CONVENTION APPLICATION FOR A PATENT

(This form may be signed by the applicant or by the Australian Patent Attorney)

Insert full name(s) and address(es) of applicant(s)

XX
We
SANDOZ LTD.,
of Lichtstrasse 35,
CH-4002 Basle,
Switzerland,

hereby apply for the grant of a Patent for an invention entitled

"VYNYLCYCLOHEXATRIMETHYLENE Y"

which is described in the accompanying complete specification. The application is a
Convention application and is based on the application(s) for patent or similar protec-
tion made in SWITZERLAND

on 24th June, 1975 under No. 8173/75
24th June, 1975 under No. 8174/75

APPLICATION ACCEPTED AND AMENDMENTS
ALLOWED

Dated this 22nd day of June, 1976.

(a) Signature(s) of applicant(s).
If a Company, form to
be executed in a manner
pending on the Company
according to its Articles
of Association or the
laws of the country.

(b) Seal of Company
(if any).

Note: Initial all Alterations.

THE COMMISSIONER OF PATENTS
COMMONWEALTH
PATENTS ACT 1932-1969

DECLARATION IN SUPPORT OF CONVENTION OR NON-CONVENTION APPLICATION FOR A PATENT OR PATENT OF ADDITION

(The declarant shall be made by the applicant, or, if the applicant is a body corporate, by a person authorized by the body corporate to make the declaration on its behalf).

In support of the Application made for a patent or patent of addition for an invention entitled

"IMPROVEMENTS IN OR RELATING TO ORGANIC COMPOUNDS"

1520376

We, Jean Kramer and Peter Rass, both of SANDOZ LTD., of Lichtistrasse 35, CH-4002, Basle, Switzerland,

do solemnly and sincerely declare as follows:

1. (a) I am the applicant for the patent of addition. We are the applicant for the patent of addition.

(b) I am authorized by SANDOZ LTD.,

the applicant for the patent of addition to make this declaration on its behalf.

2. (a) I am the actual inventor of the invention.

(b) Jean-Michel Bastian, of 29 Nelkenstrasse, CH-4106 Therwil, Switzerland,

is the actual inventor of the invention. We are the facts upon which the applicant is entitled to make the application are as follows:

The inventor has assigned the invention to the applicant.

(Paragraphs 3 and 4 apply only to Convention applications).

3. The basic application, made in Switzerland, was the first application, the subject of the application.

SPITZERLAND on the 24th June, 1975
by JEAN-MICHEL BASSTIAN

SPITZERLAND on the 24th June, 1975
by JEAN-MICHEL BASSTIAN

4. The basic application, referred to in paragraph 3 of this Declaration were the first application, made in a Convention country in respect of the invention the subject of the application.

Declared at BASLE this 24th day of May, 1976.

SAN D O Z LTD.
Claim 1. A process for the production of a compound of formula I,

wherein $R_1$ is hydrogen or alkyl of 1 to 4 carbon atoms,
$R_2$ is alkyl of 1 to 4 carbon atoms

.../2
which comprises

(a) for the production of a compound of formula Ia,

\[ \text{II} \]

wherein \( R^I_1 \) is alkyl of 1 to 4 carbon atoms, and

\[ R^I_2 \] is as defined above,

splitting off water from a compound of formula II,

\[ \text{III} \]

wherein \( R^I_1 \) and \( R^I_2 \) are as defined above, or

(b) for the production of a compound of formula Ib,

\[ \text{IV} \]

wherein \( R^I_2 \) is as defined above,

splitting off the group \( R^I_3 \) from a compound of formula III,
wherein $R_2$ is as defined above, and

$R_3$ is a group capable of being split off.

Claim 2. A compound of formula I, as defined in Claim 1.
Name of Applicant: SANDOZ LTD.,

Address of Applicant: Lichtstrasse 35, CH-4002 BASLE, Switzerland,

Actual Inventor(s): JEAN-MICHEL BASTIAN

Address for Service: DAVIES & COLLISON, Patent Attorneys,
Grahamwell-Building, 34 Bourke Street, Melbourne, 3000

Complete Specification for the invention entitled: "BENZOCYCLOHEPTATHIOPHINES"

The following statement is a full description of this invention, including the best method of performing it known to us :-
This invention relates to benzocycloheptathiophenes.

The present invention provides compounds of formula I,

\[
\begin{array}{c}
\text{R}_2 \\
\text{R}_1
\end{array}
\]

wherein \( \text{R}_1 \) is hydrogen or alkyl of 1 to 4 carbon atoms,

\( \text{R}_2 \) is alkyl of 1 to 4 carbon atoms,

When \( \text{R}_1 \) is alkyl, it is preferably methyl or ethyl.

\( \text{R}_2 \) is preferably in the 6 or 7 position of the benzo[4,5]-cyclohepta[1,2-b] thiophene nucleus. \( \text{R}_2 \) is preferably methyl.

Especially preferred compounds are those wherein \( \text{R}_1 \) is hydrogen or methyl, and \( \text{R}_2 \) is methyl in the 6 or 7 position.
The present invention also provides a process for the production of compounds of formula I which comprises

a) for the production of a compound of formula Ia,

\[
\begin{align*}
\text{Ia} & \\
& R_2 \quad \text{wherein } R \text{ is alkyl of 1 to 4 carbon atoms, and} \\
& R_2 \text{ is as defined above,}
\end{align*}
\]

splitting off water from a compound of formula II,

\[
\begin{align*}
\text{II} & \\
& R_2 \quad \text{wherein } R_1 \text{ and } R_2 \text{ are as defined above, or}
\end{align*}
\]

b) for the production of a compound of formula Ib,
wherein \( R_2 \) is as defined above, splitting off the group \( R_3 \) from a compound of formula III, wherein \( R_2 \) is as defined above, and \( R_3 \) is a group capable of being split off.

Process a) may be effected in conventional manner for the dehydration of analogous carbinols, for example using a suitable dehydrating agent optionally in the presence of an inert solvent, e.g. a lower alcohol. As dehydrating agents may be used for example mineral acids, or strong organic acids or anhydrides thereof or acid halides thereof.

Process b) may be effected in conventional manner for the splitting off of an amino protecting group from
a heterocyclic amine, for example using hydrogenolytic methods or solvolytic, especially hydrolytic methods. Suitable groups which may be split off under solvolytic or hydrolytic conditions include alkoxycarbonyl, especially lower alkoxycarbonyl, aryloxycarbonyl, or nitrile. The solvolysis may, according to the type of group R₃ used, be preferably effected in an acid medium, for example in the presence of a strong mineral acid or in an alkaline medium, for example in the presence of an inorganic base. Suitable groups which may be split off under hydrogenolytic conditions include, for example optionally substituted benzyl groups. The hydrogenolysis may be effected in conventional manner, for example using catalytic hydrogenation in the presence of a platinium or palladium catalyst.

The starting materials may be obtained, for example, as follows:

a') Compounds of formula II may be obtained by reacting a ketone of formula IV,

\[
\text{IV: } R_2
\]

wherein \( R_2 \) is as defined above, with a Grignard compound of formula V,
wherein $R^I_1$ is as defined above, and

X is chlorine, bromine or iodine,

the resulting complex being then hydrolysed.

b') Compounds of formula III may be obtained by

1. reacting a ketone of formula IV with a Grignard compound of formula VI,

$$X-Mg \quad \text{N-R}^I_1$$

wherein $R^I_1$ is methyl or a group capable of being split off under hydrogenolytic conditions, and

$X$ is as defined above,

the resulting complex being hydrolysed, and

(ii) splitting off water from the resulting product in a manner analogous to process a), and

(iii) converting any group $R^I_4$ which is methyl in the resulting product in conventional manner, e.g. using a chloroformic ester, or bromocyanide, into a group $R^I_3$ which is capable of being split off under solvolytic conditions.

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

Free base forms of compounds of formula I may be converted into acid addition salt forms in conventional manner and vice versa. Suitable acids for salt formation include hydrochloric acid, and fumaric acid.

In the following Examples all temperatures are in degrees Centigrade and are uncorrected.
EXAMPLE 1: 4-(9,10-dihydro-7-methyl-4H-benzo[4,5]cyclohepta[1,2-b]thiophen-4-ylidene)-1-methylpiperidine

A solution of 21.5 g of 9,10-dihydro-7-methyl-4-(1-methyl-4-piperidyl)-4H-benzo[4,5]cyclohepta[1,2-b]thiophen-4-ol in 210 ml of acetic acid anhydride is heated to the boil for 18 hours, is concentrated by evaporation at reduced pressure and the residue is poured onto 1 litre of icewater. The resulting solution is adjusted to pH 14 with caustic soda solution, stirred for 30 minutes at room temperature and extracted with methylene chloride. The extracts are washed neutral with water, dried over potassium carbonate, and concentrated by evaporation. The resulting residue is dissolved in 500 ml of methylene chloride and is filtered over 200 g of aluminium oxide of activity II-III. After concentrating the solvent by evaporation, the title compound remaining as residue is converted into its fumarate in methanol and is recrystallized once. M.Pt.: 200° - 201°.

The starting material may be produced as follows:-

a) A solution of 52 ml of bromine in 300 ml of benzene and a solution of 5.0 g of α,α'-azoisobutyronitrile are simultaneously added dropwise within 40 minutes to a boiling solution of 131 g of 2,4-dimethyl-benzonitrile in 600 ml of anhydrous benzene. The reaction
mixture is stirred for 3.5 hours at the boiling temperature and for 12 hours at room temperature. At 70° 183 ml of triethyl phosphite are added dropwise during the course of 30 minutes while stirring, and the temperature is slowly raised to 115° - 120°, whereupon the resulting ethyl bromide is distilled off with the benzene. Stirring is continued at this temperature for 3 hours. The reaction mixture is fractionated in a high vacuum, whereupon a mixture of (2-cyano-5-methylbenzyl)- and (4-cyano-3-methylbenzyl)phosphonic acid diethyl esters is obtained at 165° - 172°/0.1 Torr.

b) A solution of 15.7 g of the mixture obtained in step a) and 65 g of 2-thiophenaldehyde are added dropwise during the course of approximately 20 minutes to a suspension of 37 g of sodium methylate in 1000 ml of N,N-dimethyl-formamide at 35° to 40°. The reaction mixture is stirred for another hour at 40°, cooled to 20° and poured into icewater. The organic products are extracted with ether and the extracts are washed with saturated common salt solution, dried over magnesium sulphate and concentrated by evaporation. The volatile components are removed in a high vacuum at 100° - 110° and a mixture of 4-methyl-2-[2-(2-thienyl)vinyl]benzonitrile and 2-methyl-4-[2-(2-
thienyl)vinyl]benzonitrile is obtained. The 2-methyl isomer is separated by crystallisation in ethanol from the mixture and the enriched 4-methyl-2-[2-(2-thienyl)vinyl]benzonitrile is distilled in a high vacuum. B.Pt. = 210° - 220°/0.1 Torr.

c) A solution of 45 g of the distillate obtained in step b) in 500 ml of anhydrous ethanol is hydrogenated in the presence of 15 g of 5% palladium on charcoal at 100° and 25 Atm for 24 hours. After filtering and concentrating the filtrate by evaporation, the hydrogenation product, 4-methyl-2-[2-(2-thienyl)ethyl]benzonitrile containing a small amount of 2-methyl-4-[2-(2-thienyl)ethyl]benzonitrile is further worked up without any purification.

d) A solution of 38 g of the product obtained in step c) in 50 ml of diethylene glycol monoethyl ether is added dropwise to a solution of 74 g of potassium hydroxide in 200 ml of diethylene glycol monoethyl ether at 180° within 30 minutes. The reaction mixture is stirred for 3 hours at the same temperature, cooled to 100°, and poured into 1 litre of water. The resulting solution is washed with ether (after cooling to room temperature). The aqueous solution is
adjusted to pH 1 with 4 N sulphuric acid while cooling and is extracted several times with ether. The extracts are washed with water, dried over magnesium sulphate and concentrated by evaporation. The residue is dissolved in 1 litre of methylene chloride, filtered through silica gel and concentrated by evaporation. 

\[
\text{2-methyl-2-[2-(2-thienyl)ethyl]benzoic acid (slightly contaminated with 2-methyl-4-[2-(2-thienyl)ethyl]benzoic acid) crystallizes from the evaporation residue from ether/petroleum ether. M.Pt.: 75° - 78°.}
\]

e) A mixture of 22 g of 4-methyl-2-[2-(2-thienyl)ethyl]-benzoic acid and 110 g of polyphosphoric acid is stirred for 20 minutes at 90°, cooled, poured into 300 ml of water and is extracted several times with ether. The ethereal solutions are washed with water, 5% ammonia solution and again with water, are dried over magnesium sulphate and concentrated by evaporation. The resulting residue is purified by column chromatography over 600 g of neutral aluminium oxide activity stage II-III with methylene chloride as eluant and the resulting 9,10-dihydro-7-methyl-4H-benzo[4,5]cyclohepta[1,2-b]thiophen-4-one is used in the next reaction stage without further purification.
f) Portions of 10 ml of anhydrous tetrahydrofuran are added to 3.1 g of magnesium filings and the latter are then catalysed with iodine and 1 to 2 drops of ethylene bromide. Upon commencement of the reaction, a solution of 17.4 g of 4-chloro-1-methylpiperidine in 70 ml of anhydrous tetrahydrofuran is added dropwise such that the reaction is maintained. After the dropwise addition, the reaction mixture is stirred for 2 hours at the boiling temperature, cooled to 20° and then at this temperature a solution of 15.6 g of 9,10-dihydro-7-methyl-4H-benzo[4,5]cyclohepta-[1,2-b]thiophen-4-one obtained in step d) in 60 ml of anhydrous tetrahydrofuran is added dropwise. The reaction mixture is subsequently stirred at room temperature for 2 hours, poured into 300 ml of 20% ammonium chloride solution and extracted with ether several times. The ethereal solutions are washed with water, dried over potassium carbonate and concentrated by evaporation. The 9,10-dihydro-7-methyl-4-(1-methyl-4-piperidyl)-4H-benzo[4,5]cyclohepta[1,2-b]thiophen-4-ol remaining as solid residue is recrystallized from ether/petroleum ether. M.Pt.: 151° - 154° (sintering 147°).
In analogous manner to Example 1, the following 4-(9,10-dihydro-9,10-diazatricyclo[6.1.0.0²,5]non-4-yliden)-1-alkylpiperidine derivatives may be obtained by distilling off water from the corresponding 9,10-dihydro-9,10-diazatricyclo[6.1.0.0²,5]non-4-yliden)-1-alkylpiperidine derivatives. Derivatives are obtained in formula 1-

<table>
<thead>
<tr>
<th>Ex. No.</th>
<th>R₁</th>
<th>R₂</th>
<th>M.Pt.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>CH₃</td>
<td>6-CH₃</td>
<td>Hfu*: Z** from 202°</td>
</tr>
<tr>
<td>1B</td>
<td>CH₃</td>
<td>8-CH₃</td>
<td>Hfu*: Z** from 231°</td>
</tr>
<tr>
<td>1C</td>
<td>C₂H₅</td>
<td>7-CH₃</td>
<td>***</td>
</tr>
<tr>
<td>1D</td>
<td>nC₄H₉</td>
<td>7-CH₃</td>
<td>***</td>
</tr>
</tbody>
</table>

* Hfu = Hydrogenumurate
** Z = Decomposition
*** = Elemental C and H analysis agrees with calculated value (free base form)
EXAMPLE 2: 4-(9,10-dihydro-7-methyl-4H-benzo[4,5]cyclohepta[1,2-b]thiophen-4-ylidene)-1-piperidinecarboxylic acid ethyl ester

A solution of 8.0 g of chloroformic acid ethyl ester in 30 ml of anhydrous benzene is added dropwise within 30 minutes to a solution, preheated to 40°, of 5.9 g of 4-(9,10-dihydro-7-methyl-4H-benzo[4,5]cyclohepta[1,2-b]thiophen-4-ylidene)-1-methylpiperidine in 150 ml of anhydrous benzene. The reaction mixture is stirred for one hour at the same temperature and for 3 hours at the boil, is cooled to room temperature and washed with 0.5 N hydrochloric acid and water. The benzene solution is dried over sodium sulphate and concentrated by evaporation to yield crude 4-(9,10-dihydro-7-methyl-4H-benzo[4,5]cyclohepta[1,2-b]thiophen-4-ylidene)-1-piperidinecarboxylic acid ethyl ester.

20 g of crude 4-(9,10-dihydro-7-methyl-4H-benzo[4,5]cyclohepta[1,2-b]thiophen-4-ylidene)-1-piperidinecarboxylic acid ethyl ester is taken up in 250 ml of 48% hydrobromic acid and is heated to the boil for 30 minutes. Upon cooling, the reaction solution is diluted with water, made alkaline with concentrated caustic soda solution and is extracted with methylene chloride. The organic solution is washed with water, dried over sodium sulphate and concentrated by evaporation. The title...
compound remaining as residue is converted into the hydrogen fumarate. M.P.: decomposition from 210° (ethanol).

EXAMPLE 3: Capsules containing 4-(9,10-dihydro-7-methyl-4H-benzo[4,5]cyclohepta[1,2-b]thiophen-4-ylidene)-1-methylpyridine

Composition:

4-(9,10-dihydro-7-methyl-4H-benzo[4,5]cyclohepta[1,2-b]thiophen-4-ylidene)-1-methylpyridine 1.0 mg/dose
Powdered lactose 72.5 "
Corn Starch 25.0 "
Magnesium stearate 1.0 "
Highly dispersed silicic acid 0.5 "

The ingredients were mixed and filled into capsules (hard gelatine).
The compounds of formula I exhibit pharmacological activity. In particular the compounds of formula I in general exhibit analgesic activity as indicated, for example, in standard tests, for example in the mouse on p.o. administration of from 0.5 to 20 mg/kg animal body weight in the phenylbenzoquinone syndrome test and in the mouse on p.o. or s.c. administration of from 3 to 50 mg/kg animal body weight in the tail flick test.

The compounds wherein $R_1$ is hydrogen or methyl exhibit activity greater than expected for such compounds in the above tests.

The compounds of formula I are therefore indicated for use as analgesics, possibly for the treatment of acute or chronic pains.

For this use an indicated daily dose is from about 10 to about 100 mg, conveniently administered in divided doses in unit dosage form containing from about 0.5 to about 50 mg, or in sustained release form.

Additionally the compounds exhibit antagonism against various biogenic amines, as indicated in standard tests, for example histaminolytic, serotonin and/or acetylcholine antagonistic properties in well known histamine, serotonin and acetylcholine toxicity tests in guinea pigs on administration s.c. of from 0.01 to 20 mg/kg animal body weight.
The compounds are therefore further indicated for use as antihistaminic agents, possibly as an anti-histaminic or for the treatment of migraine. For this use an indicated daily dose is from about 10 to about 100 mg, conveniently administered in divided doses in unit dosage form containing from about 0.5 to about 50 mg, or in sustained release form.

The compounds of formula I may be administered in pharmaceutically acceptable acid addition salt form. Such acid addition salt forms exhibit the same order of activity as the free base forms and are readily prepared in conventional manner. The present invention also provides a pharmaceutical composition comprising 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.

A group of compounds comprise those of formula I other than 4-(9,10-dihydro-6-methyl-4H-benzo[4,5]cyclohepta[1,2-b]thiophen-4-ylidene)-1-methylpiperidine. A sub-group comprises compounds of formula I other than those wherein R₁ is hydrogen or methyl.

In another group of compounds R₂ is methyl. In a sub-group R₁ is hydrogen. In another sub-group R₁ is alkyl.

The Example 1 compound shows particularly interesting activity.
Further the present invention also provides a process for the production of a pharmaceutical composition which comprises mixing a compound of formula I in free base form or in pharmaceutically acceptable acid addition salt form in a purity sufficient for pharmaceutical acceptability with a pharmaceutical carrier or diluent.

The pharmaceutical compositions may be in a appropriate solid or liquid form for enteral, preferably oral, or parenteral application. If desired retard agents may be present. Examples of such pharmaceutical compositions for enteral application are powders, granulates, tablets, capsules, dragées, sirups, drops, and suppositories, and for parenteral application are injectable solutions, or injectable aqueous or oil-based suspensions. For oral application unit dosage forms such as tablets containing 0.5, 1, 2 or 5 mg of compound per dose are particularly suitable.

The production of the pharmaceutical compositions may be effected in conventional manner known in the galenical art, using solid or liquid pharmaceutical diluents or carriers. Solid carriers or diluents include physiologically tolerable substances like mannitol, lactose, starch, organic or inorganic calcium salts. If a retard effect is required, then the release of the active agent may be delayed using physiologically neutral
polymers such as cellulose derivatives, or synthetic polymers, fatty alcohols, and other waxy substances known in the art. The conventional substances for the production of suppositories may be used. As liquid pharmaceutical carriers or diluents there may be used water, ethanol or physiologically tolerable oils. Additionally, other pharmaceutical diluents and carriers may be used, for example the usual tabletting agents such as binding agents, e.g. polyvinyl pyrrolidone, dispersing agents, lubricating agents such as magnesium stearate, and preserving agents, buffering substances, and flavouring agents.
The claims defining the invention are as follows:

1. A process for the production of a compound of formula I,

\[
\begin{align*}
R_2 & \quad \text{II} \\
\end{align*}
\]

wherein \( R_1 \) is hydrogen or alkyl of 1 to 4 carbon atoms,

\[
\begin{align*}
R_2 & \quad \text{is alkyl of 1 to 4 carbon atoms,} \\
\end{align*}
\]

which comprises

a) for the production of a compound of formula Ia,

\[
\begin{align*}
R_2 & \quad \text{Ia} \\
\end{align*}
\]
wherein $R_1$ is alkyl of 1 to 4 carbon atoms, and $R_2$ is as defined above,

splitting off water from a compound of formula II,

wherein $R_1$ and $R_2$ are as defined above, or

5 b) for the production of a compound of formula Ib,

wherein $R_2$ is as defined above,

splitting off the group $R_3$ from a compound of formula III,
wherein \( R_2 \) is as defined above, and
\( R_3 \) is a group capable of being split off.

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

3. A compound according to Claim 2 wherein, when
\( R_1 \) is hydrogen, \( R_2 \) is other than 6-methyl.

4. A compound according to Claim 2 wherein \( R_1 \) is
other than hydrogen or methyl.

5. A compound according to Claim 1 or 2 wherein \( R_1 \)
is hydrogen and \( R_2 \) is methyl.

6. A compound according to Claim 2 wherein \( R_1 \) is
methyl and \( R_2 \) is 7-methyl.

7. A compound according to Claim 2 wherein \( R_1 \) is
hydrogen and \( R_2 \) is 7-methyl.

8. A compound according to any one of Claims 2 to
7 in acid addition salt form.

9. A pharmaceutical composition comprising a com-
 pound according to any one of Claims 1 to 7 in free base
form or in pharmaceutically acceptable acid addition salt
form in association with a pharmaceutical diluent or car-
rier therefor.

DATED this 12 day of February 1980.

DAVIES & COLLISON
Patent Attorneys for
SANDOZ LTD.