

## PATENT SPECIFICATION

NO DRAWINGS

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The inventors of this invention in the sense of being the actual devisers thereof within the meaning of Section 16 of the Patents Act, 1949 are:— ERNST JUCKER of Steinweg 28, Ettingen, Switzerland; ADOLF LINDENMANN of Birmanngasse 19, Basle, Switzerland, and FULVIO GADIENT of Rheinparkstrasse 5, Birsfelden, Switzerland; all Swiss citizens.

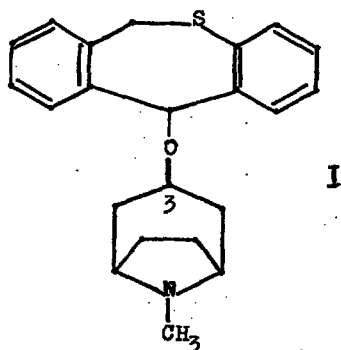
## COMPLETE SPECIFICATION

## New 11-(3-Tropanyloxy)-6,11-Dihydro-Dibenzo[b,e]Thiepins and Process for Their Production

We, SANDOZ LTD., of Lichtstrasse 35, Basle, Switzerland, a Swiss Body Corporate, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

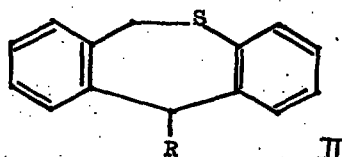
The present invention relates to new tropane ethers and a process for their production.

The present invention provides 11 - (3 - tropanyloxy) - 6, 11 - dihydro - dibenzo [b,e]thiepins of formula I,



and their salts with inorganic and organic acids.

The present invention further provides a process for the production of the compounds of formula I and their acid addition salts, characterized in that 6, 11 - dihydro - dibenzo [b,e]thiepin derivative of formula II,



in which R signifies a halogen atom or an organo-sulphonyloxy radical, is reacted with a tropan-3-( $\alpha$ - or  $\beta$ -)ol, optionally in the presence of an acid binding agent, and the resulting compound of formula I is optionally converted into its acid addition salts with organic or inorganic acids. This process is preferably effected at 80—140° C.

It is to be understood that reference herein to the compounds I and to the tropan-3-ol starting materials includes the 3 $\alpha$ - and 3 $\beta$ -isomers.

One method of effecting the process of the invention consists in that a solution of a 11 - halogeno - 6, 11 - dihydro - dibenzo [b,e]thiepin in an anhydrous inert organic solvent, e.g. absolute xylene, is added dropwise at a temperature of 80—140° C to a solution of tropine or pseudotropine (tropan-3 $\alpha$ - or -3 $\beta$ -ol) in the same solvent and optionally in the presence of an acid binding agent, e.g. sodium, potassium or calcium carbonate, or a tertiary organic base, e.g. triethylamine. The reaction mixture is kept at an elevated temperature for some time and the reaction product is isolated therefrom in man-

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ner known *per se*, e.g. by shaking out between a water-immiscible organic solvent and an aqueous acid solution. Purification is effected by distillation in a high vacuum or preferably by conversion into a suitable salt.

When a 6, 11 - dihydro - dibenzo[b, e]thiepin, in which R signifies an organo-sulphonyloxy radical, is used as starting material the process is preferably effected in that this compound, e.g. 11 - *p* - toluene-sulphonyloxy - 6, 11 - dihydro - dibenzo[b, e]thiepin, and tropine or pseudotropine in an anhydrous inert organic solvent, e.g. absolute xylene, are heated to the boil at reflux for about 1/2 hour. The cooled reaction mixture is subsequently made alkaline with an aqueous dilute alkali solution and the final product is isolated therefrom in manner known *per se* and purified by distillation in a high vacuum and/or conversion into a salt.

The 11 - sulphonyloxy - 6, 11 - dihydro - dibenzo[b, e]thiepins used as starting materials may be produced in that 6, 11 - dihydro - dibenzo[b, e]thiepin - 11 - ol is treated with an organic sulphonie acid halide, e.g. *p* - toluenesulphonyl - chloride, *p* - bromobenzenesulphonyl - bromide, methane-sulphonyl - chloride, in a suitable organic basic solvent, e.g. pyridine, or a lower trialkylamine, at a temperature of 0—50° C, preferably at room temperature, for 1 to 24 hours. The reaction may also be effected in an inert organic solvent with the addition of the calculated amount of pyridine or trialkylamine. The solvent is then distilled off in a vacuum, whereupon it is advantageous to add water to remove the solvent completely and the reaction mixture is subjected to an azeotropic distillation.

Starting materials of formula II, in which R signifies chlorine, bromine or iodine, may be obtained in that 6, 11 - dihydro - dibenzo[b, e]thiepin - 11 - ol is dissolved in an anhydrous inert organic solvent, e.g. absolute benzene, and a stream of hydrogen chloride, hydrogen bromide or hydrogen iodide is passed through this solution whilst cooling with ice. After drying the benzene solution, e.g. over calcium chloride, and subsequent filtration, the solvent and excess hydrogen halide are removed at reduced pressure, preferably in an atmosphere of nitrogen, whereby the desired 11-chloro-, 11-bromo- or 11-iodo-compound is obtained as residue. The 11-iodo-derivative may also be produced from the 11-bromo-compound by reacting with sodium iodide in acetone.

11 - fluoro - 6, 11 - dihydro - dibenzo[b, e]thiepin is advantageously obtained by treating 11-chloro- or 11 - bromo - 6, 11 - dihydro - dibenzo[b, e]thiepin with a metal fluoride, e.g. silver fluoride, mercury(II) fluoride or antimony trifluoride. This compound may, however, also be obtained from the 11 - toluenesulphonyloxy-compound des-

cribed above by reacting with potassium fluoride in a high-boiling solvent, e.g. diethylene glycol.

Compounds I are viscous oils at room temperature; with inorganic and organic acids they form stable salts which are crystalline at room temperature. Examples of acids for acid addition salt formation with compounds I are: hydrochloric, hydrobromic, methanesulphonic, oxalic, tartaric, malic, maleic, fumaric, citric and benzoic acid.

The compounds of the invention especially the (3 $\alpha$ ) compound, show pronounced, predominantly peripheral anticholinergic properties. In tests effected with animals they inhibit the reactions produced by acetylcholine and by the excitation of cholinergic nerves. Furthermore, they have a distinct histamine inhibiting and a moderate serotonin inhibiting effect. They inhibit the formation of experimentally induced gastric ulcers. They are also characterized by the typical effects of antidepressants. Their mydriatic effect is small, and they exhibit considerable fibrinolytic activity *in vitro*.

The compounds I, particularly the (3 $\alpha$ ) compound, are therefore indicated for use in the treatment of disorders occurring as a result of an increased vagotonus, e.g. spasms of the smooth muscles of the bronchial, gastrointestinal and urogenital tract, hypersecretion and bradycardia, and in the treatment of gastric and duodenal ulcers. They are also indicated for use in the treatment of allergies of various origins and in the ambulant and stationary therapy of depressive conditions and psychosomatic disorders, and in the treatment of thrombosis and embolism.

A suitable daily dosage is from 0.1 to 10 mg.

The compounds of the invention and/or an acid addition salt thereof may be used as pharmaceuticals on their own or in the form of appropriate medicinal preparations for administration, e.g. enterally or parenterally. In order to produce suitable medicinal preparations the compounds are worked up with inorganic or organic adjuvants which are inert and physiologically acceptable. Examples of such adjuvants are:

for tablets and dragées:

lactose, starch, talc and stearic acid;

for injectable solutions:

water, alcohols, glycerin and vegetable oils;

for suppositories:

natural or hardened oils and waxes.

The preparations may furthermore contain suitable preserving, stabilizing and wetting agents, solubilizers, sweetening and colouring substances and flavourings. The present invention further includes pharmaceutical compositions containing, in addition to a physio-

logically acceptable carrier, a compound I and/or an acid addition salt thereof.

The term "in manner known *per se*" as utilized herein designates methods in use or described in the literature on the subject.

In the following non-limitative Examples all temperatures are indicated in degrees Centigrade; the melting and boiling points are uncorrected.

#### EXAMPLE 1:

11 - (3 $\alpha$  - tropanyloxy) 6, 11 - dihydro - dibenzo[b, e]thiepin.

7.3 g of thionyl chloride are added to 14.0 g of 6, 11 - dihydro - dibenzo[b, e]thiepin - 11 - ol in 40 ml of absolute xylene and heating is effected to 70° for one hour. After cooling to room temperature, 3.0 g of calcium chloride are added and the xylene phase is filtered in the absence of moisture. The xylene phase is subsequently added dropwise during the course of 15 minutes to a boiling mixture of 8.6 g of tropine (tropan-3 $\alpha$ -ol) and 24.6 g of sodium carbonate in 50 ml of absolute xylene. The reaction mixture is heated at reflux for 6 hours and after cooling, is diluted with 200 ml of diethyl ether and shaken out twice, each time with 100 ml of water. The organic phase is extracted with 100 ml of N hydrochloric acid, the hydrochloric acid extract is made alkaline with 2N sodium hydroxide and shaken out thrice, each time with 300 ml of diethyl ether. After drying the ether extract over sodium sulphate, concentration is effected and the oily residue is distilled, wherein 11 - (3 $\alpha$  - tropanyloxy) 6, 11 - dihydro - dibenzo[b, e]thiepin distils at 190—200° and 0.02 mm of Hg.

The salts are produced in that a molar amount of the desired acid in ethanol is added to a solution of the base in ethanol and the salt which crystallizes is filtered off.

Acid oxalate:

melting point 207—210° from ethanol.

Acid succinate:

melting point 188—190° from ethanol.

Acid maleate:

melting point 180—182° from ethanol.

Acid malate:

melting point 188—190° from ethanol.

Acid fumarate:

melting point 234—236° from ethanol.

Methanesulphonate:

melting point 207—209° from ethanol.

Acid citrate:

melting point 168—169° from ethanol.

#### EXAMPLE 2:

11 - (3 $\alpha$  - tropanyloxy) 6, 11 - dihydro - dibenzo[b, e]thiepin.

A stream of hydrogen chloride is passed through a suspension of 45.4 g of 6, 11 - dihydro - dibenzo[b, e]thiepin - 11 - ol in 80 ml of absolute benzene whilst cooling with ice during the course of 10 minutes. 10 g of

calcium chloride are subsequently added, filtration is effected after 5 minutes and the solvent is removed at 14 mm of Hg in an atmosphere of nitrogen. The residue is then dissolved in 120 ml of absolute xylene and this solution is added dropwise during the course of 10 minutes to a boiling solution of 28.2 g of tropine in 100 ml of absolute xylene. The reaction mixture is subsequently heated to the boil at reflux for one hour, is then cooled to room temperature and taken up in 200 ml of ether and 200 ml of water. After the addition of 10 ml of 2N hydrochloric acid, the aqueous phase is separated, is made strongly alkaline with 2N sodium hydroxide and shaken out thrice, each time with 150 ml of ether. After drying the ether extract over magnesium sulphate and purifying over animal charcoal, the solvent is distilled off and the crude, oily 11 - (3 $\alpha$  - tropanyloxy) - 6, 11 - dihydro - dibenzo[b, e]thiepin is converted into the acid oxalate without further purification. Melting point 207—210° from ethanol.

#### EXAMPLE 3:

11 - (3 $\alpha$  - tropanyloxy) 6, 11 - dihydro - dibenzo[b, e]thiepin.

A stream of hydrogen bromide is passed through a suspension of 10.0 g of 6, 11 - dihydro - dibenzo[b, e]thiepin - 11 - ol in 50 ml of absolute benzene whilst cooling with ice during the course of 15 minutes. 2 g of calcium chloride are subsequently added, filtration is effected after 5 minutes and the solvent is removed at 14 mm of Hg in an atmosphere of nitrogen, whereby 11 - bromo - 6, 11 - dihydro - dibenzo[b, e]thiepin crystallizes; melting point 110—112° from chloroform/pentane.

8.7 g of 11 - bromo - 6, 11 - dihydro - dibenzo[b, e]thiepin are dissolved in 50 ml of absolute xylene and added dropwise to a boiling solution of 4.2 g of tropine in 50 ml of absolute xylene during the course of 5 minutes. The reaction mixture is heated to the boil at reflux for one hour, is subsequently cooled to room temperature and worked up in a manner analogous to that described in Example 2. Acid oxalate: melting point 207—210° from ethanol.

#### EXAMPLE 4:

11 - (3 $\beta$  - tropanyloxy) 6, 11 - dihydro - dibenzo[b, e]thiepin.

A stream of hydrogen chloride is passed through a suspension of 11.35 g of 6, 11 - dihydro - dibenzo[b, e]thiepin - 11 - ol in 40 ml of absolute benzene for 5 minutes whilst cooling with ice. 3 g of calcium chloride are subsequently added, filtration is effected after 5 minutes and the solvent is removed at 14 mm of Hg in an atmosphere of nitrogen. The oily residue is dissolved in 80 ml of absolute xylene and this solution is added dropwise during the course of 5 minutes to a

boiling solution of 7.1 g of pseudotropine (tropan-3 $\beta$ -ol) in 50 ml of absolute xylene. The reaction mixture is heated to the boil at reflux for one hour and the crystalline precipitate, the hydrochloride of the compound mentioned in the heading, is filtered off whilst hot. The salt is washed twice, each time with 30 ml of benzene and then twice, each time with 20 ml of ethanol, and dried. Melting point 273—278°.

Acid maleate: melting point 175—177°.

Acid succinate: melting point 162—165°.

Acid fumarate: melting point 207—209°.

#### EXAMPLE 5:

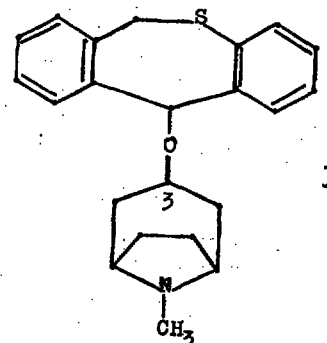
11 - (3 $\alpha$  - tropanyloxy)-6, 11 - dihydro - dibenzo[b, e]thiepin.

A solution of 11.3 g of 6, 11 - dihydro - dibenzo [b, e]thiepin - 11 - ol and 10.5 g of *p*-toluenesulphonyl chloride in 150 ml of absolute pyridine is stirred at room temperature for 5 hours. The pyridine is subsequently distilled off at 15 mm of Hg and is completely removed azeotropically whilst adding water thrice, each time 100 ml. The residue is subsequently dissolved in 50 ml of chloroform and the solution shaken out thrice, each time with 50 ml of water. After drying over magnesium sulphate, the volume of the chloroform solution is somewhat reduced and ether is added, whereby the *p*-toluenesulphonic acid ester of 6, 11 - dihydro - dibenzo[b, e]thiepin - 11 - ol crystallizes with 1 mol of pyridine of crystallization. Melting point 178—184°.

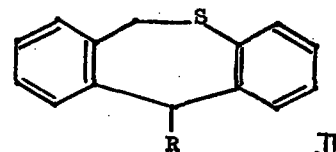
9.2 g of the ester obtained above and 2.8 g of tropine are then heated to the boil at reflux in 50 ml of absolute xylene for 1/2 hour, the solution is subsequently cooled to room temperature and 40 ml of N sodium hydroxide solution are added thereto. The xylene phase is then separated and the aqueous phase is shaken out twice, each time with 30 ml of ether. The combined xylene and ether extracts are washed with water until neutral, dried over magnesium sulphate and purified over animal charcoal. After distilling off the solvent, the crude oily 11 - (3 $\alpha$  - tropanyloxy) 6, 11 - dihydro - dibenzo[b, e]thiepin is converted as such into the acid succinate. Melting point 188—190° from ethanol.

#### WHAT WE CLAIM IS:—

1. A process for the preparation of 11 - (3 - tropanyloxy) - 6, 11 - dihydro - dibenzo [b, e]thiepins of formula I,



and their acid addition salts, characterized in that a 6, 11 - dihydro - dibenzo[b, e]thiepin derivative of formula II,



in which R signifies a halogen atom or an organo-sulphonyloxy radical, is reacted with a tropan-3-( $\alpha$ - or  $\beta$ -)ol and, when an acid addition salt is desired, salification is effected.

2. A process according to Claim 1, in which the reaction is effected in the presence of an acid binding agent.

3. A process according to either one of Claims 1 and 2, in which the process is effected at 80—140° C.

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

5. Compounds of the formula I stated in Claim 1 and their acid addition salts, whenever produced by a process as claimed in any one of Claims 1 to 4.

6. Compounds of the formula I stated in Claim 1 and their acid addition salts.

7. 11 - (3 $\alpha$  - tropanyloxy) - 6, 11 - dihydro - dibenzo[b, e]thiepin.

8. 11 - (3 $\beta$  - tropanyloxy) - 6, 11 - dihydro - dibenzo[b, e]thiepin.

9. Pharmaceutical compositions containing, in addition to an inert and physiologically acceptable carrier, a compound of the formula I defined in Claim 1 and/or an acid addition salt thereof.

- boiling solution of 7.1 g of pseudotropine (tropan-3 $\beta$ -ol) in 50 ml of absolute xylene. The reaction mixture is heated to the boil at reflux for one hour and the crystalline precipitate, the hydrochloride of the compound mentioned in the heading, is filtered off whilst hot. The salt is washed twice, each time with 30 ml of benzene and then twice, each time with 20 ml of ethanol, and dried. Melting point 273—278°.

Acid maleate: melting point 175—177°.  
 Acid succinate: melting point 162—165°.  
 Acid fumarate: melting point 207—209°.

#### EXAMPLE 5:

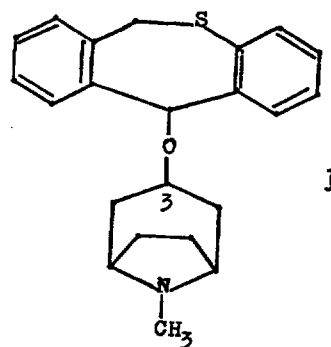
- 11 - (3 $\alpha$  - tropanyloxy)6, 11 - dihydro - dibenzo[b, e]thiepin.

- A solution of 11.3 g of 6, 11 - dihydro - dibenzo [b, e]thiepin - 11 - ol and 10.5 g of *p*-toluenesulphonyl chloride in 150 ml of absolute pyridine is stirred at room temperature for 5 hours. The pyridine is subsequently distilled off at 15 mm of Hg and is completely removed azeotropically whilst adding water thrice, each time 100 ml. The residue is subsequently dissolved in 50 ml of chloroform and the solution shaken out thrice, each time with 50 ml of water. After drying over magnesium sulphate, the volume of the chloroform solution is somewhat reduced and ether is added, whereby the *p*-toluenesulphonic acid ester of 6, 11 - dihydro - dibenzo[b, e]thiepin - 11 - ol crystallizes with 1 mol of pyridine of crystallization. Melting point 178—184°.

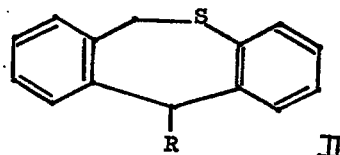
- 9.2 g of the ester obtained above and 2.8 g of tropine are then heated to the boil at reflux in 50 ml of absolute xylene for 1/2 hour, the solution is subsequently cooled to room temperature and 40 ml of N sodium hydroxide solution are added thereto. The xylene phase is then separated and the aqueous phase is shaken out twice, each time with 30 ml of ether. The combined xylene and ether extracts are washed with water until neutral, dried over magnesium sulphate and purified over animal charcoal. After distilling off the solvent, the crude oily 11 - (3 $\alpha$  - tropanyloxy) 6, 11 - dihydro - dibenzo[b, e]thiepin is converted as such into the acid succinate. Melting point 188—190° from ethanol.

#### WHAT WE CLAIM IS:—

1. A process for the preparation of 11 - (3 - tropanyloxy) - 6, 11 - dihydro - dibenzo [b, e]thiepins of formula I,



and their acid addition salts, characterized in that a 6, 11 - dihydro - dibenzo[b, e]thiepin derivative of formula II,



in which R signifies a halogen atom or an organo-sulphonyloxy radical, is reacted with a tropan-3-( $\alpha$ - or  $\beta$ -)ol and, when an acid addition salt is desired, salification is effected.

2. A process according to Claim 1, in which the reaction is effected in the presence of an acid binding agent.

3. A process according to either one of Claims 1 and 2, in which the process is effected at 80—140° C.

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

5. Compounds of the formula I stated in Claim 1 and their acid addition salts, whenever produced by a process as claimed in any one of Claims 1 to 4.

6. Compounds of the formula I stated in Claim 1 and their acid addition salts.

7. 11 - (3 $\alpha$  - tropanyloxy) - 6, 11 - dihydro - dibenzo[b, e]thiepin.

8. 11 - (3 $\beta$  - tropanyloxy) - 6, 11 - dihydro - dibenzo[b, e]thiepin.

9. Pharmaceutical compositions containing, in addition to an inert and physiologically acceptable carrier, a compound of the formula I defined in Claim 1 and/or an acid addition salt thereof.



10. Pharmaceutical compositions as claimed  
in Claim 9, in which the amount of active  
ingredient present is suitable for the adminis-  
tration of a daily dosage of from 0.1 to 10  
5 mg.

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