

PATENT SPECIFICATION

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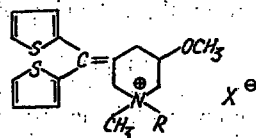
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(54) DI-(2-THIENYL)-(N-METHYL-5-METHOXY-3-PIPERIDYLIDENE)-METHANE AND ACID ADDITION SALTS AND QUATERNARY COMPOUNDS THEREOF

(71) We, TANABE SEIYAKU COMPANY LIMITED, a Company registered under the Laws of Japan, of No. 21 Doshomachi, 3-chome, Higashi-ku, Osaka, Japan, 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:—

By the present invention there is provided di - (2 - thienyl) - (N - methyl - 5 - methoxy - p - 3 - piperidylidene) - methane, its mineral acid addition salts and quaternary compounds of the formula:



(I)

wherein R represents an alkyl radical, and X represents an anionic residue of a pharmaceutically acceptable acid.

We have found that the quaternary ammonium compounds (I) of the present invention have a potent anti-spasmodic activity. The parasympathetic blocking activity of the compound of the present invention is comparable or superior to that of atropine sulfate. For instance, di - (2 - thienyl) - (N - methyl - 5 - methoxy - 3 - piperidylidene) - methane methobromide exhibits an inhibitory activity about 3 times greater than that of atropine sulfate on gastric contractions induced by electrical stimulation of the cervical vagus nerve in rats. The inhibitory activity (ED₅₀) of the compound which would suppress 50% of said stimulation-induced gastric contractions was 10 µg/kg, when the stimulation for the distal end of

the cervical vagus nerve of rats was carried out every 2 minutes at the rate of supra-maximal square waves (about 1.5 V, 10 cycle/second) one minute after injecting a test compound into the femoral vein. In contrast thereto, the ED₅₀ of atropine sulfate showed 30 µg/kg under the same conditions as above. Moreover, when examined using isolated guinea pig ileum, the anticholinergic activity (pA₂) of the compound was 8.37. In contrast thereto, atropine sulfate showed 8.57. (pA₂ was the value of negative logarithm of the molar concentration of a test compound which caused the shift of log₂ to high concentration in the dose response curve of methacholine).

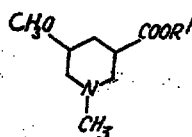
It is well known that the parasympathicolitics show unfavorable side effects such as mydriatic and antisialogogue activity. Such side effects of the compound of the present invention are relatively less as compared with the parasympathicolitics in the prior art. For instance, the mydriatic and anti-sialogogue activity of di - (2 - thienyl) - (N - methyl - 5 - methoxy - 3 - piperidylidene) - methane methobromide are about 1/10 to 1/20 times that of atropine sulfate. The quaternary ammonium compounds of the present invention have almost no central anti-cholinergic activity.

Additionally, the toxicity of the quaternary ammonium compounds of the present invention is relatively low. For instance, when administered orally, the acute toxicity (LD₅₀) of di - (2 - thienyl) - (N - methyl - 5 - methoxy - 3 - piperidylidene) - methane methobromide is more than 700 mg/kg.

Di - (2 - thienyl) - (N - methyl - 5 - methoxy - 3 - piperidylidene) - methane can be prepared by a process, provided in accordance with the present invention, which comprises reacting a 2 - thienyl magnesium halide or 2 - thienyl lithium (II) with N - methyl - 5 - methoxy - nipecotic acid ester of the formula:

[Price 25p]

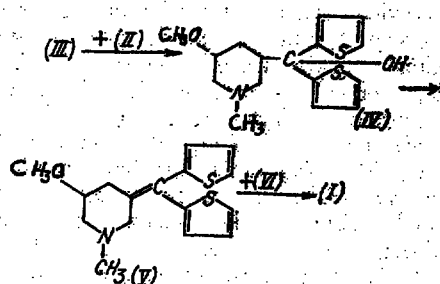
Price 75p



(III)

wherein R' represents an ester residue, and dehydrating the carbinol derivative (IV) thereby formed. The piperidylidene compound (V) thus obtained may be reacted with a compound of the formula: RX (VI), wherein R and X have the same meaning as defined above, to yield a quaternary ammonium compound of the formula (I).

The above-mentioned reactions can be represented by the following scheme:



The starting compound (III) is readily obtained. For instance, an alkyl ester of *N*-methyl-5-methoxy-nipicotic acid may be prepared by refluxing 5-bromo-nicotinic acid with a mixture of sodium hydroxide, copper sulfate and copper powder, treating the thus obtained 5-hydroxy-nicotinic acid with a dimethyl sulfate in nitrogen atmosphere, and then subjecting the resulting compound to catalytic reduction in the presence of Raney-nickel.

Preferred examples of the starting compound (VI) are an alkyl halide (e.g., methyl iodide, methyl bromide, methyl chloride, ethyl iodide, ethyl bromide, ethyl chloride), an alkyl ester of alkanesulfonic acid (e.g., methyl methylsulfonate, methyl ethylsulfonate, ethyl ethylsulfonate), an alkyl ester of aromatic sulfonic acid (e.g., methyl *p*-toluenesulfonate, methyl benzenesulfonate, ethyl *p*-toluene-sulfonate, ethyl benzenesulfonate), and di-alkylsulfate (e.g., dimethyl sulfate, diethylsulfate). The ester residue (R') includes a lower alkyl radical (e.g., methyl, ethyl, propyl radical).

The preparation of the carbinol derivative (IV) can be carried out by mixing the compounds (II) and (III) at room temperature or under refluxing in an inert solvent. Ether, tetrahydrofuran or benzene, for example, are suitable as the reaction solvent.

The subsequent dehydration reaction may be accomplished by heating the compound (IV) at about 60° to 80°C in the presence

of a dilute mineral acid (e.g., diluted hydrochloric acid, diluted sulfuric acid) to yield the di-(2-thienyl)-(N-methyl-5-methoxy-3-piperidylidene)-methane in the form of an acid addition salt with the mineral acid. The free base may then be obtained by extraction with ether from an alkaline solution of the salt. Alternatively, the reaction may be carried out by refluxing the compound (IV) with an inert solvent (e.g., benzene, toluene) in the presence of an arylsulfonic acid (e.g., *p*-toluenesulfonic acid, benzenesulfonic acid).

The quaternary ammonium compound (I) may be prepared in a conventional manner. For instance, it is readily obtained by mixing the compounds (V) and (VI) in an inert solvent (e.g., benzene, acetone, ether) at room temperature. When a methyl ester of an alkanesulfonic acid or a methyl ester of an aromatic sulfonic acid is employed as the compound (VI), it is preferred to carry out the reaction in the presence of a catalyst such as alkali metal iodide (e.g., potassium iodide, sodium iodide).

The compound (I) thus obtained is useful as an anti-spasmodic agent. This compound is also useful for the treatment and/or prevention of gastric ulcers, and for the control of gastric secretion. The compound may be used in the form of a pharmaceutical preparation for enteral or parental administration at a daily dose of 0.05 to 50 mg/kg.

Practical and presently-preferred embodiments of the present invention are illustratively shown in the following Examples.

Example 1

50 g of 5-bromonicotinic acid are added to the solution containing 50 g of sodium hydroxide, 15 g of copper sulfate 5 hydrate, 2 g of copper powder and 400 ml of water. The mixture is refluxed for 20 hours under stirring and then cooled. Hydrogen sulfide gas is introduced into the mixture. Then, the mixture is decolorized with activated carbon and filtered. The filtrate is adjusted to pH 3-4 with hydrochloric acid. The precipitated crystals are collected by filtration. crystallization of the crystals from methanol gives 30 g of 5-hydroxynicotinic acid. M.P. 298-299° (decomp.).

120 g of 5-hydroxynicotinic acid are dissolved in one liter of methanol. After saturating with dry-hydrogen chloride gas at 0°C, the solution is refluxed for 3 hours. Then, the solution is concentrated to dryness. The residue thus obtained is dissolved in water. The solution is made alkaline with sodium bicarbonate. The precipitated crystals are collected by filtration, washed with water and then dried. 126 g of methyl 5-hydroxy-nicotinate are obtained. Yield; 93% M.P. 184-186°C.

460 g of methyl 5-hydroxynicotinate and

21 g of potassium carbonate are suspended in 200 ml of tetrahydrofuran-methanol (4:1). 1134 g of dimethylsulfate are added dropwise to the suspension in nitrogen atmosphere at room temperature. The mixture is stirred at the same temperature for a night and then filtered. The filtrate is concentrated to dryness. The residue thus obtained is mixed with 1.6 liters of methanol and 280 ml of Raney-nickel, and subjected to hydrogenation at room temperature in an autoclave of 85 atmospheric pressure for a night. 200 g of Raney-nickel are added to the reaction mixture. The mixture is adjusted to pH 9.5 with triethylamine, and is further subjected to hydrogenation at 70°C in an autoclave of 100 atmospheric pressure for 20 hours. Potassium carbonate and a small amount of ice are added to the reaction mixture to bring the pH to 11. The mixture is extracted with ether. After drying, the ether layer is filtered. The filtrate is evaporated to remove ether. The residue thus obtained is distilled under reduced pressure. 450 g of methyl N - methyl - 5 - methoxy - nipecotate are obtained. Yield: 80% B.p. 80—81°C/0.5 mmHg.

A solution of 18 g of 2 - thienyl bromide in 30 ml of tetrahydrofuran is gradually added to a mixture of 2.6 g of magnesium and 80 ml of tetrahydrofuran under stirring at 50°C. The mixture is stirred for 5 hours at room temperature until the magnesium is entirely dissolved in the solution. 6.2 g of methyl N - methyl - 5 - methoxy - nipecotate are added to the mixture. Then, the mixture is refluxed for 4 hours. After the reaction is completed, tetrahydrofuran is distilled off under reduced pressure. An aqueous ammonium chloride solution is added to the residue, and the solution is extracted with chloroform. The extract is dried and then evaporated to remove chloroform. The viscous oil thus obtained is recrystallized from a mixture of benzene and ether. 7 g of di - (2 - thienyl) - (N - methyl - 5 - methoxy - 3 - piperidyl) - carbinol are obtained as crystals. M.p. 142°—146°C.

7 g of the product are dissolved in 150 ml of 10% hydrochloric acid, and the solution is heated at 80°C for 30 minutes. After the reaction is completed, the solution is made alkaline with sodium hydroxide and then extracted with ether. The extract is washed with water, dried and evaporated to remove ether. 5 g of di - (2 - thienyl) - (N - methyl - 5 - methoxy - 3 - piperidylidene) - methane are obtained as pale yellow oil.

Infrared absorption spectrum:
 $\nu_{\max}^{\text{liquid}} \text{ cm}^{-1}$: 1460, 1440, 1360, 1105, 855, 705

N.M.R. (60 mc) (in CDCl_3):
 2.75 (m, 3H), 3.05 (m, 3H), 6.67 (s, 3H), 7.71 (s, 3H)

365 mg of di - (2 - thienyl) - (N - methyl -

5 - methoxy - 3 - piperidylidene) - methane are dissolved in 15 ml of ether. One ml of methyl bromide is added to the solution. Then, the solution is stirred over night. The precipitated crystals are collected by filtration and recrystallized from a mixture of acetone and ether. 390 mg of di - (2 - thienyl) - (N - methyl - 5 - methoxy - 3 - piperidylidene) - methane methobromide are obtained as colourless crystals. M.p. 198°—200°C.

Infrared absorption spectrum:
 $\nu_{\max}^{\text{Nujol}} \text{ cm}^{-1}$: 1460, 1378, 1100, 834, 800, 715, 700

Example 2

A solution of 2 - thienyl lithium in 200 ml of ether is prepared from 1.4 g of metal lithium and 18 g of 2 - thienyl bromide by conventional manner. 4 g of methyl N - methyl - 5 - methoxy nipecotate are added dropwise to the solution. The solution is refluxed for 8 hours and then allowed to stand at room temperature. The solution is evaporated to remove ether. Ice-water is added to the residue, and the mixture is extracted with chloroform. The extract is dried and then evaporated to remove chloroform. The viscous oil thus obtained is recrystallized from a mixture of benzene and ether. 5 g of di - (2 - thienyl) - (N - methyl - 5 - methoxy - 3 - piperidyl) - carbinol are obtained. M.p. 140—145°C.

75 g of the product are dissolved in 230 ml of 10% hydrochloric acid, and the solution is heated at 70—80°C for 2 hours. After cooling, the solution is made alkaline with sodium hydroxide to pH 9.0 and then extracted with benzene. The extract is dried and evaporated to remove benzene. The residue thus obtained is purified by distillation and then suspended into ether. The precipitated crystals are collected by filtration. 64 g of di - (2 - thienyl) - (N - methyl - 5 - methoxy - 3 - piperidylidene) - methane are obtained as colorless crystals. M.p. 70—71°C.

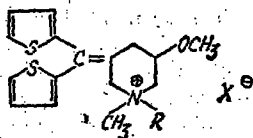
500 mg of di - (2 - thienyl) - (N - methyl - 5 - methoxy - 3 - piperidylidene) - methane are dissolved in 10 ml of acetone. A solution of 1.25 g of ethyl iodide in 10 ml of acetone is added to the solution under stirring at room temperature, and the mixture is stirred for a night. Then, the mixture is evaporated to remove solvent. The residue thus obtained is recrystallized from a mixture of acetone, methanol and isopropanol. 650 mg of di - (2 - thienyl) - (N - methyl - 5 - methoxy - 3 - piperidylidene) - methane ethiodide are obtained as pale yellow crystals. Recrystallization of the crystals gives colorless granular crystals. M.p. 201—202°C.

Infrared absorption spectrum:
 $\nu_{\max}^{\text{Nujol}} \text{ cm}^{-1}$: 1460, 1450, 1370, 1093, 1065, 1013, 828, 750, 700

- The invention includes within its scope pharmaceutical compositions comprising new active materials according to the invention in association with pharmaceutically acceptable carrier. Such carrier may be, for example, an inert solid diluent, e.g. talc, provided to increase the bulk and so render the active material more easy to dispense, solid materials by which the active material is formed into pills or tablets or a liquid medium in which the active material is dissolved or suspended to render it suitable for administration by injection. The amount of active material present in the composition when it is provided in the form of dosage units such as pills, tablets or capsules should be arranged such that a patient's requirements can be met by a small number, preferably not more than six, dosage units per day. In the case of a composition for injection, the concentration should be such that the patient's requirements may be met conveniently by the injection of a whole number of half cubic centimetres per day.
- The group R may be a straight- or branched-chain lower alkyl group other than the methyl and ethyl groups referred to. Alkyl groups containing from 1 to 4 carbon atoms are preferred.

WHAT WE CLAIM IS:—

1. Di - (2 - thienyl) - (N - methyl - 5 - methoxy - 3 - piperidylidene) - methane.
2. Di - (2 - thienyl) - (N - methyl - 5 - methoxy - 3 - piperidylidene) - methane in the form of an acid addition salt thereof with a mineral acid.
3. A compound represented by the formula:



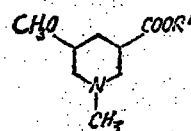
- wherein R represents an alkyl radical and X represents an anionic residue of a pharmaceutically acceptable acid.
4. A compound as claimed in Claim 3, wherein R is a methyl or ethyl radical.
 5. A compound as claimed in Claim 3, wherein X⁻ is a halide, arylsulfonate, or alkylsulfonate ion.
 6. A compound as claimed in Claim 3, wherein X⁻ is an iodide, bromide, chloride, p - toluenesulfonate, benzenesulfonate, methylsulfonate or ethylsulfonate ion.
 7. Di - (2 - thienyl) - (N - methyl - 5 - methoxy - 3 - piperidylidene) - methane methobromide.
 8. Di - (2 - thienyl) - (N - methyl - 5 - methoxy - 3 - piperidylidene) - methane ethoxide.

9. A process for preparing a compound as claimed in Claim 3, which comprises converting di - (2 - thienyl) - (N - methyl - 5 - methoxy - 3 - piperidyl) - carbinol to di - (2 - thienyl) - (N - methyl - 5 - methoxy - 3 - piperidylidene) methane by dehydration and reacting the product with a compound of the formula: R—X, wherein R and X are as defined in Claim 3.

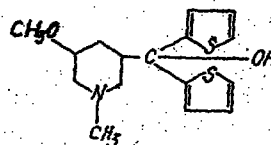
10. A process as claimed in Claim 9, wherein the di(2 - thienyl) - (N - methyl - 5 - methoxy - 3 - piperidyl) - carbinol is prepared by reacting 2 - thienyl magnesium halide or 2 - thienyl lithium with an ester of N - methyl - 5 - methoxy - nipecotic acid.

11. A process as claimed in either of Claims 9 or 10, wherein the compound of the formula R—X is an alkyl halide, an alkyl ester of an aromatic sulfonic acid or alkane sulfonic acid, or a di-alkylsulfate.

12. A process for the production of di - (2 - thienyl) - (N - methyl - 5 - methoxy - 3 - piperidylidene) - methane which comprises reacting a 2 - thienyl magnesium halide or 2 - thienyl lithium with an N - methyl - 5 - methoxy - nipecotic acid ester of the formula:



in which R' represents an ester residue to form a carbinol derivative of the formula:



and dehydrating the carbinol derivative.

13. A process according to Claim 12, in which the dehydration is carried out by heating the carbinol derivative in the presence of a dilute mineral acid to yield the di - (2 - thienyl) - (N - methyl - 5 - methoxy - 3 - piperidylidene) - methane in the form of an acid addition salt thereof with the mineral acid.

14. A process according to Claim 12 in which the dehydration is carried out by refluxing the carbinol derivative with an inert solvent in the presence of an arylsulfonic acid.

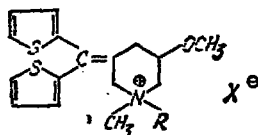
15. A process according to Claim 14, in which the arylsulfonic acid is p - toluenesulfonic acid or benzenesulfonic acid.



The invention includes within its scope pharmaceutical compositions comprising new active materials according to the invention in association with pharmaceutically acceptable carrier. Such carrier may be, for example, an inert solid diluent, e.g. talc, provided to increase the bulk and so render the active material more easy to dispense, solid materials by which the active material is formed into pills or tablets or a liquid medium in which the active material is dissolved or suspended to render it suitable for administration by injection. The amount of active material present in the composition when it is provided in the form of dosage units such as pills, tablets or capsules should be arranged such that a patient's requirements can be met by a small number, preferably not more than six, dosage units per day. In the case of a composition for injection, the concentration should be such that the patient's requirements may be met conveniently by the injection of a whole number of half cubic centimetres per day. The group R may be a straight- or branched-chain lower alkyl group other than the methyl and ethyl groups referred to. Alkyl groups containing from 1 to 4 carbon atoms are preferred.

WHAT WE CLAIM IS:—

1. Di - (2 - thienyl) - (N - methyl - 5 - methoxy - 3 - piperidylidene) - methane.
2. Di - (2 - thienyl) - N - methyl - 5 - methoxy - 3 - piperidylidene) - methane in the form of an acid addition salt thereof with a mineral acid.
3. A compound represented by the formula:



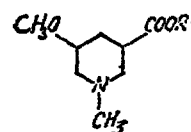
- wherein R represents an alkyl radical and X represents an anionic residue of a pharmaceutically acceptable acid.
4. A compound as claimed in Claim 3, wherein R is a methyl or ethyl radical.
5. A compound as claimed in Claim 3, wherein X⁻ is a halide, arylsulfonate, or alkylsulfonate ion.
6. A compound as claimed in Claim 3, wherein X⁻ is an iodide, bromide, chloride, p - toluenesulfonate, benzenesulfonate, methylsulfonate or ethylsulfonate ion.
7. Di - (2 - thienyl) - (N - methyl - 5 - methoxy - 3 - piperidylidene) - methane methobromide.
8. Di - (2 - thienyl) - (N - methyl - 5 - methoxy - 3 - piperidylidene) - methane ethoxide.

9. A process for preparing a compound as claimed in Claim 3, which comprises converting di - (2 - thienyl) - (N - methyl - 5 - methoxy - 3 - piperidyl) - carbinol to di - (2 - thienyl) - (N - methyl - 5 - methoxy - 3 - piperidylidene) methane by dehydration and reacting the product with a compound of the formula: R—X, wherein R and X are as defined in Claim 3.

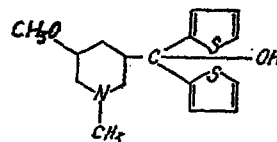
10. A process as claimed in Claim 9, wherein the di(2 - thienyl) - (N - methyl - 5 - methoxy - 3 - piperidyl) - carbinol is prepared by reacting 2 - thienyl magnesium halide or 2 - thienyl lithium with an ester of N - methyl - 5 - methoxy - nipecotic acid.

11. A process as claimed in either of Claims 9 or 10, wherein the compound of the formula R—X is an alkyl halide, an alkyl ester of an aromatic sulfonic acid or alkane sulfonic acid, or a di-alkylsulfate.

12. A process for the production of di - (2 - thienyl) - (N - methyl - 5 - methoxy - 3 - piperidylidene) - methane which comprises reacting a 2 - thienyl magnesium halide or 2 - thienyl lithium with an N - methyl - 5 - methoxy - nipecotic acid ester of the formula:



in which R' represents an ester residue to form a carbinol derivative of the formula:



- and dehydrating the carbinol derivative.
13. A process according to Claim 12, in which the dehydration is carried out by heating the carbinol derivative in the presence of a dilute mineral acid to yield the di - (2 - thienyl) - (N - methyl - 5 - methoxy - 3 - piperidylidene) - methane in the form of an acid addition salt thereof with the mineral acid.
14. A process according to Claim 12 in which the dehydration is carried out by refluxing the carbinol derivative with an inert solvent in the presence of an arylsulfonic acid.
15. A process according to Claim 14, in which the arylsulfonic acid is p - toluenesulfonic acid or benzenesulfonic acid.

16. Di - (2 - thienyl) - (N - methyl -
5 - methoxy - 3 - piperidylidene) - methane
when produced by a process substantially as
hereinbefore described or an obvious chemical
equivalent thereof.

17. A mineral acid addition salt of di -
(2 - thienyl) - (N - methyl - 5 - methoxy -
3 - piperidylidene) - methane when produced
by a process substantially as hereinbefore
described or an obvious chemical equivalent
thereof.

18. A compound of the formula given in

Claim 3, when prepared by a process in
accordance with any one of Claims 9 to 11.

19. A pharmaceutical composition which
comprises a compound according to any one
of Claims 1 to 8 or Claims 16 to 18 in asso-
ciation with a pharmaceutically acceptable
carrier.

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