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PATENT SPECIFICATION

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1355 539

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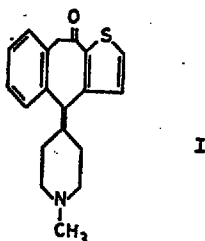
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(54) A BENZOCYCLOHEPTATHIOPHENE DERIVATIVE

(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 benzocycloheptathiophene derivatives, especially the compound of formula I,



which is 4 - (1 - methyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2 - b]thiophen - 10(9H) - one.

This application is a divided-out application of our copending application No. 23482/71 (Serial No. 1355537) which describes and claims processes for the production of the compound of formula I and analogous compounds.

The compound of formula I exhibits specific histaminolytic properties, as shown by the histamine toxicity test in guinea pigs. The specificity of the histaminolytic effect of the compound of formula I is indicated by the results of the serotonin toxicity test and of the acetylcholine toxicity test in guinea pigs, because no or low serotonin - antagonistic and anticholinergic properties have been detected.

[Price

Owing to the above property the compound is indicated for use in the treatment of allergic diseases requiring specific histaminolytic treatment.

The indicated daily dosage is in the range from about 0.5 to 10 mg, conveniently administered in divided doses 2 to 3 times a day in unit dosage form, in which the amount of compound of formula I is in the range from about 0.15 to 5 mg, or in sustained release form.

The compound of formula I may be administered in pharmaceutically acceptable acid addition salt form. Such salts possess the same order of activity as the free base form and are readily prepared in conventional manner. Suitable such salt forms include the fumarate.

A pharmaceutical composition may comprise the compound of formula I, in free base form or in pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent.

The compound of formula I is prepared in accordance with the following examples, in which all temperatures are indicated in degrees Centigrade.

EXAMPLE 1

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

A mixture of 24.6 g of crude 4 - (1 - methyl - 4 - piperidylidene) - 9 - piperidino - 4H - benzo[4,5]cyclohepta[1,2 - b]thiophene base and 4 - (1 - methyl - 4 - piperidylidene) - 10 - piperidino - 4H - benzo[4,5]cyclohepta[1,2 - b]thiophene base is dissolved in 250 cc. of 2N hydrochloric acid, and the solution is heated under reflux for 1 hour. The reaction mixture is subsequently made alkaline with a concentrated

caustic soda solution while cooling at 20—25°, and the precipitated base is extracted portionwise with a total of 400 cc of chloroform. The combined chloroform extracts are washed thrice with 30 cc amounts of water, are dried over sodium sulphate and concentrated. The residue is dissolved in 50 cc of chloroform and adsorbed on 1000 g of silica gel. Elution is effected with chloroform containing 3% of methanol. The first 6 liters of eluate are discarded, the following 4 liters are jointly concentrated. An oily material, mainly consisting of the two isomers 4 - (1 - methyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2 - b]thiophen - 9(10) - one and 4 - (1 - methyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2 - b]thiophen - 10(9H) - one, is obtained as residue. The mixture is separated by dissolving 19.7 g of the residue in 200 cc of isopropanol and boiling with 7 g of fumaric acid. The reaction mixture is subsequently allowed to crystallize at room temperature for approximately three hours. The crystals are filtered off and the isopropanolic filtration mother liquor is concentrated by evaporation in a vacuum. 100 cc of water and 6 g of potash are added to the evaporation residue, and the liberated base is extracted portionwise with 200 cc of chloroform. The chloroform extracts are washed with 50 cc of water and dried over sodium sulphate. After concentrating the chloroform solution, an oily residue is obtained, which is crystallized by boiling with 20 cc of ethyl acetate. After cooling overnight at 0—5°, the product is filtered off and dried. The pure 4 - (1 - methyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2 - b]thiophen - 10(9H) - one base, having a M.P. of 152—153°, is obtained in this manner. Microanalysis agrees with the formula $C_{19}H_{19}NOS$. The structure was ascertained with the infrared, nuclear magnetic resonance and mass spectrograph spectra.

The fumarate is produced by dissolving 8 g of the pure base with 3.2 g of fumaric acid in 100 cc of absolute ethanol at the boil and allowing the solution to crystallize over night at 0—5°. After filtration and drying, the pure 4 - (1 - methyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2 - b]thiophen - 10(9H) - one hydrogen fumarate, having a M.P. of 192° (decomp.), is obtained.

The mixture of 4 - (1 - methyl - 4 - piperidylidene) - 9 - piperidino - 4H - benzo[4,5]cyclohepta[1,2 - b]thiophene base and 4 - (1 - methyl - 4 - piperidylidene) - 10 - piperidino - 4H - benzo[4,5]cyclohepta[1,2 - b]thiophene base, used as starting material, may, for example, be produced as follows:

A mixture of 129 g of 9,10 - dihydro - 4H - benzo[4,5]cyclohepta[1,2 - b]thiophen - 4 - one, 214 g of N - bromosuccinimide, 1.2

g of benzoyl peroxide and 2000 cc of absolute carbon tetrachloride is boiled under reflux while stirring for 3 hours. The mixture is subsequently filtered whilst hot and the filtrate is concentrated to one third of its original volume. After allowing to stand at room temperature for several hours, the crystalline product is filtered off and dried. This crude product is recrystallized from a 7-fold quantity of chloroform. Pure 9,10 - dibromo - 9,10 - dihydro - 4H - benzo[4,5]cyclohepta[1,2 - b]thiophen - 4 - one, having a M.P. of 134—135° (decomp.), is obtained in this manner. Microanalysis agrees with the formula $C_{19}H_{15}Br_2OS$. The structure was ascertained with the nuclear magnetic resonance spectrum.

A mixture of 70 g of 9,10 - dibromo - 9,10 - dihydro - 4H - benzo[4,5]cyclohepta[1,2 - b]thiophen - 4 - one, 31.6 g of potassium hydroxide and 3200 cc of methanol is heated under reflux while stirring for 2 hours. The mixture is subsequently stirred at 0—5° for approximately 4 hours, and the crystalline product is filtered off. After recrystallizing from a 100-fold quantity of methanol, pure 9(10) - bromo - 4H - benzo[4,5]cyclohepta[1,2 - b]thiophen - 4 - one, having a M.P. of 134—135°, is obtained. Microanalysis agrees with the formula $C_{19}H_{15}BrOS$. In accordance with the nuclear magnetic resonance spectrum the bromine atom is in the 9 or 10 position (probably in the 10 position).

5 g of magnesium activated with iodine are covered with a layer of 15 cc of absolute tetrahydrofuran, and the mixture is heated to reflux temperature. 2 g of freshly distilled 1 - methyl - 4 - chloropiperidine and a few drops of 1,2 - dibromoethane are subsequently added, whereby the Grignard reaction commences. 22.8 g of freshly distilled 1 - methyl - 4 - chloropiperidine, dissolved in 30 cc of absolute tetrahydrofuran, are then added dropwise, without heating, at such a rate that the mixture boils continuously. After the dropwise addition is complete, the mixture is boiled under reflux for a further 2 hours, whereafter the magnesium is practically completely converted. A warm solution of 30 g of 9(10) - bromo - 4H - benzo[4,5]cyclohepta[1,2 - b]thiophen - 4 - one in 160 cc of absolute tetrahydrofuran is subsequently added dropwise while cooling at 20—25° during the course of 1 hour. After stirring at 20—25° for 1 1/2 hour, the reaction mixture is poured onto a mixture of 250 g of ice water and 35 g of ammonium chloride, and the precipitated base is extracted portionwise with a total of 600 cc of chloroform. The combined chloroform phases are washed with 50 cc of water, dried over sodium sulphate and concentrated in a vacuum. The crude 9(10) - bromo - 4 - (1 - methyl - 4 - piperidyl) - 4H - benzo-

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total of
chloro-
of water,
centrated
- 4 -
benzo-

[4,5]cyclohepta[1,2 - b]thiophen - 4 - ol
base is obtained as residue and is worked up
in conventional manner.

A solution of 51 g of crude 9(10) -
bromo - 4 - (1 - methyl - 4 - piperidyl) -
4H - benzo[4,5]cyclohepta[1,2 - b]thiophen -
4 - ol and 420 cc of a 14% solution of
hydrobromic acid in ethanol is boiled under
reflux at an oil bath temperature of 100°
for 1 hour. The mixture is subsequently con-
centrated in a vacuum and the residue dis-
solved in 100 cc of water. The solution is
made alkaline with a concentrated caustic
soda solution, whereupon the precipitated
base is extracted thrice with 100 cc of
chloroform. The combined chloroform
extracts are washed with 50 cc of water,
dried over sodium sulphate and concentrated
by evaporation in a vacuum. The residue is
dissolved in 70 cc of chloroform containing
5% of methanol and is adsorbed on 1000 g
of silica gel. Elution is effected with chloro-
form containing 5% of methanol. The first
8 liters of eluate are discarded, the following
4 liters are jointly concentrated by evapora-
tion. An oily evaporation residue is obtained,
which is dissolved by boiling in 50 cc of
isopropanol and is crystallized over night at
0-5°. After filtering off the crystalline pro-
duct and drying, the pure 9(10) - bromo -
4 - (1 - methyl - 4 - piperidylidene) - 4H -
benzo[4,5]cyclohepta[1,2 - b]thiophene base,
having a M.P. of 149-150°, is obtained.
Microanalysis agrees with the formula
C₁₆H₁₈BrNS. In accordance with the nuclear
magnetic resonance spectrum the bromine
atom is in the 9 or 10 position (probably
in the 10 position).

A mixture of 24.2 g of 9(10) - bromo -
4 - (1 - methyl - 4 - piperidylidene) - 4H -
benzo[4,5]cyclohepta[1,2 - b]thiophene, 160
cc of piperidine, 330 cc of absolute dioxane
and 14.6 g of potassium *tert.* butylate is
boiled under reflux at an oil bath tempera-
ture of 130° while stirring for 2 hours. The
mixture is subsequently cooled, filtered and
concentrated by evaporation in a vacuum.
The residue is dissolved in 300 cc of benzene,
and this solution is washed out thrice with 50
cc amounts of water. After drying the benzene
solution over sodium sulphate, this is con-
centrated by evaporation in a vacuum. A
mixture of the crude, oily 4 - (1 - methyl -
4 - piperidylidene) - 9 - piperidino - 4H -
benzo[4,5]cyclohepta[1,2 - b]thiophene base
and the 4 - (1 - methyl - 4 - piperidylidene) -
10 - piperidino - 4H - benzo[4,5]cyclo-
hepta[1,2 - b]thiophene base is obtained as
residue and is further worked up in conven-
tional manner.

EXAMPLE 2

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

A mixture of 23.5 g of crude 9 - *tert.*-
butoxy - 4 - (1 - methyl - 4 - piperidyl-
idene) - 4H - benzo[4,5]cyclohepta[1,2 - b]-
thiophene base and 10 - *tert.*butoxy - 4 -
(1 - methyl - 4 - piperidylidene) - 4H -
benzo[4,5]cyclohepta[1,2 - b]thiophene base
is dissolved at 50° in 235 cc of 3N hydro-
chloric acid. This solution is subsequently
boiled under reflux at an oil bath tempera-
ture of 130° for half an hour. The reaction
mixture is subsequently cooled to room tem-
perature and made alkaline with a concen-
trated caustic soda solution. The precipitated
base is extracted portionwise with 300 cc of
chloroform. The combined chloroform extracts
are washed with 100 cc of water, dried over
sodium sulphate and concentrated. The
evaporation residue is dissolved in 200 cc
of chloroform containing 3% of methanol and
is adsorbed on 500 g of silica gel. Elution
is effected with chloroform containing 3% of
methanol. The first 2 liters of eluate are dis-
carded, the following 1.5 liters are jointly
concentrated. An oily material, mainly con-
sisting of the two isomers 4 - (1 - methyl -
4 - piperidylidene) - 4H - benzo[4,5]cyclo-
hepta[1,2 - b]thiophen - 9(10) - one and
4 - (1 - methyl - 4 - piperidylidene) - 4H -
benzo[4,5]cyclohepta[1,2 - b]thiophen -
10(9H) - one is obtained as residue. The
mixture is separated by dissolving 15 g of
the residue in 45 cc of isopropanol and
adding a hot solution of 5.65 g of fumaric
acid in 130 cc of isopropanol. The reaction
solution is subsequently allowed to crystallize
over night at 40°. The crystalline product is
filtered off with suction and the isopropanolic
filtration mother liquor is concentrated in a
vacuum. 100 cc of water are added to the
evaporation residue, and this is made alkaline
with a concentrated caustic soda solution. The
precipitated base is extracted portionwise with
90 cc of chloroform. The chloroform extracts
are washed with 30 cc of water, dried over
sodium sulphate and concentrated. An oily
base is obtained, which is crystallized from
25 cc of isopropanol. After cooling over night
the crystalline product is filtered off and dried.
The crude 4 - (1 - methyl - 4 - piperidyl-
idene) - 4H - benzo[4,5]cyclohepta[1,2 - b]-
thiophen - 10(9H) - one base, having a M.P.
of 152-153°, is obtained in this manner.

The mixture of 9 - *tert.*butoxy - 4 - (1 -
methyl - 4 - piperidylidene) - 4H - benzo-
[4,5]cyclohepta[1,2 - b]thiophene base and
10 - *tert.*butoxy - 4 - (1 - methyl - 4 -

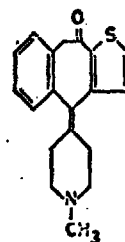
piperidylidene) - 4H - benzo[4,5]cyclohepta-[1,2 - b]thiophene base, used as starting material, may, for example, be produced as follows:

- 5 A mixture of 30 g of 9(10) - bromo - 4 - (1 - methyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2 - b]thiophene base, produced as described in Example 1, 300 cc of dioxane and 18.1 g of potassium *tert*.butylate
- 10 is stirred at 20—22° for 21 hours. The reaction mixture is subsequently filtered and the filtrate is concentrated in a vacuum. 300 cc of benzene are added to the residue and the solution is washed out thrice with 40 cc
- 15 amounts of water. The benzene solution is subsequently dried over sodium sulphate and concentrated. A mixture of crude, oily 9 - *tert*.butoxy - 4 - (1 - methyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2 - b]thiophene base and 10 - *tert*.butoxy - 4 -
- 20 (1 - methyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2 - b]thiophene base is obtained as residue and is further worked up as such.

- 25 In so far as the production of the starting materials used in the above Examples is not particularly described above, the compounds are known or may be produced in accordance with known processes.

WHAT WE CLAIM IS:—

1. The compound of formula I,



- which is 4 - (1 - methyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta-[1,2 - b]thiophen - 10(9H) - one.
2. The compound according to Claim 1, in acid addition salt form.
3. The compound according to Claim 1, in free base form.
4. The pharmaceutical composition which comprises the compound according to Claim 1, in free base form or in pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent.

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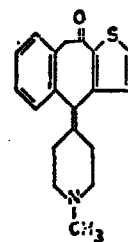


piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2 - b]thiophene base, used as starting material, may, for example, be produced as follows:

- 5 A mixture of 30 g of 9(10) - bromo - 4 - (1 - methyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2 - b]thiophene base, produced as described in Example 1, 300 cc of dioxane and 18.1 g of potassium *tert*.butylate
- 10 is stirred at 20—22° for 21 hours. The reaction mixture is subsequently filtered and the filtrate is concentrated in a vacuum. 300 cc of benzene are added to the residue and the solution is washed out thrice with 40 cc
- 15 amounts of water. The benzene solution is subsequently dried over sodium sulphate and concentrated. A mixture of crude, oily 9 - *tert*.butoxy - 4 - (1 - methyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2 - b]thiophene base and 10 - *tert*.butoxy - 4 - (1 - methyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2 - b]thiophene base is obtained as residue and is further worked up as such.
- 25 In so far as the production of the starting materials used in the above Examples is not particularly described above, the compounds are known or may be produced in accordance with known processes.

WHAT WE CLAIM IS:—

1. The compound of formula I,



I

which is 4 - (1 - methyl - 4 - piperidylidene) - 4H - benzo[4,5]cyclohepta[1,2 - b]thiophen - 10(9H) - one.

2. The compound according to Claim 1, in acid addition salt form.

3. The compound according to Claim 1, in free base form.

4. The pharmaceutical composition which comprises the compound according to Claim 1, in free base form or in pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent.

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