes is filtered off at 0—5°. The crude hydrochloride is recrystallized from 85% ethanol. The pure 4 -

(1 - *p* - chlorobenzyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2-b]thiophen - 10(9H) - one hydrochloride, having a M.P. of 269—273° (decomp.), is obtained in this manner. Microanalysis agrees with the formula $C_{25}H_{22}ClNOS \cdot HCl$.

WHAT WE CLAIM IS:—

1. A compound of formula I,



10 wherein

R_1 is hydrogen, chlorine, bromine or alkoxy of 1 to 4 carbon atoms and is in the 6 or 7 position of the benzocycloheptathiophene nucleus,

15 R_2 is alkyl of 1 to 4 carbon atoms; benzyl; fluoro, chloro or bromo substituted benzyl; diphenylmethyl; or fluoro, chloro or bromo substituted diphenylmethyl, and either one of

20 A and B is hydroxymethylene or hydroxyiminomethylene and the other is methylene, or each of

A and B is carbonyl, or, when R_2 is benzyl; fluoro, chloro or bromo substituted benzyl; diphenylmethyl; or fluoro, chloro or bromo substituted diphenylmethyl, then one of

A and B is carbonyl and the other is methylene.

25 2. A compound of Claim 1, wherein A is hydroxymethylene and B is methylene, A is methylene and B is hydroxyiminomethylene, A is carbonyl and B is methylene, or each of A and B is carbonyl.

30 3. A compound of Claim 1, wherein A is methylene and B is hydroxymethylene, A is hydroxyiminomethylene and B is methylene, or A is methylene and B is carbonyl.

35 4. A compound of Claim 1, wherein either one of A and B is hydroxymethylene or hydroxyiminomethylene and the other is methylene.

40 5. A compound of Claim 1, wherein A is methylene and B is carbonyl.

45 6. A compound of Claim 1, wherein each of A and B is carbonyl.

7. A compound of any one of Claims 1 to 6, wherein R_1 is hydrogen.

50 8. A compound of any one of Claims 1 to 7, wherein R_2 is alkyl of 1 to 4 carbon atoms, benzyl, or chloro substituted benzyl.

9. The compound of Claim 1, which is 9,10 - dihydro - 4 - (1 - methyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2-b]thiophen - 9 - ol.

10. The compound of Claim 1, which is 4 - (1 - ethyl - 4 - piperidylidene) - 9,10 - dihydro - 4H - benzo[4,5]cyclohepta[1,2-b]thiophen - 9 - ol.

11. The compound of Claim 1, which is 9,10 - dihydro - 4 - (1 - methyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2-b]thiophen - 10 - ol.

12. The compound of Claim 1, which is 9,10 - dihydro - 9 - hydroxyimino - 4 - (1 - methyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2-b]thiophene.

13. The compound of Claim 1, which is 9,10 - dihydro - 10 - hydroxyimino - 4 - (1 - methyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2-b]thiophene.

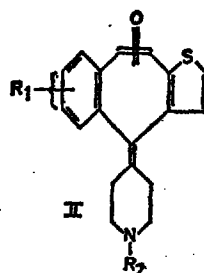
14. The compound of Claim 1, which is 4 - (1 - methyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2-b]thiophene - 9,10 - dione.

15. The compound of Claim 1, which is 4 - (1 - benzyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2-b]thiophen - 10(9H) - one.

16. 4 - (1 - *p* - chlorobenzyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2-b]thiophen - 10(9H) - one.

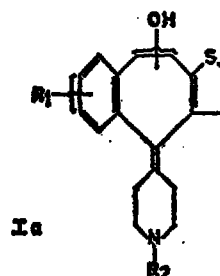
17. A process for the production of a compound of formula I as claimed in claim 1 which comprises

a) reducing a compound of formula II,



wherein

R_1 and R_2 are as defined above, and the oxo group is in the 9 or 10 position of the benzocycloheptathiophene nucleus, to produce a compound of formula Ia,



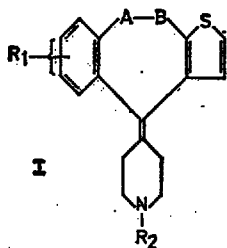
wherein

R_1 and R_2 are as defined above, and the hydroxy group is in the 9 or 10 position of the benzocycloheptathiophene nucleus,

(1 - *p* - chlorobenzyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2-b]thiophen - 10(9H) - one hydrochloride, having a M.P. of 269—273° (decomp.), is obtained in this manner. Microanalysis agrees with the formula $C_{25}H_{22}ClNOS \cdot HCl$.

WHAT WE CLAIM IS:—

1. A compound of formula I,



10 wherein

R_1 is hydrogen, chlorine, bromine or alkoxy of 1 to 4 carbon atoms and is in the 6 or 7 position of the benzocycloheptathiophene nucleus,

15 R_2 is alkyl of 1 to 4 carbon atoms; benzyl; fluoro, chloro or bromo substituted benzyl; diphenylmethyl; or fluoro, chloro or bromo substituted diphenylmethyl, and either one of

20 A and B is hydroxymethylene or hydroxyiminomethylene and the other is methylene, or each of

A and B is carbonyl, or, when R_2 is benzyl; fluoro, chloro or bromo substituted benzyl; diphenylmethyl; or fluoro, chloro or bromo substituted diphenylmethyl, then one of

A and B is carbonyl and the other is methylene.

2. A compound of Claim 1, wherein A is hydroxymethylene and B is methylene, A is methylene and B is hydroxyiminomethylene, A is carbonyl and B is methylene, or each of A and B is carbonyl.

3. A compound of Claim 1, wherein A is methylene and B is hydroxymethylene, A is hydroxyiminomethylene and B is methylene, or A is methylene and B is carbonyl.

4. A compound of Claim 1, wherein either one of A and B is hydroxymethylene or hydroxyiminomethylene and the other is methylene.

5. A compound of Claim 1, wherein A is methylene and B is carbonyl.

6. A compound of Claim 1, wherein each of A and B is carbonyl.

7. A compound of any one of Claims 1 to 6, wherein R_1 is hydrogen.

8. A compound of any one of Claims 1 to 7, wherein R_2 is alkyl of 1 to 4 carbon atoms, benzyl, or chloro substituted benzyl.

9. The compound of Claim 1, which is 9,10 - dihydro - 4 - (1 - methyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2-b]thiophen - 9 - ol.

10. The compound of Claim 1, which is 4 - (1 - ethyl - 4 - piperidylidene) - 9,10 - dihydro - 4H - benzo[4,5]cyclohepta[1,2-b]thiophen - 9 - ol.

11. The compound of Claim 1, which is 9,10 - dihydro - 4 - (1 - methyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2-b]thiophen - 10 - ol.

12. The compound of Claim 1, which is 9,10 - dihydro - 9 - hydroxyimino - 4 - (1 - methyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2-b]thiophene.

13. The compound of Claim 1, which is 9,10 - dihydro - 10 - hydroxyimino - 4 - (1 - methyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2-b]thiophene.

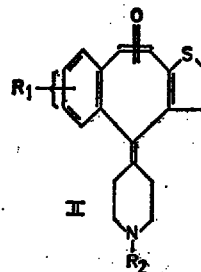
14. The compound of Claim 1, which is 4 - (1 - methyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2-b]thiophene - 9,10 - dione.

15. The compound of Claim 1, which is 4 - (1 - benzyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2-b]thiophen - 10(9H) - one.

16. 4 - (1 - *p* - chlorobenzyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2-b]thiophen - 10(9H) - one.

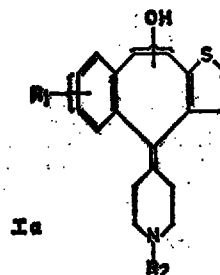
17. A process for the production of a compound of formula I as claimed in claim 1 which comprises

a) reducing a compound of formula II,



wherein

R_1 and R_2 are as defined above, and the oxo group is in the 9 or 10 position of the benzocycloheptathiophene nucleus, to produce a compound of formula Ia,

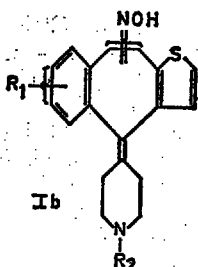


wherein

R_1 and R_2 are as defined above, and the hydroxy group is in the 9 or 10 position of the benzocycloheptathiophene nucleus,



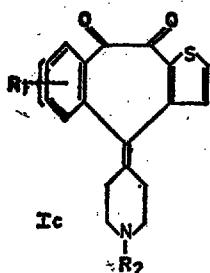
b) reacting a compound of formula II with hydroxylamine, to produce a compound of formula Ib,



5 wherein

R₁ and R₂ are as defined above, and the hydroxyimino group is in the 9 or 10 position of the benzocycloheptathiophene nucleus,

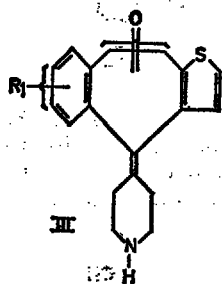
10 c) oxidizing a compound of formula II to produce a compound of formula Ic,



wherein

R₁ and R₂ are as defined above, or

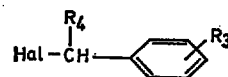
d) reacting a compound of formula III,



wherein

R₁ is as defined above, and the oxo group

is in the 9 or 10 position of the benzocycloheptathiophene nucleus, with a compound of formula IV,

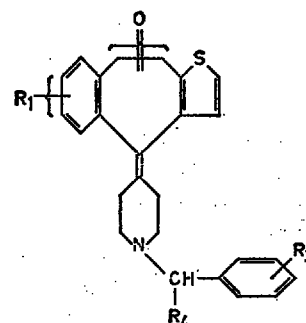


wherein

R₃ is hydrogen, fluorine, chlorine or bromine,

R₄ is hydrogen, phenyl, or fluoro, chloro, or bromo substituted phenyl, and

Hal is chlorine or bromine, to produce a compound of formula Id,



wherein

R₁, R₃ and R₄ are as defined above, and the oxo group is in the 9 or 10 position of the benzocycloheptathiophene nucleus.

18. A process according to claim 17 substantially as hereinbefore described with reference to any one of the Examples.

19. A compound of formula I whenever produced by the process of claim 17 or 18.

20. A compound of any one of Claims 1 to 10 and 19, in acid addition salt form.

21. A pharmaceutical composition which comprises a compound of any one of Claims 1 to 16 and 19, in free base or pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent.

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