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PATENT SPECIFICATION

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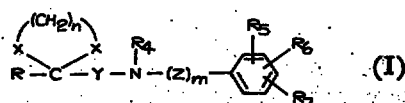


(54) DITHIOLANES AND DITHIANES

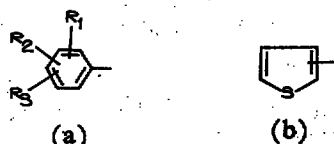
(71) We, F. HOFFMANN-LA ROCHE & CO., AKTIENGESELLSCHAFT, a Swiss Company of 124-184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to sulphur-containing derivatives. More particularly, the invention is concerned with sulphur-containing derivatives, a process for the manufacture thereof and pharmaceutical preparations containing same.

The sulphur-containing derivatives provided by the present invention are compounds of the general formula



wherein R represents a group of the formula

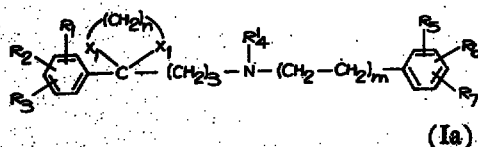


in which R₁, R₂ and R₃ each represent a hydrogen or halogen atom or a lower alkyl, lower alkoxy, aryl-(lower alkoxy), aryl-oxy, phenyl, nitro, amino, lower alkylthio, trifluoromethyl, hydroxy, cyano, di(lower alkyl)amino, lower alkanoylamino, carboxyl, lower alkoxy-carbonyl, lower alkylsulphonyl, hydroxymethyl, lower alkanoyloxy, amido, lower alkanoyl, sulphonamoyl, mono(lower alkyl)sulphonamoyl, di(lower alkyl)sulphonamoyl, aminocarbonyloxy, mono(lower alkyl)-aminocarbonyloxy, di(lower alkyl) aminocar-

bonyloxy or (lower alkylamino)-(lower alkyl) group or two adjacent R₁, R₂ and R₃ symbols together represent a methylenedioxy, ethylenedioxy or butadien-1,3-ylene-1,4 group, R₄ represents a hydrogen atom or a lower alkyl group, R₅, R₆ and R₇ each represent a hydrogen or halogen atom or a lower alkyl, lower alkoxy, hydroxy or benzyloxy group or two adjacent R₅, R₆ and R₇ symbols together represent a methylenedioxy or ethylenedioxy group, X represents a sulphur atom, SO or SO₂, Y represents a straight-chain or branched-chain, optionally hydroxy-substituted, aliphatic group containing 2-8 carbon atoms, of which 2-4 carbon atoms are present in the chain, and Z represents a straight-chain or branched-chain, optionally hydroxy-substituted, aliphatic group containing 1-8 carbon atoms, of which 1-4 carbon atoms are present in the chain, m stands for zero or 1 and n stands for 2 or 3, and acid addition salts thereof.

As used in this description and in the accompanying claims, the term "lower alkyl" means straight-chain or branched-chain alkyl groups containing 1-6 carbon atoms (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, amyl and hexyl). The term "lower alkoxy" means lower alkyl ether groups in which the "lower alkyl" moiety has the aforementioned significance. The term "halogen" means fluorine, chlorine, bromine and iodine. The term "lower alkanoyl" means alkanoyl groups containing up to 6 carbon atoms (e.g. formyl, acetyl, propionyl and butyryl). The term "aryl" means unsubstituted or substituted phenyl, the substituent(s) being selected from halogen, lower alkyl, lower alkoxy, nitro and amino. The term "leaving atom or group" used hereinafter means known atoms and groups such as, for example, halogen, preferably bromine or chlorine, arylsulphonyloxy such as tosyloxy, alkylsulphonyloxy such as mesyloxy or an epoxy group.

Preferred compounds of formula I are, for example, those of the following general formula



- 5 wherein R_1-R_7 and m have the significance given earlier, R_4 represents a methyl or ethyl group and X_1 represents a sulphur atom or SO_2 .

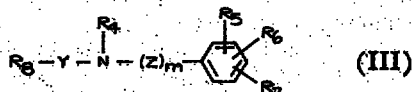
Preferred compounds falling within formula Ia are those in which one of the symbols R_1 , R_2 and R_3 represents a hydrogen atom and the other symbols each represent a lower alkoxy group, especially methoxy, or together represent a butadien-1,3-ylene-1,4 group and those in which two of the symbols R_1 , R_2 and R_3 each represent a hydrogen atom and the third symbol represents a nitro group and one of the symbols R_6 , R_7 and R_8 represents a hydrogen atom and the other two symbols each represent a lower alkoxy group, especially methoxy. An especially preferred compound is N - (3,4 - dimethoxyphenethyl) - 2 - (3,4-dimethoxyphenyl) - N - methyl - m - dithiane-2 - propylamine - 1,1,3,3 - tetraoxide.

25 According to the process provided by the present invention, the sulphur-containing derivatives aforesaid (i.e. the compounds of formula I and their acid addition salts) are manufactured by

- 30 a) reacting a compound of the general formula

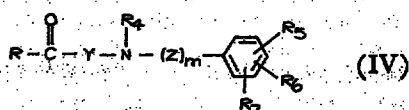


- 35 wherein R , X and n have the significance given earlier, with a compound of the general formula

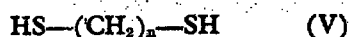


wherein R_1-R_7 , Y , Z and m have the significance given earlier and R_8 represents a leaving atom or group, or

- 40 b) reacting a compound of the general formula



45 wherein R , R_1-R_7 , Y , Z and m have the significance given earlier, with a compound of the general formula

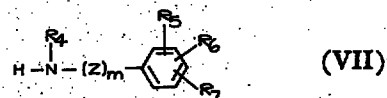


wherein n has the significance given earlier, or

- c) reacting a compound of the general formula



wherein R , R_8 , X , Y and n have the significance given earlier, with a compound of the general formula

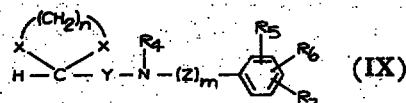


wherein R_1-R_7 , Z and m have the significance given earlier, or

- d) reacting a compound of the general formula

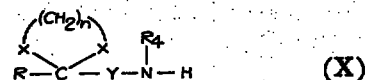


wherein R and R_8 have the significance given earlier, with a compound of the general formula



wherein R_1-R_7 , X , Y , Z , n and m have the significance given earlier, or

- e) reacting a compound of the general formula

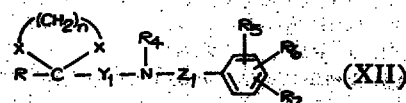


wherein R , R_4 , X , Y and n have the significance given earlier, with a compound of the general formula

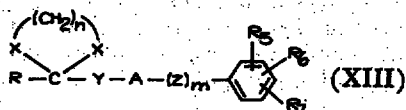


wherein R_1-R_7 , Z and m have the significance given earlier, or

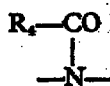
- f) reducing the carbonyl group or the group denoted by A in a compound of the general formula



or



wherein $R_1, R_2, R_3, X, Y, Z, m$ and n have the significance given earlier, Y_1 and Z_1 represent respectively a group corresponding to Y or Z containing a carbonyl group and A represents the group



in which R_1 has the significance given earlier, if desired oxidising a compound of formula I in which X represents a sulphur atom to a compound of formula I in which X represents SO or SO_2 , if desired N -(lower alkylating) a compound of formula I in which R_1 represents a hydrogen atom, if desired converting a lower alkoxy group or an aryl-(lower alkoxy) group into a hydroxy group, if desired reducing a nitro group to an amino group, if desired saponifying a cyano group to a carboxyl group, if desired esterifying or amidating or reducing a carboxyl group, if desired etherifying or esterifying or carbamoylating a hydroxy group, if desired mono(lower alkylating) or di(lower alkylating) an amino group, if desired oxidising an alkylthio group to an alkylsulphonyl group and, also if desired, converting a base obtained into an acid addition salt.

The reaction of a compound of formula II with a compound of formula III according to embodiment a) of the process can be carried out in a manner known *per se*. The reaction is expediently carried out in an organic solvent which is inert under the reaction conditions and at a temperature from -80°C to the reflux temperature of the reaction mixture, preferably from 0°C to 50°C and especially at about room temperature. As solvents, there may be mentioned ethers (e.g. diethyl ether, tetrahydrofuran or dioxane), aromatic hydrocarbons (e.g. benzene, toluene or xylene), dimethylformamide or dimethyl sulphoxide. The reaction is carried out in the presence of a strong base such as butyl lithium, a Grignard compound, sodium or sodium hydride. An especially strong base such as butyl lithium or a Grignard compound is expediently used when X represents a sulphur atom.

The starting materials of formula (IIa), (VI), (IX), (X), (XII) and (XIII) *per se* and a process for their production form the subject matter of our copending application 23144/77 (Specification Serial No. 1489087). The starting materials of formula (IV) *per se* and a process for their production form the subject matter of our copending application 23143/77 (Specification Serial No. 1489088).

The reaction of a compound of formula IV with a compound of formula V according to embodiment b) of the process can be carried out in a manner known *per se*. The reaction is expediently carried out in an organic solvent

which is inert under the reaction conditions, preferably in a polar solvent such as a halogenated hydrocarbon (e.g. chloroform or methylene chloride) or ethyleneglycol dimethyl ether. The reaction is also expediently carried out in the presence of a water-cleaving agent (e.g. sulphuric acid, a hydrohalic acid or phosphoric acid) and at a temperature from 0°C to the reflux temperature of the reaction mixture, preferably at room temperature.

The starting materials of formula V are known and can be prepared in a known manner.

The compounds of formula XIVa are partly known and partly novel. The novel compounds can be prepared in a manner known *per se*, namely in a manner analogous to the preparation of the known compounds. The compounds of formula VII are known.

The reaction of a compound of formula VI with a compound of formula VII in accordance with embodiment c) of the process can be carried out in a manner known *per se*. The reaction is expediently carried out in an inorganic solvent which is inert under the reaction conditions, such as an ether (e.g. dibutyl ether, dioxane or tetrahydrofuran), an alkanol (e.g. ethanol or propanol), an aromatic hydrocarbon (e.g. benzene, toluene or xylene), acetonitrile, dimethylformamide or dimethyl sulphoxide. The reaction can be carried out at from room temperature to the reflux temperature of the reaction mixture. The reaction is preferably carried out at the reflux temperature. The reaction is expediently carried out in the presence of a base (e.g. a tertiary amine such as trimethylamine, N -ethyl- N,N -diisopropylamine or N,N -dimethylaniline) in the case where acid is cleaved during the reaction.

The starting materials of formula VII are known.

The reaction of a compound of formula VIII with a compound of formula IX in accordance with embodiment d) of the process can be carried out in a manner known *per se*. The reaction is expediently carried out in an organic solvent which is inert under the reaction conditions, such as an ether (e.g. tetrahydrofuran, dioxane or diethyleneglycol diethyl ether), acetonitrile or dimethylformamide. The reaction is carried out at from room temperature to the reflux temperature of the reaction mixture, preferably at the reflux temperature. The reaction is carried out in the presence of a strong base such as butyl lithium, a Grignard compound, sodium or sodium hydride. An especially strong base such as butyl lithium or a Grignard compound is expediently used when X represents a sulphur atom.

The starting materials of formula VIII are known.

The compounds of formula XV are known. The compounds of formula III are partly

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novel and partly known. The novel compounds of formula III can be prepared in a manner known *per se*, in a manner analogous to the preparation of the known compounds.

5 The reaction of a compound of formula X with a compound of formula XI in accordance with embodiment e) of the process can be carried out in a manner known *per se*. The reaction is expediently carried out in an organic solvent which is inert under the reaction conditions, such as an ether (e.g. dibutyl ether, dioxane or tetrahydrofuran), an alkanol (e.g. ethanol or propanol), an aromatic hydrocarbon (e.g. benzene, toluene or xylene), acetonitrile, dimethylformamide or dimethyl sulphoxide. The reaction can be carried out at from room temperature to the reflux temperature of the reaction mixture, preferably at the reflux temperature. The reaction is expediently carried out in the presence of a base (e.g. a tertiary amine such as triethylamine, N-ethyl-N,N-diisopropylamine or N,N-dimethylaniline) in the case where acid is cleaved during the reaction.

25 The starting materials of formula XI are known.

The reduction of a carbonyl group or a group A in a compound of formula XII or XIII in accordance with embodiment f) of the process can be carried out in a manner known *per se*.

30 Thus, an amide of formula XII or XIII (i.e. a compound in which the carbonyl group is bonded directly to the nitrogen atom) can be reduced by treatment with a metal hydride (e.g. lithium aluminium hydride or diisobutyl aluminium hydride) or with diborane. This reduction is expediently carried out in an organic solvent which is inert under the reduction conditions (e.g. an ether such as diethyl ether, tetrahydrofuran or diglyme) and at a temperature from 0°C to the reflux temperature of the reduction mixture, preferably at about room temperature.

45 The reduction of other carbonyl groups (i.e. those which are not bonded directly to the nitrogen atom) can also be carried out in a manner known *per se*. In particular, the reduction can be carried out in such a manner that it either leads to a hydroxymethylene group, which can then be further reduced to a methylene group, or leads directly to a methylene group.

55 The reduction to a hydroxymethylene group can be carried out by treatment with a complex metal hydride such as an alkali metal aluminium hydride or an alkali metal borohydride.

60 The reduction using an alkali metal aluminium hydride or an alkali metal borohydride can be expediently carried out at room temperature or at a temperature below or above room temperature and in an inert organic solvent. Suitable solvents which can

be used in the case of reduction using an alkali metal aluminium hydride include, inter alia, anhydrous ethers such as diethyl ether and tetrahydrofuran. Suitable solvents which can be used in the case of reduction using an alkali metal borohydride include alkanols containing 1-4 carbon atoms (e.g. methanol or ethanol) or dioxane. Lithium aluminium hydride is preferably used as the alkali metal aluminium hydride and sodium borohydride is preferably used as the alkali metal borohydride.

The further reduction of a hydroxymethylene group to a methylene group can be carried out in a manner known *per se*, especially by conversion into a corresponding sulphonic acid ester or into a halide and reduction thereof with a complex metal hydride. These reductions can be carried out in a manner analogous to the reduction of carbonyl groups described hereinbefore.

The direct reduction of a carbonyl group to a methylene group can be carried out by means of a Wolff-Kishner reaction in a manner known *per se*, namely by reaction of the ketone with hydrazine to give the corresponding hydrazone and decomposition of the hydrazone under basic conditions.

The conversion of a compound of formula I in which X represents a sulphur atom into a compound of formula I in which X represents SO or SO₂ can be carried out by oxidation, in a suitable solvent, with a peracid such as peracetic acid, perphthalic acid or m-chloroperbenzoic acid. Peracetic acid can, for example, be formed in situ from glacial acetic acid and hydrogen peroxide.

Compounds of formula I in which R₁ represents a hydrogen atom can be N-(lower alkylated) in a manner known *per se*; for example, using a lower alkyl halide. In this procedure, the particular compound of formula I is expediently reacted directly with the alkyl halide at a low temperature.

The conversion of a lower alkoxy group or an aryl-(lower alkoxy) group into a hydroxy group can be carried out in a manner known *per se*; for example, by heating with a concentrated hydrohalic acid, especially constant boiling hydrobromic acid.

The reduction of a nitro group to an amino group can be carried out chemically or catalytically in a manner known *per se*; for example, using tin/hydrochloric acid or hydrogen in the presence of a noble metal catalyst. The hydrogenation is preferably carried out in an alkanol, especially ethanol, in the presence of palladium/carbon or platinum oxide under normal pressure at room temperature.

The saponification of a cyano group can be carried out using an acid or a base in a manner known *per se*.

The esterification or amidation of a carbonyl group can be carried out in a manner known *per se*; for example, by treatment with

an appropriate alcohol or an appropriate amine.

An amino group present can be alkylated as described hereinbefore or can be acylated by treatment with an acid halide or acid anhydride in a manner known *per se*.

The etherification or esterification of a hydroxy group present can be carried out in a manner known *per se*; for example, by reaction with an appropriate halide or with an appropriate acid halide or acid anhydride.

The reduction of a carboxyl group can be carried out in a manner known *per se*; for example using diborane or lithium aluminium hydride in an inert organic solvent.

The oxidation of an alkylthio group can be carried out in a manner known *per se*; for example, using hydrogen peroxide.

The compounds of formula I can be converted into acid addition salts, for example by treatment with an inorganic acid such as a hydrohalic acid (e.g. hydrochloric acid or hydrobromic acid), sulphuric acid or phosphoric acid or with an organic acid such as oxalic acid, tartaric acid, citric acid or methanesulphonic acid. Of the acid addition salts of compounds of formula I, the pharmaceutically acceptable acid addition salts are preferred. If, in the course of the process of this invention, an acid addition salt of a compound of formula I is obtained, then such a salt can be converted into the free base in a known manner (e.g. by treatment with alkali) and the free base can, if desired, be converted into another acid addition salt.

Those compounds of formula I which contain an asymmetric carbon atom can be present in a racemic or optically active form and it will be understood that this invention includes not only the racemic but also the optically active forms. A racemate can, if desired, be resolved into the optical antipodes in a manner

known *per se*; for example, by fractional crystallisation of the corresponding salts with an optically active acid.

The compounds of formula I and their acid addition salts possess valuable coronary-dilating properties and can accordingly be used, *inter alia*, for the treatment of angina pectoris.

The coronary-dilating activity can be measured by the following method:

Mongrels weighing between 20 and 38 kg are used for the tests. The test animals are anaesthetised with ca 30 mg/kg i.v. pentobarbital and the anaesthesia is maintained with chloralose-urethane. The animals are artificially respired with atmospheric air. After opening the thorax, the heart is exposed and a previously calibrated flow-probe of an electromagnetic flowmeter for measuring the blood flow-rate is placed around the ramus circumflexus of the left coronary artery. The arterial blood pressure is measured with a pressure via a catheter in the arterial femoralis. Further, a calibrated extensible measuring strip for the direct measurement of the myocardial contraction force is sutured on to the surface of the left ventricle. The pulse wave of the blood pressure triggers a tachograph for measuring the heart frequency. Water-soluble compounds are administered intravenously dissolved in an isotonic sodium chloride solution, water-insoluble compounds are administered dissolved in propylene glycol or the compounds are administered intraduodenally as a suspension in gum arabic. The maximum activity of a compound is calculated according to each dosage in per cent of the starting value and represented graphically. In the measurement of the coronary blood-flow, the duration of activity is also carefully observed.

The results obtained are compiled in the following Table, n denoting the number of animals used.

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TABLE

Compound	DL 50 mg/kg p.o.	Coronary flow increase (CF)					
		1 mg i.v.			3 mg i.v.		
		CF %	Time in minutes		CF %	Time in minutes	n
N-(3,4-Dimethoxyphenethyl)-2-(3,4-dimethoxyphenyl)-N-methyl-m-dithiane-2-propylamine	250-500	+138.6 ± 8.4	10.4 ± 1.6		+109 ± 11.8	23.4 ± 5.5	5
N-(3,4-Dimethoxyphenethyl)-2-(3,4-dimethoxyphenyl)-N-methyl-m-dithiane-2-propylamine-1,1,3,3-tetraoxide	250-500	+142.6 ± 23.3	20.2 ± 3.9		+230.4 ± 20.9	54.0 ± 8.6	5
N-(3,4-Dimethoxyphenethyl)-2-(2-naphthyl)-N-methyl-m-dithiane-2-propylamine	250-500	+213	25		+194	45	2
N-(3,4-Dimethoxyphenethyl)-2-(m-nitrophenyl)-N-methyl-m-dithiane-2-propylamine-1,1,3,3-tetraoxide	500-1000	+202	25		+170	30	2
N-(3,4-Dimethoxyphenethyl)-2-(3,4-dimethoxyphenyl)-N-ethyl-m-dithiane-2-propylamine-1,1,3,3-tetraoxide	500-1000	+197	8		+267	15	2

The compounds of formula I and their pharmaceutically acceptable acid addition salts may be used as medicaments in the form of pharmaceutical preparations which contain them in association with a compatible pharmaceutical carrier material. This carrier material may be an organic or inorganic, inert carrier material suitable for enteral or parenteral administration such as, for example, water, gelatine, gum arabic, lactose, starch, magnesium stearate, talc, vegetable oils, polyalkyleneglycols or petroleum jelly. The pharmaceutical preparations can be made up in a solid form (e.g. as tablets, dragées or capsules) or in a liquid form (e.g. as solutions, suspensions or emulsions). The pharmaceutical preparations may be sterilised and/or may contain adjuvants such as preservatives, stabilisers, wetting agents, emulsifiers, salts for varying the osmotic pressure or buffers.

The daily dose in the case of oral administration is from 10 mg to 200 mg. The daily dose in the case of intravenous administration is from 1 mg to 20 mg.

The aforementioned dosages are, however, only given by way of example and can be modified according to the severity of the case to be treated and the directions of the attending physician.

The following Examples 3 to 18 illustrate the process provided by the present invention; Examples 1 and 2 describe the preparation of starting materials.

Example 1.

74.7 g of 3,4-dimethoxybenzaldehyde are dissolved in 1250 ml of chloroform, treated with 50 ml of 1,3-propanedithiol and cooled at 0°C with stirring. 20 ml of boron trifluoride etherate are added and the mixture is left to stand in a refrigerator for 18 hours. The mixture is then washed three times successively with 500 ml of a 7% potassium hydroxide solution and 500 ml of a 10% sodium chloride solution. The organic extracts are combined, dried over magnesium sulphate and evaporated. The residue is recrystallised twice from ether. There are obtained 102.6 g of 2 - (3,4-dimethoxyphenyl) - m - dithiane of melting point 99°—101°C.

The following dithianes can be manufactured in an analogous manner:

2 - (o - methoxyphenyl) - m - dithiane of melting point 126°—127°C (from methylene chloride/isopropyl ether);

2 - phenyl - m - dithiane of melting point 72°—73°C (from methylene chloride/isopropyl ether);

2 - (p - chlorophenyl) - m - dithiane of melting point 87°—88°C (from methylene chloride/isopropyl ether);

2 - (m - methoxyphenyl) - m - dithiane of melting point 62°—63°C (from isopropyl ether);

2 - (3,4,5 - trimethoxyphenyl) - m - dithiane of melting point 88°—89°C (from methylene chloride/isopropyl ether);

2 - (m - chlorophenyl) - m - dithiane of melting point 63°—64°C (from cyclohexane);

2 - (3,5 - dimethoxyphenyl) - m - dithiane of melting point 90°—91°C (from cyclohexane);

p - (m - dithian - 2 - yl) - N,N - dimethylaniline of melting point 118°—119°C (from cyclohexane);

2 - (m - nitrophenyl) - m - dithiane of melting point 117°—118°C (from methylene chloride/methanol);

2 - (3,4 - methylenedioxyphenyl) - m - dithiane of melting point 86°—87°C (from cyclohexane);

2 - p - tolyl - m - dithiane of melting point 89°—90°C (from ether/hexane);

2 - (m - bromophenyl) - m - dithiane of melting point 78°—79°C (from cyclohexane);

2 - (2 - naphthyl) - m - dithiane of melting point 110°—111°C (from cyclohexane);

2 - (2,4,5 - trimethoxyphenyl) m - dithiane of melting point 156°—157°C (from methylene chloride/methanol);

2 - (p - fluorophenyl) - m - dithiane of melting point 105°—106°C (from cyclohexane);

2 - (4 - biphenyl) - m - dithiane of melting point 148°—151°C (from tetrahydrofuran/cyclohexane);

2 - (a,a,a - trifluoro - p - tolyl) - m - dithiane of melting point 103°—104°C (from cyclohexane);

2 - (1 - naphthyl) - m - dithiane of melting point 147°—148°C (from cyclohexane);

2 - (3 - benzyloxy - 4 - methoxyphenyl) - m - dithiane of melting point 168°—170°C (from cyclohexane);

2 - (4 - benzyloxy - 3 - methoxyphenyl) - m - dithiane of melting point 118°—119°C (from cyclohexane);

2 - (2 - thienyl) - m - dithiane of melting point 74°—75°C (from cyclohexane);

2 - (a,a,a - trifluoro - m - tolyl) - m - dithiane of melting point 69°—71°C (from heptane);

2 - (p - isopropylphenyl) - m - dithiane of melting point 58°—59°C (from hexane);

2 - (3,4 - xyl) - m - dithiane of melting point 74°—75°C (from petroleum ether);

2 - (3 - butoxy - 4 - methoxyphenyl) - m - dithiane;

2 - (4 - ethoxy - 3 - methoxyphenyl) - m - dithiane of melting point 88°—90°C (from methylene chloride/isopropyl ether);

m - (m - dithian - 2 - yl) - benzonitrile of melting point 84°—86°C (from isopropyl ether);

6 - (m - dithian - 2 - yl) - 1,4 - benzo-dioxan of melting point 140°—142°C (from methylene chloride/isopropyl ether);

2 - (4 - methoxy - m - tolyl) - m - dithiane

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of melting point 75°—77°C (from cyclohexane).

Example 2.

60 g of 2 - (3,4 - dimethoxyphenyl) - m-dithiane (prepared as described in Example 1) are dissolved in 470 ml of glacial acetic acid and treated at room temperature with 235 ml of 30% hydrogen peroxide, the temperature of the solution rising to ca 40°C. The solution is left to stand overnight at room temperature. The solution is then heated for 2 hours at 100°C. After cooling to room temperature, the crystalline precipitate is filtered off under a vacuum, washed with some glacial acetic acid, dried in vacuo at 60°C overnight and then recrystallised from acetonitrile. There are obtained 57.1 g of 2 - (3,4 - dimethoxyphenyl) - m - dithiane - 1,1,3,3 - tetraoxide of melting point 243°—245°C.

The following dithiane tetraoxides can be manufactured in an analogous manner:

2 - (m - bromophenyl) - m - dithiane - 1,1,3,3 - tetraoxide of melting point 230°—231°C (from acetonitrile);

2 - (p - fluorophenyl) - m - dithiane - 1,1,3,3 - tetraoxide of melting point 283°—284°C (from acetonitrile);

2 - (m - nitrophenyl) - m - dithiane - 1,1,3,3 - tetraoxide of melting point 256°—257°C (from acetonitrile);

2 - (3,4,5 - trimethoxyphenyl) - m-dithiane - 1,1,3,3 - tetraoxide of melting point >310°C (from acetonitrile);

2 - (2 - naphthyl) - m - dithiane - 1,1,3,3 - tetraoxide of melting point 277°—278°C (from acetone/acetonitrile);

2 - p - tolyl - m - dithiane - 1,1,3,3 - tetraoxide of melting point 284°—285°C (from acetonitrile);

2 - (4 - benzyloxy - 3 - methoxyphenyl) - m - dithiane - 1,1,3,3 - tetraoxide of melting point 220°—223°C (from acetone/acetonitrile);

2 - (3,4 - dimethoxyphenyl) - 1,3 - dithiolane - 1,1,3,3 - tetraoxide of melting point 194°—196°C (from acetone/acetonitrile);

2 - (3,4 - methylenedioxyphenyl) - m-dithiane - 1,1,3,3 - tetraoxide of melting point >300°C (from acetone/acetonitrile);

2 - (2' - thienyl) m - dithiane - 1,1,3,3 - tetraoxide of melting point 300°C (from acetone/acetonitrile);

2 - (3,4 - dichlorophenyl) - m - dithiane - 1,1,3,3 - tetraoxide of melting point 254°—255°C (from glacial acetic acid/water);

2 - (α,α,α - trifluoro - m - tolyl) - m-dithiane - 1,1,3,3 - tetraoxide of melting point 239°—242°C (from glacial acetic acid/water);

2 - (p - isopropylphenyl) - m - dithiane - 1,1,3,3 - tetraoxide of melting point 204°—205°C (from acetonitrile/ethanol);

2 - (3,4 - xylyl) - m - dithiane - 1,1,3,3 - tetraoxide of melting point 268°—269°C (from acetonitrile/methanol);

2 - (3 - butoxy - 4 - methoxyphenyl) - m-dithiane - 1,1,3,3 - tetraoxide of melting point 225°—227°C (from glacial acetic acid/water);

2 - (4 - ethoxy - 3 - methoxyphenyl) - m-dithiane - 1,1,3,3 - tetraoxide of melting point 242°—244°C (from acetone/acetonitrile);

m - (m - dithian - 2' - yl) - benzonitrile-1',1',3',3' - tetraoxide of melting point 259°—260°C (from glacial acetic acid/water);

6 - (m - dithian - 2' - yl) - 1,4 - benzo-dioxan - 1',1',3',3' - tetraoxide of melting point 232°C (decomposition) (from glacial acetic acid/water);

2 - (4 - methoxy - m - tolyl) - m - dithiane-1',1',3',3' - tetraoxide of melting point 225°—227°C (from glacial acetic acid/water).

Example 3.

19.2 g of 2 - (3,4 - dimethoxyphenyl) - m - dithiane (prepared as described in Example 1) and 200 ml of tetrahydrofuran are cooled to -60°C in a sulphonation flask while gassing with argon and slowly treated with 33 ml of butyl lithium in hexane. The mixture is then stirred at -20°C for 2 hours. A solution of 18 g of N - (3 - chloropropyl) - 3,4 - dimethoxy - N - methyl - phenethylamine in 200 ml of tetrahydrofuran is added dropwise thereto at -70°C within 15 minutes. The mixture is then left to stand for 18 hours at -20°C in a deep-freezer and for 3 hours at room temperature. The solution is then poured on to water and extracted three times with ether. The ethereal extracts are extracted three times with 250 ml of 1-N hydrochloric acid. The acidic extracts are treated with 3-N sodium hydroxide up to pH > 12 and the separated oil is extracted with ether. The organic extracts are dried over magnesium sulphate and evaporated. The thus obtained oil (30g) is dissolved in ethyl acetate and treated with ethereal hydrogen bromide. The precipitate which separates is recrystallised from ethanol. There is obtained N - (3,4 - dimethoxyphenethyl) - 2 - (3,4 - dimethoxyphenyl) - N - methyl - m - dithiane-2 - propylamine hydrobromide of melting point 170—172°C.

Analysis for $C_{26}H_{37}NO_4S_2.HBr$

Calculated:

C 54.54 H 6.69 N 2.45 Br 13.95

Found:

C 54.54 H 6.74 N 2.31 Br 14.05

The N - (3 - chloropropyl) - 3,4 - dimethoxy - N - methyl - phenethylamine used as the starting material can be prepared as follows:

292.5 g of N - methyl - homoveratrylamine are dissolved in 1000 ml of dimethylformamide and treated with 415 g of anhydrous potassium carbonate. The mixture is stirred at 5°C, treated with 237 g of 1,3-bromochloropropane in 500 ml of dimethylform-

amide, stirred for a further 4 hours at room temperature and then poured into 6 litres of water. The separated oil is extracted three times with 2 litres of ether each time. The organic extracts are dried with magnesium sulphate and evaporated in vacuo. The residual oil is distilled at between 69°C and 70°C with a mercury diffusion pump at 0.005 Torr. There are obtained 206.7 g of N - (3-chloropropyl) - 3,4 - dimethoxy - N - methylphenethylamine of boiling point 69°—70°C/0.005 Torr.

The following compounds can be manufactured in an analogous manner to that described in this Example:

- 5 N - (3,4 - dimethoxyphenethyl) - 2 - (methoxyphenyl) - N - methyl - m - dithiane - 2 - propylamine hydrochloride of melting point 113°—115°C (from acetone);
- 10 N - (3,4 - dimethoxyphenethyl) - 2 - (3,4 - trimethoxyphenyl) - N - methyl - m - dithiane - 2 - propylamine hydrochloride of melting point 147°—150°C (from acetone);
- 15 N - (3,4 - dimethoxyphenethyl) - 2 - (p-methoxyphenyl) - N - methyl - m - dithiane - 2 - propylamine hydrochloride of melting point 160°—161°C (from acetone);
- 20 N - (3,4 - dimethoxyphenethyl) - 2 - (o-methoxyphenyl) - N - methyl - m - dithiane - 2 - propylamine hydrochloride of melting point 151°—152°C (from acetone);
- 25 2 - (p - chlorophenyl) - N - (3,4 - dimethoxyphenethyl) - N - methyl - m - dithiane - 2 - propylamine hydrochloride of melting point 137°—139°C (from acetone);
- 30 N - (3,4 - dimethoxyphenethyl) - N - methyl - 2 - phenyl - m - dithiane - 2 - propylamine hydrochloride of melting point 170°—172°C (from acetone);
- 35 N - (3,4 - dimethoxyphenethyl) - N - methyl - 2 - (3,4 - methylene dioxyphenyl) - m - dithiane - 2 - propylamine hydrochloride of melting point 139°—141°C (from acetone);
- 40 N - (3,4 - dimethoxyphenethyl) - N - methyl - 2 - (p - tolyl) - m - dithiane - 2 - propylamine hydrochloride of melting point 139°—141° (from acetone);
- 45 2 - m - (chlorophenyl) - N - (3,4 - dimethoxyphenyl) - N - methyl - m - dithiane - 2 - propylamine hydrochloride of melting point 108°—110°C (from acetone);
- 50 N - (3,4 - dimethoxyphenethyl) - 2 - (3,5-dimethoxyphenyl) - N - methyl - m - dithiane - 2 - propylamine oxalate (1:1) of melting point 155°—156°C (from acetone);
- 55 N - (3,4 - dimethoxyphenethyl) - 2 - (p-dimethylaminophenyl) - N - methyl - m - dithiane - 2 - propylamine hydrochloride of melting point 183°—184°C (from acetone);
- 60 N - (3,4 - dimethoxyphenethyl) - N - methyl - 2 - (2 - naphthyl) - m - dithiane - 2 - propylamine hydrochloride of melting point 195°—196°C (from acetone);
- 65 N - (3,4 - dimethoxyphenethyl) - N - methyl - 2 - (2,4,5 - trimethoxyphenyl) - m - dithiane - 2 - propylamine hydrochloride of melting point 156°—158°C (from acetone);
- 70 N - (3,4 - dimethoxyphenethyl) - 2 - (p-fluorophenyl) - N - methyl - m - dithiane - 2 - propylamine hydrochloride of melting point 138°—139°C (from acetone);
- 75 2 - (4 - biphenyl) - N - (3,4 - dimethoxyphenethyl) - N - methyl - m - dithiane - 2 - propylamine oxalate (1:1) of melting point 167°—169°C (from acetone);
- 80 N - (p - chlorophenethyl) - N - methyl - 2 - phenyl - m - dithiane - 2 - propylamine hydrochloride of melting point 145°—147°C (from acetone), starting from 2 - phenyl - m - dithiane and N - (3 - chloropropyl) - 4-chloro - N - methyl - phenethylamine;
- 85 N - methyl - N - phenethyl - 2 - phenyl - m - dithiane - 2 - propylamine hydrochloride of melting point 136°—137°C (from acetone), starting from 2 - phenyl - m - dithiane and N - (3 - chloropropyl) - N - methyl - phenethylamine (boiling point 78°—80°C/0.001 Torr);
- 90 N - (3,4 - dimethoxyphenethyl) - N - methyl - 2 - phenyl - m - dithiane - 2 - ethylamine hydrochloride of melting point 172°—174°C (from acetone), starting from 2 - phenyl - phenyl - m - dithiane and N - (2-chloroethyl) - 3,4 - dimethoxy - N - methylphenethylamine;
- 95 N - (3,4 - dimethoxyphenethyl) - N - methyl - 2 - (2 - thienyl) - m - dithiane - 2 - propylamine hydrochloride of melting point 138°—140°C (from acetone);
- 100 rac - N - (3,4 - dimethoxyphenethyl) - 2 - (3,4 - dimethoxyphenyl) - N_β - dimethyl - m - dithiane - 2 - propylamine oxalate (1:1) of melting point 138°—139°C (from acetone/ethyl acetate), starting from 2 - (3,4 - dimethoxyphenyl) - m - dithiane and N - (3-chloro - 2 - methylpropyl) - 3,4 - dimethoxy - N - methyl - phenethylamine;
- 105 2 - (3,4 - dimethoxyphenyl) - N - [4-(3,4 - dimethoxyphenylbutyl) - N - methyl - m - dithiane - 2 - propylamine.
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Example 4.

35.2 g of 2 - (3,4 - dimethoxyphenyl) - m - dithiane - 1,1,3,3 - tetraoxide (prepared as described in Example 2) are suspended in 180 ml of absolute dioxane and treated with 2.53 g of sodium. The mixture is boiled under argon for 20 hours, the sodium passing completely into solution. 27.2 g of N - (3 - chloropropyl) - 3,4 - dimethoxy - N - methylphenethylamine (prepared as described in Example 3) are then added at room temperature, the cloudy solution is stirred at room temperature for 1 hour and boiled at reflux for 3 hours. The mixture is poured on to ice/water and extracted three times with ethyl acetate. The ethyl acetate extracts are combined and extracted three times with 1-N hydrochloric acid. The acidic extracts are

made alkaline and extracted three times with chloroform. The chloroform extracts are combined, washed with water, dried over magnesium sulphate and evaporated. The crystalline residue is recrystallised from methanol and there are obtained crystals of melting point 143°—145°C.

For the preparation of the hydrochloride, the base is dissolved in acetone and treated in an ice-bath with 20 ml of hydrogen chloride in dioxane. The crystalline salt is filtered off under a vacuum and recrystallised from acetonitrile/acetone (1:3). The thus-obtained N-(3,4-dimethoxyphenethyl)-2-(3,4-dimethoxyphenyl) N-methyl-m-dithiane-2-propylamine-1,1,3,3-tetraoxide hydrochloride is dried overnight in a high vacuum at 120°C. There are obtained 38.9 g of a substance of melting point 167°—169°C.

Analysis:

Calculated:

C 52.74 H 6.47 N 2.36 Cl 5.99
S 10.83

Found:

S 52.58 H 6.58 N 2.16 Cl 6.19
S 10.53

The following compounds can be manufactured in an analogous manner to that described in this Example:

N-(3,4-dimethoxyphenethyl)-N-methyl-2-(2-naphthyl)-m-dithiane-2-propylamine-1,1,3,3-tetraoxide oxalate (1:1) of melting point 190°—191°C (from acetone/methanol);

N-(3,4-dimethoxyphenethyl)-N-methyl-2-(3,4,5-trimethoxyphenyl)-m-dithiane-2-propylamine-1,1,3,3-tetraoxide oxalate (1:1) of melting point 146°—148°C (from acetone/ethyl acetate);

2-(m-bromophenyl)-N-(3,4-dimethoxyphenethyl)-N-methyl-m-dithiane-2-propylamine-1,1,3,3-tetraoxide hydrochloride of melting point 158°—160°C (from methanolic hydrogen chloride/ethyl acetate);

2-(m-nitrophenyl)-N-(3,4-dimethoxyphenethyl) N-methyl-m-dithiane-2-propylamine-1,1,3,3-tetraoxide hydrochloride of melting point 212°—214°C (from acetone);

N-(3,4-dimethoxyphenethyl)-2-(p-fluorophenyl)-N-methyl-m-dithiane-2-propylamine-1,1,3,3-tetraoxide hydrochloride of melting point 234°—236°C (from methanol);

N-(3,4-dimethoxyphenethyl)-N-methyl-2-phenyl-m-dithiane-2-propylamine-1,1,3,3-tetraoxide hydrochloride of melting point 149°C (decomposition) (from methanol);

N-(3,4-dimethoxyphenethyl)-2-(3,4-dimethoxyphenyl)-N-ethyl-m-dithiane-2-propylamine-1,1,3,3-tetraoxide oxalate

(1:1) of melting point 177°—179°C (from methanol/acetone) [from 2-(3,4-dimethoxyphenyl)-m-dithiane-1,1,3,3-tetraoxide and N-(3-chloropropyl)-3,4-dimethoxy-N-ethyl-phenethylamine];

N-(3,4-dimethoxyphenethyl)-2-(4-isopropylphenyl)-N-methyl-m-dithiane-2-propylamine-1,1,3,3-tetraoxide hydrochloride of melting point 225°—227°C (from hydrogen chloride in dioxane/ethyl acetate);

N-(3,4-dimethoxyphenethyl)-2-(3-trifluoromethylphenyl)-N-methyl-m-dithiane-2-propylamine-1,1,3,3-tetraoxide oxalate of melting point 128°—130°C (from acetone);

N,2-bis(3,4-dimethoxyphenyl)-N-methyl-m-dithiane-2-propylamine-1,1,3,3-tetraoxide;

2-(3,4-dimethoxyphenyl)-N-[4-(3,4-dimethoxyphenyl)butyl]-m-dithiane-2-propylamine-1,1,3,3-tetraoxide;

N-(3,4-dimethoxyphenethyl)-N-methyl-2-(3,4-xylyl)-m-dithiane-2-propylamine-1,1,3,3-tetraoxide hydrochloride of melting point 176°—178°C (from acetonitrile);

2-(3-butoxy-4-methoxyphenyl)-N-(3,4-dimethoxyphenethyl)-N-methyl-m-dithiane-2-propylamine-1,1,3,3-tetraoxide of melting point 84°—85°C (from methanol/isopropyl ether);

N-[3-(2'-(3,4-dimethoxyphenyl)-m-dithiane-2'-yl)-propyl]-N-methyl-1,4-benzodioxan-6-ethylamine-1',1'-3',3'-tetraoxide hydrochloride of melting point 208°—210°C (from acetonitrile);

N-[4-(3,4-dimethoxyphenyl)-butyl]-2-(p-isopropylphenyl)-N-methyl-m-dithiane-2-propylamine-1,1,3,3-tetraoxide hydrochloride of melting point 148°—150°C (from ethyl acetate/hydrogen chloride in dioxane);

rac-2-(3,4-dimethoxyphenyl)-N-[3-(3,4-dimethoxyphenyl)-1-methylpropyl]-N-methyl-m-dithiane-2-propylamine-1,1,3,3-tetraoxide of melting point 115°—117°C.

N-(3,4-dimethoxyphenethyl)-2-(4-ethoxy-3-methoxyphenyl)-N-methyl-m-dithiane-2-propylamine-1,1,3,3-tetraoxide hydrochloride of melting point 190°—192°C (from acetonitrile);

m-{2'-[3-[3,4-dimethoxyphenethyl)-methylamino]-propyl}-m-dithiane-2'-yl}-benzonitrile-1',1'-3',3'-tetraoxide hydrochloride of melting point 160°C (decomposition);

2-(1,4-benzodioxan-6-yl)-N-(3,4-dimethoxyphenethyl)-N-methyl-m-dithiane-2-propylamine-1,1,3,3-tetraoxide hydrochloride of melting point 146°C (204°C);

N-(3,4-dimethoxyphenethyl)-2-(4-methoxy-m-tolyl)-N-methyl-m-dithiane-2-propylamine-1,1,3,3-tetra-

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oxide hydrochloride of melting point 146°C (decomposition) (from acetone);

5 m { 2' [3 - [4 - (3,4 - dimethoxyphenyl)-butyl] - methylaminopropyl] - m - dithiane-2' - yl } - benzonitrile - 1',1',3,3' - tetraoxide hydrochloride of melting point 120°—122°C (from water);

10 2 - (3,4 - dimethoxyphenyl) - N - methyl - N - (p - methylphenethyl) - m - dithiane-2 - propylamine - 1,1,3,3 - tetraoxide hydrochloride of melting point 169°—171°C (from acetone/ethyl acetate).

Example 5.

15 6.08 g of 2 - (3,4 - methylenedioxyphenyl) - m - dithiane - 1,1,3,3 - tetraoxide (prepared as described in Example 2) are stirred under argon with 25 ml of absolute dimethylformamide and treated with 0.8 g of a 55% sodium hydride suspension. The mixture is left to react for 0.5 hour at room temperature and for 1 hour at 40°C. After cooling to room temperature, 4.8 g of N - (3 - chloropropyl) - 3,4-dimethoxy - N - methyl - phenethylamine (prepared as described in Example 3) are added and the mixture is heated at 100°C for 16 hours. The cooled mixture is then poured on to ice and extracted three times with ethyl acetate. The organic extracts are washed with water, dried over magnesium sulphate and evaporated in vacuo. The residual oil is dissolved in acetone and treated with 5 ml of a 6-N hydrogen chloride solution in dioxane. The precipitate, which is filtered off under vacuum, is recrystallised from acetone. There are obtained 7.5 g of N - (3,4 - dimethoxyphenethyl) - N - methyl - 2 - (3,4 - methylenedioxyphenyl) - m - dithiane - 2 - propylamine - 1,1,3,3 - tetraoxide hydrochloride of melting point 247°—248°C.

40 Analysis:

Calculated:

C 52.12 H 5.95 N 2.43

Found:

C 51.91 H 5.86 N 2.23

45 The following compounds can be manufactured in a manner analogous to that described in this Example:

50 N - (3,4 - dimethoxyphenethyl) - N - methyl - 2 - p - tolyl - m - dithiane - 2 - propylamine - 1,1,3,3 - tetraoxide hydrochloride of melting point 203°—207°C (from acetonitrile/acetone);

55 2 - (4 - benzyloxy) - 3 - methoxyphenyl - N - (3,4 - dimethoxyphenethyl) - N - methyl - m - dithiane - 2 - propylamine - 1,1,3,3 - tetraoxide hydrochloride of melting point 220°—221°C (from ethanol);

60 N - (3,4 - dimethoxyphenethyl) - N - methyl - 2 - (2' - thieryl) - m - dithiane-2 - propylamine - 1,1,3,3 - tetraoxide hydrochloride of melting point 179°—182°C (from acetone);

2 - (3,4 - dichlorophenyl) - N - (3,4-dimethoxyphenethyl) - N - methyl - m - dithiane - 2 - propylamine - 1,1,3,3 - tetraoxide hydrochloride of melting point 175°—177°C (from methanol);

70 N - (3,4 - dimethoxyphenethyl) - 2 - (3,4-dimethoxyphenyl) - N - methyl - m - dithiane-2 - ethylamine - 1,1,3,3 - tetraoxide oxalate (1:1) of melting point 202°—204°C (from acetone).

Example 6.

10 g of 3',4' - dimethoxy - 4 - (methylveratrylamino)butyrophenone hydrochloride are dissolved in 50 ml of chloroform and treated with 3.25 g of 1,3-propanedithiol. Hydrogen chloride is conducted into the mixture at room temperature. After standing for 24 hours, the mixture is poured on to water, made basic with 3-N sodium hydroxide and extracted with ether. After drying and evaporation of the solvent, the only residue is dissolved in acetone and treated with an equivalent amount of anhydrous oxalic acid. The crystalline precipitate is recrystallised from acetone. There is obtained 2 - (3,4 - dimethoxyphenyl) - N - methyl - N - veratryl - m - dithiane - 2 - propylamine oxalate (1:1) of melting point 133°—136°C.

Analysis:

Calculated:

C 57.12 H 6.57 N 2.47

Found:

C 56.88 H 6.64 N 2.46

The 3',4' - dimethoxy - 4 - (methylveratrylamino)butyrophenone used as the starting material can be prepared as follows:

500 g of polyphosphoric acid and 69 g of veratrol are added to a 1 litre round-bottomed flask. To this are added 61 g of 4-chlorobutyric acid in one portion, the temperature rising steadily to 55°C. After 1 hour, the entire mixture is poured on to ice. The mixture is then extracted with a mixture of ether/methylene chloride (3:1). The organic extracts are extracted with water, then with a saturated sodium bicarbonate solution and finally again with water, dried over magnesium sulphate and evaporated in vacuo. The residual crystal mass is recrystallised from ether. There are obtained 62.9 g of 3,4 - dimethoxy - γ-chlorobutyrophenone of melting point 91°—92°C.

115 12 g of 3,4 - dimethoxy - γ - chlorobutyrophenone are treated with 40 ml of N - ethyl - N,N - diisopropylamine and 9 g of N - methylhomoveratrylamine and stirred at 120°C for 6 hours. After evaporation of the solvent in vacuo, the viscous mass is treated with ether and sodium hydroxide. The organic extracts are washed with water and extracted with 1-N hydrochloric acid. The acidic extracts are then made alkaline and extracted with ether. The ether extracts are combined, dried over sodium

sulphate and evaporated. The thus-obtained 3',4' - dimethoxy - 4 - (methylveratrylamino) - butyrophene, which is pure according to thin-layer chromatography, can be used without further purification.

The following compounds can be manufactured in a manner analogous to that described in this Example:

N - (3,4 - dimethoxyphenethyl) - 2 - (3,4 - dimethoxyphenyl) - N - methyl - m - dithiane - 2 - butylamine oxalate (1:1) of melting point 134°—136°C (from acetone);

starting from

1,3 - propanedithiol and 5 - [(3,4 - dimethoxyphenethyl) - methylamino] - 3',4' - dimethoxyvalerophenone (melting point of the hydrochloride 165°—166°C),

obtained from

3,4 - dimethoxy - 8 - chlorovalerophenone and N - methyl - homoveratrylamine.

N - (3,4 - Dimethoxyphenethyl) - 2 - (3,4 - dimethoxyphenyl) - N - methyl - m - dithiane - 2 - pentylamine oxalate (1:1) of melting point 109°—111°C (from acetone);

starting from

1,3 - propanedithiol and 6 - [(3,4 - dimethoxyphenethyl) - methylamino] - 3',4' - dimethoxyhexanophenone (melting point of the hydrochloride 128°—129°C).

obtained from

6 - chloro - 3',4' - dimethoxyhexanophenone and N - methyl - homoveratrylamine.

2 - (3,4 - Dimethoxyphenyl) - N - [3 - (3,4 - dimethoxyphenyl) - propyl] - N - methyl - m - dithiane - 2 - propylamine oxalate (1:1) of melting point 116°—118°C (from acetone);

starting from

1,3 - propanedithiol and 3',4' - dimethoxy - 4 - [(3,4 - dimethoxyphenyl) - propyl] - methylamino] - butyrophene,

obtained from

3,4 - dimethoxy - γ - chlorobutyrophene and 3 - (3,4 - dimethoxyphenyl) - N - methylpropylamine.

2 - (3,4 - Dimethoxyphenyl) - N - methyl - N - (3,4 - dimethoxy α - methylphenethyl) - m - dithiane - 2 - propylamine oxalate (1:1) of melting point 131°—132°C (from acetone/ethyl acetate);

starting from

1,3 - propanedithiol and 4 - [3,4 - dimethoxy - α - methylphenethyl) - methylamino] - 3',4' - dimethoxybutyrophene,

obtained from

3,4 - dimethoxy γ - chlorobutyrophene and 3,4 - dimethoxy N, α - dimethyl - β - phenylethylamine (boiling point 130°—140°C/20 mm Hg).

N - (3,4 - Dimethoxyphenethyl) - 2 - (3,4 - dimethoxyphenyl) N - methyl - 1,3 - dithiolane - 2 - propylamine oxalate (1:1) of

melting point 150°—152°C (from acetone); starting from

4 - [(3,4 - dimethoxyphenethyl) - methylamino] - 3',4' - dimethoxybutyrophene and 1,2 - ethanedithiol.

Example 7.

10.4 g of 2 - (3 - chloropropyl) - 2 - (3,4 - dimethoxyphenyl) - m - dithiane - 1,1,3,3 - tetraoxide are treated with 5.11 g of N - methyl - homoveratrylamine, 30 ml of N - ethyl - N, N - diisopropylamine and 70 ml of dimethylformamide. The solution is heated at 120°C for 6 hours. After evaporation, the residue is worked-up in a manner analogous to that described in Example 5. There is obtained N - (3,4 - dimethoxyphenethyl) - 2 - (3,4 - dimethoxyphenyl) - N - methyl - m - dithiane - 2 - propylamine - 1,1,3,3 - tetraoxide hydrochloride of melting point 167°—169°C.

The following compounds can be manufactured in a manner analogous to the foregoing:

N - (3,4 - dimethoxyphenethyl) - N - methyl - 2 - phenyl - m - dithiane - 2 - propylamine - 1,1,3,3 - tetraoxide hydrochloride of melting point 149°C (decomposition) (from methanol);

N - (p - chlorophenethyl) - N - methyl - 2 - phenyl - m - dithiane - 2 - propylamine - 1,1,3,3 - tetraoxide hydrochloride of melting point 246°—249°C (decomposition) from methanol/methylene chloride);

N - methyl - N - phenethyl - 2 - phenyl - m - dithiane - 2 - propylamine - 1,1,3,3 - tetraoxide hydrochloride of melting point 165°—167°C (from acetone);

2 - (3,4 - dimethoxyphenyl) - N - methyl - N - veratryl - m - dithiane - 2 - propylamine - 1,1,3,3 - tetraoxide of melting point 137°—139°C (from acetone/ethanol);

N - (3,4 - dimethoxyphenethyl) - 2 - (3,4 - dimethoxyphenyl) - m - dithiane - 2 - propylamine - 1,1,3,3 - tetraoxide hydrochloride of melting point 130°—132°C (from acetone).

The 2 - (3 - chloropropyl) - 2 - 3,4 - dimethoxyphenyl) - m - dithiane - 1,1,3,3 - tetraoxide used as a starting material in this Example can be prepared as follows:

10.9 g of 3,4 - dimethoxy - γ - chlorobutyrophene (prepared as described in Example 6) are dissolved in 120 ml of chloroform and treated with 5 ml of 1,3 - propanedithiol and 1 ml of boron trifluoride etherate at room temperature. After 1 hour at room temperature, the chloroform solution is washed three times with water, three times with 1-N sodium hydroxide and again three times with water. The organic phases are dried over magnesium sulphate and evaporated in vacuo. The oily residue is immediately dissolved in 500 ml of chloroform at 0°—5°C and treated with 45.7 g of solid m-chloroperbenzoic acid in such a manner that the temperature does not exceed 5°C. The mixture is subsequently left

in a refrigerator for 64 hours. The organic phase is washed three times with 1-N sodium hydroxide and three times with water, dried over magnesium sulphate and evaporated in vacuo. The residue is recrystallised from methylene chloride/isopropyl ether. There is obtained 2 - (3 - chloropropyl) - 2 - (3,4-dimethoxy) - m - dithiane - 1,1,3,3 - tetraoxide of melting point 183°—184°C.

The 2 - (3 - chloropropyl) - 2 - phenyl-m - dithiane - 1,1,3,3 - tetraoxide also used as a starting material in this Example can be prepared as follows:

19.63 g of 2 - phenyl - m - dithiane are dissolved in 300 ml of tetrahydrofuran. 43.5 ml of a solution of butyl lithium in hexane are slowly added dropwise at -70°C while gassing with argon. The mixture is stirred for a total of 1.5 hours at -20°C. The red solution obtained is added to a solution of 15.74 g of 1,3-bromochloropropane in 250 ml of absolute tetrahydrofuran at -70°C. The thus-obtained solution is left to stand for 1 hour at -20°C and for 1 hour at room temperature. The solvent is evaporated in vacuo and the oily residue taken up in ether. The ethereal phase is washed with 1-N sodium hydroxide and with water, dried over magnesium sulphate and evaporated in vacuo. The thus-obtained 2 - (3 - chloropropyl) - 2 - phenyl-m - dithiane is peroxidised at 0°—5°C with m-chloroperbenzoic acid in chloroform as described in the previous paragraph. After recrystallisation from ethyl acetate, there is obtained 2 - (3 - chloropropyl) - 2 - phenyl-m - dithiane - 1,1,3,3 - tetraoxide of melting point 182°C.

Example 8.

3.76 g of 2 - (3,4 - dimethoxyphenyl) - 2 - (2,3 - epoxypropyl) - m - dithiane - 1,1,3,3 - tetraoxide are heated at reflux for 18 hours under argon with 50 ml of ethanol, 30 ml of chloroform and 1.95 g of N - methyl - homoveratrylamine. After evaporation of the solvent, the residue is chromatographed on silica gel with chloroform/ethanol (98:2). The oil obtained is dissolved in acetone and treated with an equivalent amount of anhydrous oxalic acid. The precipitate is filtered off and recrystallised from methanol/acetate. The racemic α - [(3,4 - dimethoxyphenethyl)-methylamino] - methyl - 2 - (3,4 - dimethoxyphenyl) - m - dithiane - 2 - ethanol - 1,1,3,3 - tetraoxide oxalate (1:1) obtained crystallises with 1 mol of acetone and melts at 162°—164°C.

Analysis:

Calculated:

C 51.73 H 6.30 N 1.95

Found:

C 51.68 H 6.53 N 2.00

The 2 - (3,4 - dimethoxyphenyl) - 2 -

(2,3 - epoxypropyl) - m - dithiane - 1,1,3,3 - tetraoxide used as the starting material can be prepared as follows:

9.6 g of 2 - (3,4 - dimethoxyphenyl) - m - dithiane - 1,1,3,3 - tetraoxide (prepared as described in Example 2) are dissolved in 35 ml of dimethylformamide and, with stirring under argon, treated with 1.2 g of sodium hydride at room temperature. The suspension is stirred at 40°C for a further 0.5 hour, then cooled and treated with 2.8 g of epichlorohydrin. The mixture is then heated at 100°C for 16 hours. After cooling to room temperature, the suspension is poured on to water and the oily material extracted with chloroform. After evaporation of the solvent, the residue is chromatographed on silica gel with chloroform/ethanol (98:2). The 2 - (3,4-dimethoxyphenyl) - 2 - (2,3 - epoxypropyl) - m - dithiane - 1,1,3,3 - tetraoxide obtained is recrystallised from methylene chloride/ethanol and has a melting point of 175°—176°C.

Example 9.

3.65 g of 2 - (3 - chloropropyl) - 2 - (3,4-dimethoxyphenyl) - m - dithiane - 1,3-dioxide, 7.8 g of N - methyl - homoveratrylamine and 20 ml of dimethyl sulphoxide are heated at 50°C under argon for 16 hours. The solution is then poured into 200 ml of water and made strongly alkaline. The excess N-methyl-homoveratrylamine is extracted with ether. The alkaline solution is then extracted with methylene chloride. The methylene chloride extracts are dried over magnesium sulphate. After evaporation of the solvent, the residue is taken up in acetone and treated with hydrogen chloride in dioxane (up to pH 2). The crystalline residue is recrystallised from acetone/acetonitrile and there is obtained N - (3,4 - dimethoxyphenethyl) - 2 - (3,4 - dimethoxyphenyl) - N - methyl - m - dithiane - 2 - propylamine - 1,3 - dioxide hydrochloride of melting point 148°—149°C (diastereomeric mixture).

The 2 - (3 - chloropropyl) - 2 - (3,4-dimethoxyphenyl) - m - dithiane - 1,3-dioxide used as the starting material can be prepared as follows:

76.9 g of 2 - (3,4 - dimethoxyphenyl) - m - dithiane (prepared as described in Example 1) are dissolved in 900 ml of absolute tetrahydrofuran, the solution is cooled to -70°C and treated with 128 ml of a butyl lithium solution in such a manner that the temperature does not exceed -60°C. The mixture is then held for 2 hours at -20°C, a precipitate forming. The mixture is again cooled to -70°C and 47.3 g of 1,3 - bromochloropropane in 750 ml of absolute tetrahydrofuran are added. The mixture is then held for 1 hour at -20°C and for 1 hour at room temperature. The tetrahydrofuran is then evaporated, the residue taken up in ether and extracted. After evaporation of the solvent,

there is obtained 2 - (3 - chloropropyl) - 2 - (3,4 - dimethoxyphenyl) - m - dithiane.

- 55.25 g of 2 - (3 - chloropropyl) - 2 - (3,4 - dimethoxyphenyl) - m - dithiane are dissolved in 500 ml of glacial acetic acid. While stirring at 5°C, a solution of 34 g of 30% hydrogen peroxide in 300 ml of glacial acetic acid is added thereto within 2 hours. The mixture is then left to stand for 60 hours at room temperature and then concentrated in vacuo at 40°C. The oil obtained is chromatographed on 1.5 kg. of silica gel with chloroform/ethanol, initially 98:2 and then 95:5. After recrystallisation from acetonitrile, there is obtained 2 - (3 - chloropropyl) - 2 - (3,4 - dimethoxyphenyl) - m - dithiane - 1,3 - dioxide of melting point 163°—164°C (diastereomeric mixture).

Example 10.

- 20 In a manner analogous to that described in Example 8, but starting from 2 - (3,4 - dimethoxyphenyl) - 2 - (2,3 - epoxypropyl) - m - dithiane and N - methyl - homoveratrylamine, there can be manufactured racemic α - [(3,4 - dimethoxyphenethyl) - methylamino] - methyl - 2 - (3,4 - dimethoxyphenyl) - m - dithiane - 2 - ethanol. The hydrobromide of this compound crystallises from acetonitrile/acetate and melts at 97°—99°C.
- 30 The 2 - (3,4 - dimethoxyphenyl) - 2 - (2,3 - epoxypropyl) - m - dithiane used as the starting material can be prepared in a manner analogous to that described in Example 9 starting from 2 - (3,4 - dimethoxyphenyl) - m - dithiane (prepared as described in Example 1) using epichlorohydrin instead of 1,3-bromochloropropane.

Example 11.

- 40 3.4 g of lithium aluminium hydride in 60 ml of tetrahydrofuran are heated to reflux. 14.7 g of N - (3,4 - dimethoxyphenethyl) - 2 - (3,4 - dimethoxyphenyl) - m - dithiane - 2 - propionamide in 80 ml of tetrahydrofuran are then added dropwise. The suspension obtained is heated at reflux for a further 3 hours, then cooled to 0°C and carefully treated with 50 ml of a saturated sodium sulphate solution. The mixture is then filtered off under a vacuum, the solution diluted with water and extracted with ether. The ethereal extracts are washed with 1-N sodium hydroxide, then with water, dried over magnesium sulphate and evaporated. The oily residue is chromatographed on silica gel using chloroform/ethanol (95:5). The base obtained is dissolved in acetone and treated with an equivalent amount of anhydrous oxalic acid. The resulting precipitate is recrystallised from methanol/acetone. The thus-obtained N - (3,4 - dimethoxyphenethyl) - 2 - (3,4 - dimethoxyphenyl) - m - dithiane - 2 - propylamine oxalate (1:1) melts at 186°—188°C.

Analysis:

Calculated:

C 57.12 H 6.57 N 2.67

Found:

C 56.97 H 6.73 N 2.39

The N - (3,4 - dimethoxyphenethyl) - 2 - (3,4 - dimethoxyphenyl) - m - dithiane - 2 - propionamide used as the starting material can be prepared as follows:

50 g of 3 - veratroylpropionic acid in 400 ml of chloroform and 22.7 of 1,3-propanedithiol are treated with hydrogen chloride up to saturation while stirring. After 3 hours at room temperature, the solution is evaporated to 50 ml and diluted with ether. The resulting solution is extracted three times with 5% sodium carbonate. The basic phases are combined and made acidic with concentrated hydrochloric acid. The precipitated product is extracted with ether/methylene chloride (1:3). The organic extracts are dried and evaporated. The residue is recrystallised from ethanol, there being obtained 2 - (3,4 - dimethoxyphenyl) - m - dithiane - 2 - propionic acid of melting point 134°—135°C.

13.2 g of 2 - (3,4 - dimethoxyphenyl) - m - dithiane - 2 - propionic acid, 4 g of triethylamine and 180 ml of tetrahydrofuran are cooled to 0°C and treated dropwise within 10 minutes with 5.44 g of chloroformic acid isobutyl ester in 80 ml of tetrahydrofuran. The mixture is then held at room temperature for 3 hours and treated at 0°C with 7.25 g of homoveratrylamine in 40 ml of tetrahydrofuran. The suspension is left to stand at 3°C for 48 hours, then evaporated, treated with water and extracted with ether/methylene chloride (3:1). The ethereal extracts are washed with water, sodium bicarbonate solution, 1-N tartaric acid and water. The organic phase is dried over magnesium sulphate and evaporated. The residue is crystallised from methylene chloride/ether at 0°C. There is obtained N - (3,4 - dimethoxyphenethyl) - 2 - (3,4 - dimethoxyphenyl) - m - dithiane - 2 - propionamide of melting point 135°—136°C.

N - (3,4 - Dimethoxyphenethyl) - 2 - (3,4 - dimethoxyphenyl) - N - methyl - m - dithiane - 2 - propylamine hydrobromide can be manufactured in a manner analogous to that described in the foregoing; melting point 170°—172°C (from ethanol).

Example 12.

0.5 g of 2 - { [3 - [2'' - (3,4 - dimethoxyphenyl) - m - dithian - 2'' - yl] - propyl] - methylamino } - 3,4' - dimethoxyacetophenone - 1'',1'',3'',3'' - tetraoxide is dissolved in 15 ml of ethanol and 30 ml of tetrahydrofuran and treated with 50 mg of sodium borohydride. After stirring for 16 hours, the mixture is treated with 15 ml of 1-N hydrochloric acid and then with 12 ml of 1-N

(23)

sodium hydroxide solution. The tetrahydrofuran is removed by evaporation and the residue extracted with methylene chloride. The organic extracts are washed with water, dried over magnesium sulphate and evaporated in a vacuum. The crystals obtained are recrystallised from methanol and there is obtained 0.3 g of α -[3-[3'-(3,4-dimethoxyphenyl)-m-dithian-2'-yl]-propyl]-methylamino}-methyl/-veratryl alcohol - 1',1',3',3'-tetraoxide of melting point 132°—133°C.

The 2-[3-[2''-(3,4-dimethoxyphenyl)-m-dithian-2''-yl]-propyl]-methylamino}-3',4'-dimethoxyacetophenone - 1'',1'',3'',3''-tetraoxide used as the starting material can be prepared by reacting 2-(3-chloropropyl)-2-(3,4-dimethoxyphenyl)-m-dithiane-1,1,3,3-tetraoxide with ω -methylamino-3,4-dimethoxyacetophenone; melting point 140°C (decomposition) (from acetone).

Example 13.

10 g of N-(3,4-dimethoxyphenethyl)-2-(3,4-dimethoxyphenyl)-N-methyl-m-dithiane-2-pentylamine (prepared as described in Example 6) are dissolved in 50 ml of glacial acetic acid and treated at room temperature with 20 ml of 30% hydrogen peroxide. After 3 hours, the mixture is heated at 35°C for 3 hours and then at 40°C for 18 hours. The solution is then poured on to water, made basic with sodium hydroxide and extracted with methylene chloride. After removal of the solvent, the residue is chromatographed on silica gel using a mixture of chloroform, methanol and saturated ammonia (97:3). The product obtained is dissolved in acetone and treated with an equivalent amount of oxalic acid. The resulting precipitate is recrystallised from acetone/methanol. There is obtained N-(3,4-dimethoxyphenethyl)-2-(3,4-dimethoxyphenyl)-N-methyl-m-dithiane-2-pentylamine-1,1,3,3-tetraoxide oxalate (1:1) of melting point 189°—191°C.

Analysis:

Calculated:

C 53.48 H 6.43 N 2.08

Found:

C 53.37 H 6.50 N 1.87

The following compounds can be manufactured in a manner analogous to that described in the foregoing:

N-(3,4-Dimethoxyphenethyl)-2-(3,4-dimethoxyphenyl)-N-methyl-m-dithiane-2-butylamine-1,1,3,3-tetraoxide oxalate of melting point 161°—163°C (from acetone/methanol), (base: 123°—126°C from ethanol),

starting from

N-(3,4-dimethoxyphenethyl)-2-(2,4-

dimethoxyphenyl)-N-methyl-m-dithiane)-2-butylamine (prepared as described in Example 6).

2-(3,4-Dimethoxyphenyl)-N-[3-(3,4-dimethoxyphenyl)-propyl]-N-methyl-m-dithiane-2-propylamine-1,1,3,3-tetraoxide hydrobromide of melting point 138°—140°C (from acetonitrile/ethyl acetate),

starting from

2-(3,4-dimethoxyphenyl)-N-[3-(3,4-dimethoxyphenyl)-propyl]-N-methyl-m-dithiane-2-propylamine (prepared as described in Example 6).

Racemic N-(3,4-Dimethoxyphenethyl)-2-(3,4-dimethoxyphenyl)-N, β -dimethyl-m-dithiane-2-propylamine-1,1,3,3-tetraoxide hydrochloride of melting point 183°—185°C (from acetone/ethyl acetate),

starting from

racemic N-(3,4-dimethoxyphenethyl)-2-(3,4-dimethoxyphenyl)-N, β -dimethyl-m-dithiane-2-propylamine (prepared as described in Example 3).

2-(3,4-Dimethoxyphenyl)-N-methyl-N-(α -methylphenethyl)-m-dithiane-2-propylamine-1,1,3,3-tetraoxide hydrochloride of melting point 185°—187°C (from acetone/ethyl acetate),

starting from

2-(3,4-dimethoxyphenyl)-N-methyl-N-(α -methylphenethyl)-m-dithiane-2-propylamine (prepared as described in Example 6).

Example 14.

11.2 g of 2-(4-benzyloxy-3-methoxyphenyl)-N-(3,4-dimethoxyphenethyl)-N-methyl-m-dithiane-2-propylamine-1,1,3,3-tetraoxide (prepared as described in Example 5) are heated with 100 ml of 48% hydrobromic acid for 2 minutes on a steam bath. The aqueous solution is then extracted with ether, evaporated in vacuo and azeotropically distilled three times with ethanol/benzene. The residue is crystallised from acetone. The thus-obtained crystalline mass is recrystallised three times from methanol/acetonitrile and there is obtained 4-{2'-[3-[(3,4-dimethoxyphenethyl)-methylamino]-propyl]-m-dithian-2'-yl}-2-methoxyphenol-1',1',3',3'-tetraoxide hydrobromide of melting point 192°C (decomposition).

Analysis for $C_{26}H_{25}NO_5S_2.HBr$

Calculated:

C 48.23 H 5.83 N 2.25

Found:

C 48.12 H 5.93 N 2.07

In an analogous manner starting from 2-(3-benzyloxy-3-methoxyphenyl)-N-(3,4-dimethoxyphenethyl)-N-methyl-m-dithiane-2-propylamine-1,1,3,3-tetraoxide there can be obtained 5-{2'-

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[3 - [(3,4 - dimethoxyphenethyl) - methyl-
amino] - propyl] - m - dithian - 2' - yl -
2 - methoxyphenol - 1',1',3',3' - tetraoxide
hydrobromide of melting point 201°C (decom-
position) (from acetonitrile).

Example 15.

2 g of 5 - {2 - [3 - (3,4 - dimethoxyphen-
ethyl) - methylaminopropyl] - m - dithian-
2' - yl} - methoxyphenol - 1',1',3',3' - tetra-
oxide are dissolved in absolute pyridine and
treated with an excess of acetic anhydride.
After leaving for 16 hours at room tempera-
ture, the solvent is removed by evaporation
and the residue chromatographed on silica
gel. The 5 - {2 - [3 - 3,4 - dimethoxyphen-
ethyl) - methylaminopropyl] - m - dithian-
2' - yl} - 2 - methoxyphenyl acetate 1',1',
3',3' - tetraoxide is obtained as a thick oil.

Analysis:

Calculated:

C 55.67 H 6.39 N 2.40

Found:

C 55.22 H 6.41 N 2.23

Example 16.

0.3 g of 2 - (3,4 - dimethoxyphenyl) - N-
methyl - m - dithiane - 2 - propylamine-
1,1,3,3 - tetraoxide are treated with 0.16 g
of 3,4 - dimethoxy - β - phenethyl chloride,
5 ml of N,N - diisopropyl - N - ethylamine
and 1.5 ml of dimethylformamide and the
mixture is heated at 130°C for 16 hours. The
solution is then partitioned between water and
ethyl acetate. The residue is chromatographed
on silica gel and there is obtained N - (3,4-
dimethoxyphenethyl) - 2 - (3,4 - dimethoxy-
phenyl) - N - methyl - m - dithiane - 2-
propylamine - 1,1,3,3 - tetraoxide of melting
point 144°C (from methanol).

The 2 - (3,4 - dimethoxyphenyl) - N-
methyl - m - dithiane - 2 - propylamine - 1,1,
3,3 - tetraoxide used as the starting material
can be prepared as follows:

3.95 g of 2 - (3 - chloropropyl) - 2 - (3,4-
dimethoxyphenyl) - m - dithiane - 1,1,3,3-
tetraoxide are dissolved in 50 ml of dimethyl-
formamide. The solution is cooled to 0°C and
treated with 15 g of methylamine. The mix-
ture is heated at 40°C under pressure for 18
hours. The solution is then concentrated and
the crystalline residue recrystallised from a
small amount of methanol. There is thus ob-
tained the desired starting material of melting
point 164°C.

Example 17.

1 g of N - (3,4 - dimethoxyphenethyl)-
2 - (3,4 - dimethoxyphenyl) - m - dithiane-
2 - propylamine is dissolved in 20 ml of
absolute pyridine and treated with 200 ml of
acetic anhydride. After 18 hours, the mixture

is concentrated and the residue partitioned
between ether and sodium carbonate (5%).
After evaporation of the solvent, there are
obtained 1.2 g of an oil which is dissolved
in 20 ml of absolute tetrahydrofuran. This
solution is slowly added dropwise to a sus-
pension of 0.4 g of lithium aluminium hydride
and 20 ml of absolute tetrahydrofuran. The
mixture is slowly treated with a concentrated
aqueous sodium sulphate solution and then
filtered under suction. After evaporation of
the solvent, the residue is partitioned between
ether and water and the organic extracts are
worked-up. The oily residue is treated with
oxalic acid in acetone/ethyl acetate, there
crystallising out N - (3,4 - dimethoxyphen-
ethyl) - 2 - (3,4 - dimethoxyphenyl) - N-
ethyl - m - dithiane - 2 - propylamine - 1,1,
3,3 - tetraoxide oxalate of melting point 126°
-127°C.

Example 18.

1 g of homoveratric acid is dissolved in 15
ml of absolute tetrahydrofuran and treated
with 0.15 g of triethylamine. 0.72 g of chloro-
formic acid isobutyl ester are then slowly
added dropwise at 0°-5°C and the mixture
is stirred for 1 hour at 5°-10°C. There is
then added dropwise a solution of 1.63 g of
2 - (3,4 - dimethoxyphenyl) - N - methyl-
m - dithiane - 2 - propylamine [prepared in
a manner analogous to that described in
Example 15 from 2 - (γ - chloropropyl) - 2-
(3,4 - dimethoxyphenyl) - m - dithiane and
methylamine] in 5 ml of tetrahydrofuran. The
resulting mixture is left to stand at room tem-
perature overnight. After evaporation of the
solvent, the residue is partitioned between 1-M
hydrochloric acid and ether. The organic ex-
tracts are washed with 5% sodium carbonate
solution and water. After drying over magne-
sium sulphate, the solvent is removed by
evaporation. The oily residue (1.5 g) is dis-
solved in 15 ml of tetrahydrofuran and added
dropwise to a suspension of 0.15 g of lithium
aluminium hydride under reflux and under
argon. The mixture is boiled for 2 hours and
then treated slowly with a concentrated sodium
sulphate solution in water and then with 10
ml of methylene chloride. The mixture is fil-
tered under suction and then concentrated.
The residue is chromatographed on silica gel
and there is obtained N - (3,4 - dimethoxy-
phenethyl) - 2 - (3,4 - dimethoxyphenyl)-
N - methyl - m - dithiane - 2 - propylamine
in the form of a thick oil.

The following Examples illustrate typical
pharmaceutical preparations containing the
sulphur-containing derivatives provided by the
present invention:

Example A.

Capsules containing the following ingre-
dients are prepared in the usual manner:

	N - (3,4 - dimethoxyphenethyl)-	
	2 - (3,4 - dimethoxyphenyl)-	
	N - methyl - m - dithiane - 2-	
	propylamine	25 mg
5	Mannitol	115 mg
	Maize starch	40 mg
	Talc	18 mg
	Magnesium stearate	2 mg
		200 mg

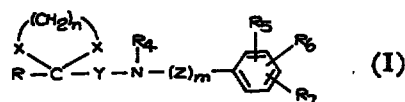
Example B.

Tablets containing the following ingredients are prepared in the usual manner:

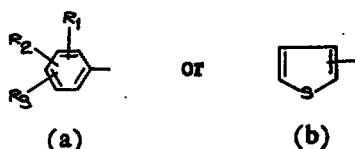
	N - (3,4 - dimethoxyphenethyl)-	
	2 - (3,4 - dimethoxyphenyl)-	
15	N - methyl - m - dithiane - 2-	
	propylamine - 1,1,3,3 - tetra-	
	oxide	25 mg
	Lactose	90 mg
	Maize starch	75 mg
20	Magnesium stearate	1 mg
	Talc	9 mg
		200 mg

WHAT WE CLAIM IS:—

1. Compounds of the general formula



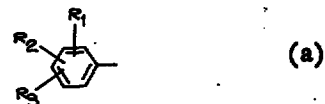
wherein R represents a group of the formula



in which R₁, R₂ and R₃ each represent a hydrogen or halogen atom or a lower alkyl, lower alkoxy, aryl-(lower alkoxy), aryloxy, phenyl, nitro, amino, lower alkylthio, trifluoromethyl, hydroxy, cyano, di(lower alkyl)-amino, lower alkanoylamino, carboxyl, lower alkoxy-carbonyl, lower alkylsulphonyl, hydroxymethyl, lower alkanoyloxy, amido, lower alkanoyl, sulphonoyl, mono(lower alkyl)-sulphonoyl, di(lower alkyl)sulphonoyl, aminocarbonyloxy, mono(lower alkyl)aminocarbonyloxy, di(lower alkyl)aminocarbonyloxy or (lower alkylamino)-(lower alkyl) group or two adjacent R₁, R₂ and R₃ symbols together represent a methylenedioxy, ethylenedioxy or butadien-1,3-ylene-1,4-group, R₄ represents a hydrogen atom or a lower alkyl group, R₅, R₆ and R₇ each represent a hydrogen or halogen atom or a lower alkyl, lower alkoxy, hydroxy or benzyloxy group or two adjacent R₅, R₆ and R₇ symbols together represent a methylenedioxy or ethylenedioxy group, X represents a sulphur atom, SO or SO₂, Y represents a straight-chain or branched-chain, optionally

hydroxy-substituted, aliphatic group containing 2—8 carbon atoms, of which 2—4 carbon atoms are present in the chain, and Z represents a straight-chain or branched-chain, optionally hydroxy-substituted, aliphatic group containing 1—8 carbon atoms, of which 1—4 carbon atoms are present in the chain, m stands for zero or 1 and n stands for 2 or 3, and acid addition salts thereof.

2. Compounds according to claim 1, wherein R represents a group of the formula



wherein R₁, R₂ and R₃ have the significance given in claim 1, and acid addition salts thereof.

3. Compounds according to claim 1 or 2, wherein one of the symbols R₁, R₂ and R₃ represents a hydrogen atom and the other symbols each represent a lower alkoxy group or together represent a butadien-1,3-ylene-1,4 group, and acid addition salts thereof.

4. Compounds according to claim 3 insofar as two of the symbols R₁, R₂ and R₃ each represent a lower alkoxy group, wherein said lower alkoxy group is a methoxy group, and acid addition salts thereof.

5. Compounds according to any one of claims 1 to 4 inclusive, wherein one of the symbols R₁, R₂ and R₃ represents a hydrogen atom and the other symbols each represent a lower alkoxy group, and acid addition salts thereof.

6. Compounds according to claim 5, wherein said lower alkoxy group is a methoxy group, and acid addition salts thereof.

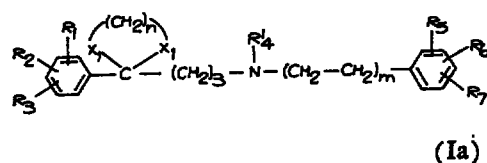
7. Compounds according to any one of claims 1 to 6 inclusive, wherein X represents a sulphur atom or SO₂ and n stands for 3, and acid addition salts thereof.

8. Compounds according to any one of claims 1 to 7 inclusive, wherein Y represents the group —(CH₂)₃—, and acid addition salts thereof.

9. Compounds according to any one of claims 1 to 8 inclusive wherein (Z)_m represents the group —(CH₂—CH₂)_m in which m stands for zero or 1, and acid addition salts thereof.

10. Compounds according to any one of claims 1 to 9 inclusive, wherein R₄ represents a hydrogen atom or a methyl or ethyl group, and acid addition salts thereof.

11. Compounds of the general formula





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	N - (3,4 - dimethoxyphenethyl)-	
	2 - (3,4 - dimethoxyphenyl)-	
	N - methyl - m - dithiane - 2-	
	propylamine	25 mg
5	Mannitol	115 mg
	Maize starch	40 mg
	Talc	18 mg
	Magnesium stearate	2 mg
		200 mg

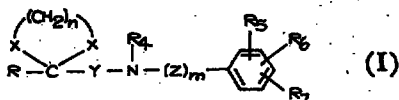
Example B.

Tablets containing the following ingredients are prepared in the usual manner:

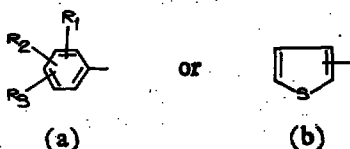
	N - (3,4 - dimethoxyphenethyl)-	
	2 - (3,4 - dimethoxyphenyl)-	
15	N - methyl - m - dithiane - 2-	
	propylamine - 1,1,3,3 - tetra-	
	oxide	25 mg
	Lactose	90 mg
	Maize starch	75 mg
20	Magnesium stearate	1 mg
	Talc	9 mg
		200 mg

WHAT WE CLAIM IS:—

1. Compounds of the general formula



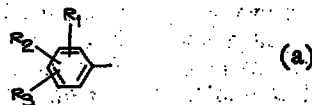
wherein R represents a group of the formula



in which R₁, R₂ and R₃ each represent a hydrogen or halogen atom or a lower alkyl, lower alkoxy, aryl-(lower alkoxy), aryloxy, phenyl, nitro, amino, lower alkylthio, trifluoromethyl, hydroxy, cyano, di(lower alkyl)-amino, lower alkanoylamino, carboxyl, lower alkoxy-carbonyl, lower alkylsulphonyl, hydroxymethyl, lower alkanoyloxy, amido, lower alkanoyl, sulphonoyl, mono(lower alkyl)-sulphonoyl, di(lower alkyl)sulphonoyl, aminocarbonyloxy, mono(lower alkyl)aminocarbonyloxy, di(lower alkyl)aminocarbonyloxy or (lower alkylamino)-(lower alkyl)-group or two adjacent R₁, R₂ and R₃ symbols together represent a methylenedioxy, ethylenedioxy or butadien-1,3-ylene-1,4-group, R₄ represents a hydrogen atom or a lower alkyl group, R₅, R₆ and R₇ each represent a hydrogen or halogen atom or a lower alkyl, lower alkoxy, hydroxy or benzyloxy group or two adjacent R₅, R₆ and R₇ symbols together represent a methylenedioxy or ethylenedioxy group, X represents a sulphur atom, SO or SO₂, Y represents a straight-chain or branched-chain, optionally

hydroxy-substituted, aliphatic group containing 2—8 carbon atoms, of which 2—4 carbon atoms are present in the chain, and Z represents a straight-chain or branched-chain, optionally hydroxy-substituted, aliphatic group containing 1—8 carbon atoms, of which 1—4 carbon atoms are present in the chain, m stands for zero or 1 and n stands for 2 or 3, and acid addition salts thereof.

2. Compounds according to claim 1, wherein R represents a group of the formula



wherein R₁, R₂ and R₃ have the significance given in claim 1; and acid addition salts thereof.

3. Compounds according to claim 1 or 2, wherein one of the symbols R₁, R₂ and R₃ represents a hydrogen atom and the other symbols each represent a lower alkoxy group or together represent a butadien-1,3-ylene-1,4 group, and acid addition salts thereof.

4. Compounds according to claim 3 insofar as two of the symbols R₁, R₂ and R₃ each represent a lower alkoxy group, wherein said lower alkoxy group is a methoxy group, and acid addition salts thereof.

5. Compounds according to any one of claims 1 to 4 inclusive, wherein one of the symbols R₅, R₆ and R₇ represents a hydrogen atom and the other symbols each represent a lower alkoxy group, and acid addition salts thereof.

6. Compounds according to claim 5, wherein said lower alkoxy group is a methoxy group, and acid addition salts thereof.

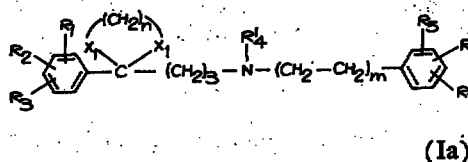
7. Compounds according to any one of claims 1 to 6 inclusive, wherein X represents a sulphur atom or SO₂ and n stands for 3, and acid addition salts thereof.

8. Compounds according to any one of claims 1 to 7 inclusive, wherein Y represents the group —(CH₂)_n—, and acid addition salts thereof.

9. Compounds according to any one of claims 1 to 8 inclusive wherein (Z)_m represents the group —(CH₂—CH₂)_m in which m stands for zero or 1, and acid addition salts thereof.

10. Compounds according to any one of claims 1 to 9 inclusive, wherein R₄ represents a hydrogen atom or a methyl or ethyl group, and acid addition salts thereof.

11. Compounds of the general formula



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wherein R_1 — R_7 and m have the significance given in claim 1, R'_1 represents a methyl or ethyl group, X_1 represents a sulphur atom or SO_2 and n stands for 3, and acid addition salts thereof.

12. Compounds according to claim 11, wherein one of the symbols R_1 , R_2 and R_3 represents a hydrogen atom and the other symbols each represent a lower alkoxy group or together represent a butadien-1,3-ylene-1,4 group, and acid addition salts thereof.

13. Compounds according to claim 12 insofar as two of the symbols R_1 , R_2 and R_3 each represent a lower alkoxy group, wherein said lower alkoxy group is a methoxy group, and acid addition salts thereof.

14. Compounds according to any one of claims 11 to 13 inclusive, wherein one of the symbols R_1 , R_2 and R_3 represents a hydrogen atom and the other symbols each represent a lower alkoxy group, and acid addition salts thereof.

15. Compounds according to claim 14, wherein said lower alkoxy group is a methoxy group, and acid addition salts thereof.

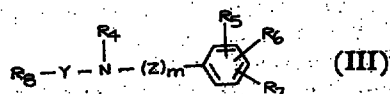
16. N - (3,4 - Dimethoxyphenethyl) - 2 - (3,4 - dimethoxyphenyl) - N - methyl - m-dithiane - 2 - propylamine - 1,1,3,3 - tetra-oxide.

17. A process for the manufacture of the sulphur-containing derivatives claimed in claim 1, which process comprises

a) reacting a compound of the general formula

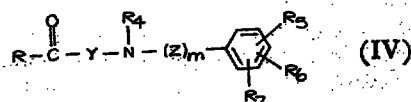


wherein R , X and n have the significance given in claim 1, with a compound of the general formula



wherein R_4 — R_7 , Y , Z and m have the significance given in claim 1 and R_8 represents a leaving atom or group, or

b) reacting a compound of the general formula

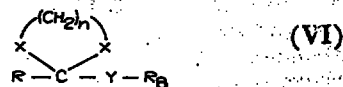


wherein R , R_4 — R_7 , Y , Z and m have the significance given in claim 1, with a compound of the general formula

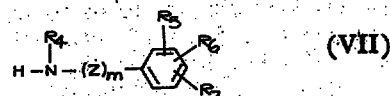


wherein n has the significance given in claim 1, or

c) reacting a compound of the general formula



wherein R , X , Y and n have the significance given in claim 1 and R_8 has the significance given earlier in this claim, with a compound of the general formula

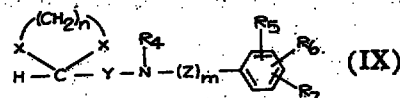


wherein R_4 — R_7 , Z and m have the significance given in claim 1, or

d) reacting a compound of the general formula

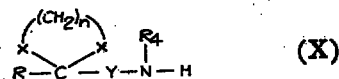


wherein R has the significance given in claim 1 and R_8 has the significance given earlier in this claim, with a compound of the general formula

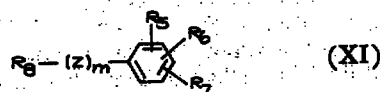


wherein R_4 — R_7 , X , Y , Z , m and n have the significance given in claim 1, or

e) reacting a compound of the general formula

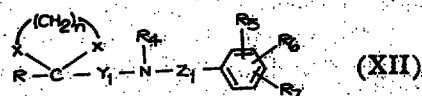


wherein R , R_4 , X , Y and n have the significance given in claim 1, with a compound of the general formula

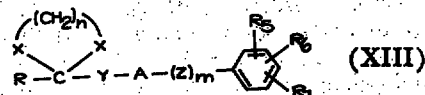


wherein R_4 , R_8 , R_7 , Z and m have the significance given in claim 1 and R_8 has the significance given earlier in this claim, or

f) reducing the carbonyl group or the group denoted by A in a compound of the general formula

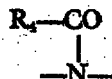


or



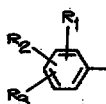


wherein $R_1, R_2, R_3, X, Y, Z, m$ and n have the significance given in claim 1, Y_1 and Z_1 represent respectively a group corresponding to Y or Z containing a carbonyl group and A represents the group



in which R_4 has the significance given in claim 1, if desired oxidising a compound of formula I in which X represents a sulphur atom to a compound of formula I in which X represents SO or SO_2 , if desired N-lower alkylating a compound of formula I in which R_4 represents a hydrogen atom, if desired converting a lower alkyl group or an aryl-(lower alkoxy) group into a hydroxyl group, if desired reducing a nitro group to an amino group, if desired saponifying a cyano group to a carboxyl group, if desired esterifying or amidating or reducing a carboxyl group, if desired etherifying or esterifying or carbamoylating a hydroxy group, if desired mono(lower alkylating) or di(lower alkylating) an amino group, if desired oxidising an alkylthio group to an alkylsulphonyl group and, also if desired, converting a base obtained into an acid addition salt.

18. A process according to claim 17, wherein there is used as the starting material a compound of formula II, IV, VI, VIII, X, XII or XIII in which R represents a group of the formula



(a)

in which R_1, R_2 and R_3 have the significance given in claim 1.

19. A process according to claim 18, wherein in the group of formula (a) one of the symbols R_1, R_2 and R_3 represents a hydrogen atom and the other symbols each represent a lower alkoxy group or together represent a butadien-1,3-ylene-1,4 group.

20. A process according to claim 19 insofar as two of the symbols R_1, R_2 and R_3 each represent a lower alkoxy group wherein said lower alkoxy group is a methoxy group.

21. A process according to any one of claims 17 to 20 inclusive, wherein there is used a starting material of formula III, IV, VII, IX, XI, XII or XIII in which one of the symbols R_5, R_6 and R_7 represents a hydrogen atom and the other symbols each represent a lower alkoxy group.

22. A process according to claim 21,

wherein said lower alkoxy group is a methoxy group.

23. A process according to any one of claims 17 to 22 inclusive, wherein there is used a starting material of formula II, VI, IX, X, XII or XIII in which X represents a sulphur atom or SO_2 and n stands for 3.

24. A process according to any one of claims 17 to 23 inclusive, wherein there is used a starting material of formula III, IV, VI, IX, X or XIII in which Y represents the group $-(CH_2)_6-$ or a compound of formula XII in which Y_1 represents a carbonyl group-containing moiety convertible into the group $-(CH_2)_6-$.

25. A process according to any one of claims 17 to 24 inclusive, wherein there is used a starting material of formula III, IV, VII, IX, XI or XIII in which $(Z)_m$ represents the group $-(CH_2-CH_2)_m$ wherein m stands for zero or 1 or a compound of formula XII in which Z_1 represents a carbonyl group-containing moiety convertible into the group $-(CH_2-CH_2)_m$.

26. A process according to any one of claims 17 to 25 inclusive, wherein there is used a starting material of formula III, IV, VII, IX, X or XII in which R_4 represents a methyl or ethyl group or a compound of formula XIII in which A represents a formyl or acetyl amino group.

27. A process according to any one of claims 17 to 26 inclusive, wherein there are used starting materials of formulae II to XIII in which R represents a 3,4-dimethoxyphenyl group, X represents SO_2 , n stands for 3, Y represents a propyl group, R_4 represents a methyl group, Z represents an ethyl group, m stands for 1, R_5 represents a hydrogen atom and R_6 and R_7 each represent a methoxy group in the 3- and 4-positions.

28. A process according to any one of claims 17 to 27 inclusive, wherein N - (3,4-dimethoxyphenethyl) - 2 - (3,4-dimethoxyphenyl) - N - methyl - m - dithiane - 2-propylamine - 1,1,3,3 - tetraoxide or an acid addition salt thereof is manufactured.

29. A process for the manufacture of the sulphur-containing derivatives claimed in claim 1, substantially as hereinbefore described with reference to any one of Examples 3 to 18.

30. A sulphur-containing derivative as set forth in claim 1, when manufactured by the process claimed in any one of claims 17 to 29 inclusive.

31. A pharmaceutical preparation containing one or more of the compounds of formula I given in claim 1 or a pharmaceutically acceptable acid addition salt thereof in association with a compatible pharmaceutical carrier.

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