1,055,055

PATENT SPECIFICATION

NO DRAWINGS

1,055,055

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The inventors of this invention in the sense of being the actual devisers thereof within the meaning of Section 16 of the Patents Act, 1949 are:— ERNST JUCKER of Steinweg 28, Ettingen, Switzerland, ANTON EBNOTHER of Bruderholzstrasse 8, Reinach/Baselland, Switzerland; JEAN-MICHEL BASTIAN of Rheinparkstrasse 5, Birsfelden, Switzerland; ERWIN RISSI of Birsigstrasse 115, Basel, Switzerland and ANDRE STOLL of Rheinparkstrasse 3, Birsfelden, Switzerland, all Swiss Citizens.

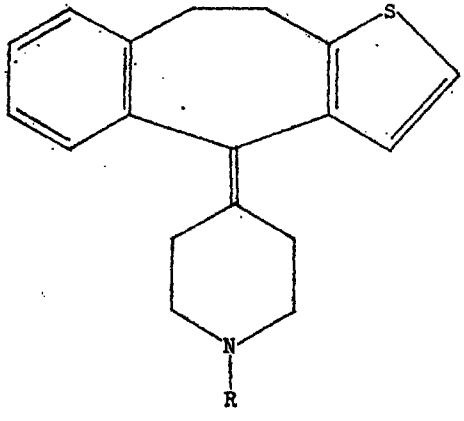
COMPLETE SPECIFICATION

Improvements in or relating to 4-[1'-Lower Alkyl Piperidylidene-(4')]-9,10-Dihydro-4H-Benzo[4,5]-Cyclohepta[1,2-b]Thiophene Derivatives

We, SANDOZ PATENTS LIMITED of 590 Jarvis Street, Toronto 5, Ontario, Canada, a Canadian 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 thiophene derivatives and a process for their production.

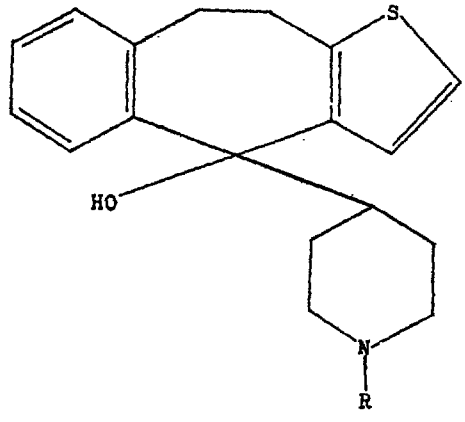
The present invention provides compounds of formula I,



I

in which R denotes an alkyl radical having 1—4 carbon atoms, acid addition salts of these and pharmaceutical compositions containing, in addition to an inert carrier, a compound I or an acid addition salt thereof.

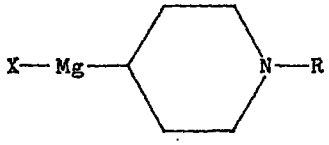
The present invention also provides a process for the production of compounds I and their acid addition salts, which comprises splitting off water from a compound of formula III,



III

in which R has the above significance, by heating with a water removing agent and, when an acid addition salt is required, reacting with an organic or inorganic acid; examples of such acids are hydrochloric, hydrobromic, sulphuric, citric, tartaric, succinic, maleic, malic, acetic, benzoic, hexahydrobenzoic, methanesulphonic, fumaric, gallic, and hydriodic acid. The compounds III may be pro-

duced by condensing 9,10-dihydro-4H-benzo [4,5]cyclohepta[1,2 - b]thiophen - (4) - one with a piperidine derivative of formula II,



II

in which R has the above significance, and X denotes a chlorine, bromine or iodine atom, and hydrolysing the condensation product.

Preferably, compounds I are produced by dropwise addition of a solution of 9,10-dihydro - 4H - benzo[4,5]cyclohepta[1,2-b] thiophen-(4)-one in an inert organic solvent to a solution of a compound II in an inert organic solvent and allowing the reaction mixture to stand for some time at room temperature, and/or heating to the boil; the resulting reaction product is hydrolysed, e.g. by treatment with ice cold aqueous ammonium chloride solution, and the resulting compound III isolated from the aqueous solution by a method known *per se* and purified, whereafter the compound I can be obtained by the action of a water removing agent, for example mineral acids, strong organic acids, acetic acid anhydrides, thionyl chloride or phosphorus oxychloride.

9,10 - dihydro - 4H - benzo[4,5]cyclohepta [1,2-b]thiophen-(4)-one is described and claimed in Patent Specification No: 5178/65; it may be produced by the method described and claimed in said specification.

The compounds I are crystalline or oily at room temperature; in general, they ~~are~~ form stable salts, which are crystalline at room temperature, with inorganic or organic acids.

The compounds I possess marked and long-lasting central and peripheral inhibiting effects against biogenic agents (serotonin, histamine, tryptamine, acetylcholine). Furthermore they are characterized by distinct sedative/neuroleptic properties and are found to be active in tests typical for antidepressants. The compounds are indicated for use in all those cases in which antaminics are indicated, i.e. allergic illnesses and asthmatic, e.g. dyspneic, affections. The central forms of the above-mentioned dysfunctions can also be treated. The compounds are also applicable to the treatment of migraine. Their damping, activating and antidepressive properties make them useful for the treatment of psychic illnesses of the schizophrenic-psychotic and depressive type, as well as of psychosomatic disturbances. They are further indicated for use in neuroses, insomnia and disturbances of the vegetative functions.

As indicated above, the compounds I may be used alone or in the form of preparations for enteral or parenteral administration, e.g. in admixture with inorganic or organic, pharmacologically inert auxiliary substances. The following auxiliary substances may, for example, be used:—

for tablets and for syrups dragées	:	lactose, starch, talc or stearic acid; cane sugar, invert sugar or glucose solutions;
for injection preparations	:	water, alcohols, glycerine or vegetable oils;
for suppositories	:	~~nate ral~~ or hardened oils or waxes;
for ointments, suspensions and emulsions	:	inorganic and organic lipo- or hydrophilic solutions, paraffin, petroleum jelly, alginates, cellulose derivatives, polyoxyethylene derivatives or bentonite.

The preparations may furthermore contain, e.g., suitable preserving agents, stabilizers, or wetting agents, solubilizers, sweetening and colouring agents or flavourings.

The compounds of the formula III above, their acid addition salts and the process for the production thereof are described and claimed in Patent Specification No. 5177/65.

In the following Examples, all temperature data are in degrees Centigrade. Melting points are uncorrected.

EXAMPLE 1:

4 - [1' - methyl - piperidylidene - (4')] 9,10 - dihydro - 4H - benzo [4,5] cyclohepta [1,2-b] thiophene hydrochloride

a) Thenylidene - (2) - phthalide

24.2g of thienyl - (2) - acetic acid, 52.0g of phthalic acid anhydride, 4.0g of anhydrous sodium acetate and 125 ml of 1-methyl-pyrrolidone-(2) are heated while stirring in an open flask for 3 hours to 205—208°, while nitrogen is passed through. It is then cooled and the viscous reaction mixture poured into 1 litre of water. The precipitated substance is filtered off, washed with water and then dissolved in 200 ml of chloroform. After filtering off some undissolved substance, shaking is effected twice with 100 ml of 2N sodium carbonate solution and then with water, drying is then carried out over sodium sulphate and evaporation in order to reduce the volume. The crude phthalide is repeatedly recrystallized from ethanol, while treating with animal charcoal. It melts at 114—115°.

b) o - [2 - thienyl - (2') - ethyl] - benzoic acid

24.0g of thenylidene - (2) - phthalide, 8.8g of red pulverised phosphorus, 240 ml of hydroiodic acid (density = 1.7) and 240 ml of glacial acetic acid are heated to boiling under nitrogen and while stirring vigorously. 70 ml of toluene are then added and 6.0g of red phosphorus added in small portions over

a period of one hour. It is then poured into 3 litres of ice water, stirred with 300 ml of chloroform and the phosphorus removed by filtration. The chloroform phase is then removed, the aqueous phase extracted twice more with 200 ml of chloroform and the united extracts shaken out 4 times, each time with 200 ml of 2N sodium hydroxide solution. The alkaline solution is then rendered acid to Congo red reagent, using hydrochloric acid and extracted three times with chloroform. After drying over sodium sulphate and evaporating the solvent, the residue is chromatographed on aluminium oxide (Activity Stage V). The substance eluted with benzene and benzene/chloroform (1:1) is recrystallized from chloroform/hexane (1:1); m.p. 107—109°.

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

200 ml of 85% phosphoric acid and 112g of phosphorus pentoxide are heated to 135°. 7.0g of *o* - [2 - thienyl - (2') - ethyl]-benzoic acid are then introduced while stirring thoroughly over a period of 30 minutes. Stirring is then continued for another hour at 135° and the reaction mixture is then stirred into 1 litre of ice water. Extraction is then effected three times, using 250 ml ether portions, the ethereal extract is washed with 2N sodium carbonate solution, dried over sodium sulphate and reduced in volume by evaporation. The residue is boiled up with 55 ml of ethanol, the solution freed of resin by decanting and then stirred at room temperature for 6 hours with animal charcoal. It is then filtered off, reduced in volume in a vacuum and the residue distilled. B.p. 120—124°/0.005 mm, $n_D^{24.5}=1.6559$.

d) 4 - [1' - methyl - piperidyl - (4')] - 9,10-dihydro - 4H - benzo[4,5]cyclohepta [1,2-b]thiophen-(4)-ol

0.94g of magnesium filings which have been activated with iodine are covered with a layer of absolute tetrahydrofuran and etched with a few drops of ethylene bromide. A solution of 5.0g of 1 - methyl - 4 - chloropiperidine in 5 ml of tetrahydrofuran is then added dropwise and boiling then effected for a further 1 hour under reflux. After cooling to room temperature, the solution of 4.5g of 9,10-dihydro - 4H - benzo[4,5]cyclohepta - [1,2-b] thiophen - (4) - one in 5 ml of tetrahydrofuran is added dropwise. Stirring is carried out first for 3 hours at room temperature and then for two hours at boiling temperature, it is then cooled and poured into 300 ml of ice-cold 20% ammonium chloride solution. It is then shaken out with methylene chloride, the methylene chloride solution washed with water and shaken three times with 30 ml portions of aqueous 2N tartaric acid solution. The tartaric acid extract is rendered alkaline while cooling thoroughly and then extracted twice with methylene chloride. After washing with water, drying over potassium carbonate and reducing in volume by evaporation, the residue is recrystallized from ethanol. M.p. 197—199°.

e) 4 - [1' - methyl - piperidylidene - (4')]-9,10 - dihydro - 4H - benzo[4,5]cyclohepta[1,2-b]thiophene hydrochloride

2g of 4 - [1' - methyl - piperidyl - (4')]-9,10 - dihydro - 4H - benzo[4,5]cyclohepta [1,2-b]thiophen - (4) - ol, 60 ml of glacial acetic acid and 20 ml of concentrated hydrochloric acid are boiled for 30 minutes under reflux. After evaporating in a vacuum, the residue is triturated with 3 ml of acetone, the precipitated hydrochloride is then filtered off and it is recrystallized from *iso*propanol/ether. M.p. 261—263° (decomposition). The free base is obtained by treating the hydrochloride with an alkali in manner known *per se*.

EXAMPLE 2:

4 - [1' - n - butyl - piperidylidene - (4')]-9,10 - dihydro - 4H - benzo[4,5]cyclohepta-[1,2-b]thiophene hydrochloride

a) Thenyl - diethyl - phosphonate

133g of 2 - thenyl - chloride (b.p. 73—75°/15 mm) are heated to 150°, and 175g of freshly distilled triethylphosphite slowly added dropwise while stirring at this temperature, following by further heating for 2 hours to 160—170° while stirring. The reaction mixture is then distilled in a high vacuum; the 2 - thenyl - diethyl - phosphonate boils at 120—124°/0.06 mm.

b) o - [2 - thienyl - (2') - ethenyl] - benzoic acid

30g of powdered, well-dried sodium methylate are added to a solution of 117g of 2 - thenyl - diethyl - phosphonate in 200 ml of freshly distilled dimethylformamide, whereupon the temperature of the solution rises to 45—50°. The flask is then placed in an ice bath and a solution of 80 g of *o*-phthalaldehydic acid in 200 ml of dimethylformamide added dropwise so that the temperature remains between 35—40° and stirring then continued for ½ to 1 hour at room temperature. 1600 ml of water (temperature 10—15°) are now added to the reaction solution, while cooling thoroughly, whereupon a red oil separates. It is then rendered alkaline with potassium carbonate, whereupon the oil redissolves; the red-brown solution is shaken out three times with benzene and the aqueous solution carefully adjusted to a pH value of 4 at 10—15° with hydrochloric acid. After several hours in a refrigerator, the precipitated acid is filtered off, dried and recrystallized from benzene. M.p. of the *o*-[2-thienyl-(2') - ethenyl] - benzoic acid 133—135°.

The mother liquor is shaken out three times with methylene chloride, the organic phase dried over sodium sulphate and reduced in volume by evaporation in a vacuum. The resi-

due is crystallized from benzene, whereupon a further portion of acid is obtained having a m.p. of 133—135°.

c) o - [2 - thienyl - (2') - ethyl] - benzoic acid

7.5g of sodium are melted under dry toluene and 375g of pure mercury are added dropwise while shaking at frequent intervals so that the toluene boils. The mixture is then heated while stirring to 120—140° and cooled as soon as all the toluene has distilled off, down to a temperature of 50°. The homogeneous amalgam is now covered with a layer of a solution of 20g of *o* - [2 - thienyl - (2') - ethenyl] - benzoic acid in 150 ml of 95% ethanol and the mixture shaken for ½ hour. The mercury is then separated, washed twice with ethanol and the united ethanolic solutions diluted with 1200 ml of water. The solution is filtered through Hyflo (Registered Trade Mark), acidified with hydrochloric acid and cooled to 5°. After several hours, the precipitated acid is filtered off and recrystallized from chloroform/hexane. M.p. 110—111°.

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

59 ml of 84% phosphoric acid and 86g of phosphorus pentoxide are first stirred for ½ hour at 125—130°. 20g of powdered *o*-[2 - thienyl - (2') - ethyl] - benzoic acid are then introduced over a period of ½ hour at this temperature. The reaction mixture is stirred for a further 2 hours at 125—130°, it is then poured into 1 litre of water, the solution filtered through Hyflo and extracted three times with methylene chloride. The organic phase is washed with 2N sodium carbonate solution, dried over magnesium sulphate, the solvent is removed by evaporation and the residue is distilled in a high vacuum, whereupon the 9,10 - dihydro - 4H - benzo[4,5]cyclohepta[1,2-b]thiophen - (4) - one distils over as a green oil at 125—140°/0.05 mm. $n_D^{24} = 1.6559$.

e) 4 - [1' - n - butyl - piperidyl - (4')] - 9,10 - dihydro - 4H - benzo[4,5]cyclohepta[1,2-b]thiophen - (4) - ol

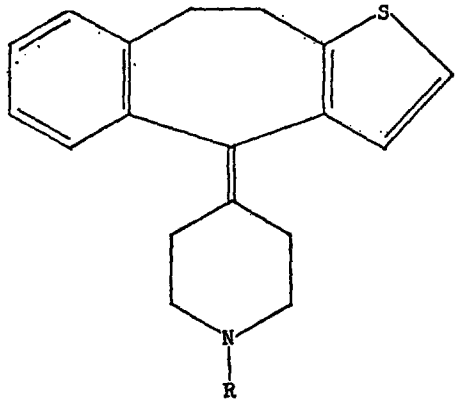
1.25g of iodine activated magnesium are covered with a layer consisting of a little absolute tetrahydrofuran and etched with a few drops of ethylene bromide. After reaction has commenced, a solution of 8.8g of 1 - *n*-butyl - 4 - chloro - piperidine in 10 ml of tetrahydrofuran is added dropwise so that the reaction mixture boils. It is heated for a further hour under reflux, cooled down, and a solution of 6.0g of 9,10-dihydro-4H-benzo[4,5]cyclohepta[1,2-b]thiophen - (4) - one in 15 ml of tetrahydrofuran are added dropwise while stirring over 15 minutes and heating carried out for a further 15 minutes to boiling. After cooling, the reaction mixture is poured into 200 ml of 20% aqueous ammonium chloride solution. 100 ml of methylene chloride are added and all filtered through Hyflo, the organic phase is separated and the aqueous solution shaken out three times more with methylene chloride. The united organic phases are shaken out three times with 2N tartaric acid, the united acid extracts slowly rendered alkaline with potassium hydroxide and extracted three times with ether. The residue left after drying and evaporating the ether is distilled in a high vacuum. The fraction which distils between 195—200° at 0.05 mm Hg is crystallized and recrystallized from CCl_4/hexane. M.p. 107—108°.

f) 4 - [1' - n - butyl - piperidylidene - (4')] - 9,10 - dihydro - 4H - benzo[4,5]cyclohepta[1,2-b]thiophene hydrochloride

A mixture of 5.0g of 4 - [1' - butyl-piperidyl - (4')] - 9,10 - dihydro - 4H-benzo[4,5]cyclohepta[1,2 - b]thiophen - (4)-ol, 90 ml of glacial acetic acid and 30 ml of concentrated hydrochloric acid is boiled under reflux for one hour. The reaction mixture is then reduced in volume by evaporation in a vacuum and the residue triturated with 3 ml of acetone. The hydrochloride which crystallizes out on cooling is recrystallized from *iso*-propanol/ether. M.p. 272—274° (decomposition). The free base is obtained from the hydrochloride by treating with an alkali in manner known *per se*.

WHAT WE CLAIM IS:—

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



I

in which R denotes an alkyl radical having 1—4 carbon atoms,

and their acid addition salts, which comprises splitting off water from a compound of formula III,

due is crystallized from benzene, whereupon a further portion of acid is obtained having a m.p. of 133—135°.

c) o - [2 - thienyl - (2') - ethyl] - benzoic acid

7.5g of sodium are melted under dry toluene and 375g of pure mercury are added dropwise while shaking at frequent intervals so that the toluene boils. The mixture is then heated while stirring to 120—140° and cooled as soon as all the toluene has distilled off, down to a temperature of 50°. The homogeneous amalgam is now covered with a layer of a solution of 20g of *o* - [2 - thienyl - (2') - ethenyl] - benzoic acid in 150 ml of 95% ethanol and the mixture shaken for ½ hour. The mercury is then separated, washed twice with ethanol and the united ethanolic solutions diluted with 1200 ml of water. The solution is filtered through Hyflo (Registered Trade Mark), acidified with hydrochloric acid and cooled to 5°. After several hours, the precipitated acid is filtered off and recrystallized from chloroform/hexane. M.p. 110—111°.

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

59 ml of 84% phosphoric acid and 86g of phosphorus pentoxide are first stirred for ½ hour at 125—130°. 20g of powdered *o*-[2 - thienyl - (2') - ethyl] - benzoic acid are then introduced over a period of ½ hour at this temperature. The reaction mixture is stirred for a further 2 hours at 125—130°, it is then poured into 1 litre of water, the solution filtered through Hyflo and extracted three times with methylene chloride. The organic phase is washed with 2N sodium carbonate solution, dried over magnesium sulphate, the solvent is removed by evaporation and the residue is distilled in a high vacuum, whereupon the 9,10 - dihydro - 4H - benzo[4,5] cyclohepta[1,2-b]thiophen - (4) - one distils over as a green oil at 125—140°/0.05 mm. $n_D^{24} = 1.6559$.

e) 4 - [1' - n - butyl - piperidyl - (4')] - 9,10 - dihydro - 4H - benzo[4,5]cyclohepta [1,2-b]thiophen - (4) - ol

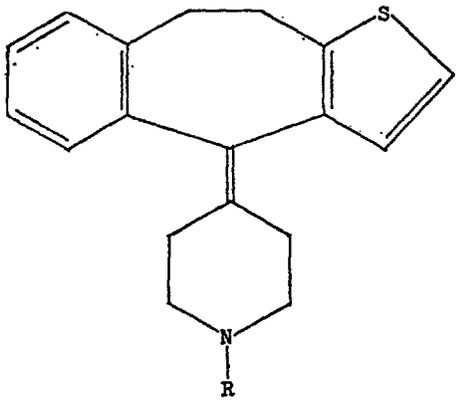
1.25g of iodine activated magnesium are covered with a layer consisting of a little absolute tetrahydrofuran and etched with a few drops of ethylene bromide. After reaction has commenced, a solution of 8.8g of 1 - *n*-butyl - 4 - chloro - piperidine in 10 ml of tetrahydrofuran is added dropwise so that the reaction mixture boils. It is heated for a further hour under reflux, cooled down, and a solution of 6.0g of 9,10-dihydro-4H-benzo [4,5]cyclohepta[1,2-b]thiophen - (4) - one in 15 ml of tetrahydrofuran are added dropwise while stirring over 15 minutes and heating carried out for a further 15 minutes to boiling. After cooling, the reaction mixture is poured into 200 ml of 20% aqueous ammonium chloride solution. 100 ml of methylene chloride are added and all filtered through Hyflo, the organic phase is separated and the aqueous solution shaken out three times more with methylene chloride. The united organic phases are shaken out three times with 2N tartaric acid, the united acid extracts slowly rendered alkaline with potassium hydroxide and extracted three times with ether. The residue left after drying and evaporating the ether is distilled in a high vacuum. The fraction which distils between 195—200° at 0.05 mm Hg is crystallized and recrystallized from CCl_4/hexane. M.p. 107—108°.

f) 4 - [1' - n - butyl - piperidylidene - (4')] - 9,10 - dihydro - 4H - benzo[4,5]cyclohepta [1,2-b]thiophene hydrochloride

A mixture of 5.0g of 4 - [1' - butyl-piperidyl - (4')] - 9,10 - dihydro - 4H-benzo[4,5]cyclohepta[1,2 - b]thiophen - (4)-ol, 90 ml of glacial acetic acid and 30 ml of concentrated hydrochloric acid is boiled under reflux for one hour. The reaction mixture is then reduced in volume by evaporation in a vacuum and the residue triturated with 3 ml of acetone. The hydrochloride which crystallizes out on cooling is recrystallized from *iso*-propanol/ether. M.p. 272—274° (decomposition). The free base is obtained from the hydrochloride by treating with an alkali in manner known *per se*.

WHAT WE CLAIM IS:—

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

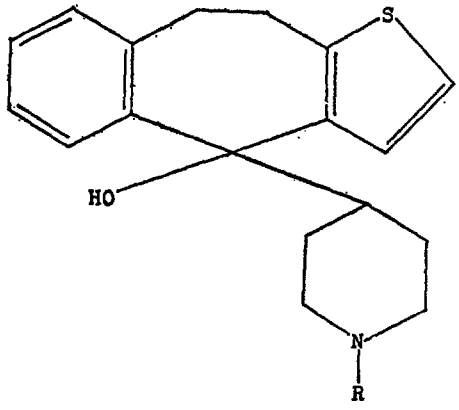


I

in which R denotes an alkyl radical having 1—4 carbon atoms,

and their acid addition salts, which comprises splitting off water from a compound of formula III,

* C L M S *

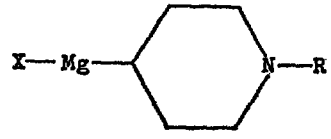


III

in which R has the above significance, by heating with a water removing agent and, when an acid addition salt is required, reacting the resulting product with an organic or inorganic acid.

2. A process according to Claim 1, in which the water removing agent is a mineral acid, a strong organic acid, an acetic acid anhydride, thionyl chloride or phosphorus oxychloride.

3. A process according to claim 1 or 2, in which the compound III is produced by condensing 9,10 - dihydro - 4H - benzo[4,5] cyclohepta[1,2-b]thiophen - (4) - one with a piperidine derivative of formula II,



II

in which R has the significance stated in claim 1, and X denotes a chlorine, bromine or iodine atom, and hydrolysing the condensation product.

4. A process for the production of the compounds I stated in claim 1 and their acid addition salts substantially as herein described with reference to any one of the Examples.

5. The compounds of formula I stated in claim 1 and their acid addition salts whenever produced by the process claimed in any one of the preceding claims.

6. The compounds of formula I stated in claim 1 and their acid addition salts.

7. 4 - [1' - methyl - piperidylidene - (4')]-9,10 - dihydro - 4H - benzo[4,5]cyclohepta [1,2-b]thiophene.

8. 4 - [1' - *n* - butyl - piperidylidene-(4')] - 9,10 - dihydro - 4H - benzo[4,5]cyclohepta[1,2-b]thiophene.

9. The acid addition salts of the compounds claimed in claims 7 and 8.

10. Pharmaceutical compositions containing in addition to a physiologically acceptable carrier a compound claimed in any one of claims 5 to 9.

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* C L M S *