PATENT SPECIFICATION

999,391

999,391

Date of Application and filing Complete Specification: August 2, 1961. No. 28117/61

Application made in United States of America (No. 46,911) on August 2, 1960.

Application made in United States of America (No. 73,490) on December 5, 1960.

Application made in United States of America (No. 110,320) on May 16, 1961.

Complete Specification Published: July 28, 1965.

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Index at Acceptance:—C2 C (3A7V1A4, 3A7V1E2, 3A7V1G2, 3A7V1H, 3A7V1K1, 3A7V1K3, 3C2).

Int. Cl.:—C 07 d.

COMPLETE SPECIFICATION

NO DRAWINGS

Ethers of Methyl 18-epi-reserpate and salts thereof and process for their manufacture

We, CIBA LIMITED, a body corporate organised according to the laws of Switzerland, of 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 provides new methyl 18-epi-O-R-reserpates in which R represents an alkyl radical having 1 to 3 carbon atoms, that is to say methyl, ethyl, *n*-propyl or iso-propyl, and their salts, and a process for their manufacture.

The new compounds display above all a sedative effect and tranquillizing properties and have practically no antihypertensive effect. In contrast to the natural Rauwolfia diester-alkaloids which have a pharmacological effect of slow onset and often of undesirably long duration, the new compounds are distinguished by a much quicker onset of action which lasts for a well-defined period. The new compounds may, consequently, also be used in emergencies, and medication is, in addition, more easily controlled. Furthermore, the physiologically tolerable salts of the new compounds, especially acid addition salts, are relatively easily water-soluble and are therefore of great importance for the preparation of aqueous injection solutions or compositions for oral administration, such as elixirs. The new compounds also display an anti-fibrillatory and local anaesthetic effect.

The compounds of the present invention can consequently be used as medicaments in human or veterinary medicine. In human medicine they may be used either as sedatives or tranquillizers for the treatment of hyperactivity, tension, agitation or in mental disturbances, or for the treatment of cardiac arrhythmia, such as extrasystoles or auricular fibrillation. The new compounds may also be used as local anaesthetics, for example in minor surgery or in the treatment of burns.

In veterinary medicine the new compounds are suitable for example in calming laboratory test animals, such as monkeys, cats or dogs, prior to treatment. Furthermore, they may be used for calming domestic animals, particularly fowl, such as chickens or turkeys, to facilitate handling, for example in the case of vaccination or transport. In addition, the new compounds are also suitable for use as local anaesthetics in surgery on animals. They may also be used as intermediate products for the preparation of other valuable compounds.

The new methyl 18-epi-O-R-reserpates and their salts are obtained surprisingly when a methyl reserpate esterified in the 18-position with an organic sulphonic acid, or a salt thereof, is subjected to alcoholysis with an alkanol of the formula R-OH in which R has the meaning given above, and, if desired, a resulting base is converted into a salt or a resulting salt into a base.

The surprising factor in this reaction is that on exchanging the 18β-sulphonyloxy radical for the alcohol radical, epimerization to the etherified 18α-hydroxyl compound takes place simultaneously.

In the starting materials the organic radical of the sulphonyloxy group stands, for example, for a hydrocarbon radical, such as a lower alkyl radical, but preferably for an unsubstituted or substituted phenyl radical. The latter may contain one or more identical or different substituents, preferably electro-negative radicals, such, for example, as the following: nitro, halogen, such as fluorine, chlorine, bromine or iodine, free of functionally converted carboxyl, for example carbalkoxy, such as carbomethoxy

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or carbethoxy; carbamyl or cyano, and also lower alkyl, especially methyl.

Alcoholysis may be performed in the absence, but preferably in the presence, of a catalyst. As catalysts there may be used, for example, bases of medium strength, such as tertiary amines, especially tertiary aliphatic amines, for example tri-lower alkylamines, such as trimethylamine or triethylamine, tetra-lower alkyl-lower alkylenediamines, such as N:N:N':N'-tetramethylpentylene-(1:5)-diamine, or cyclic bases, such as 1-methyl-pyrrolidine, 1-ethyl-piperidine, 4-methyl-morpholine, 1:4-dimethylpiperazine, pyridine or collidine.

The alkanol used for the alcoholysis may serve at the same time as solvent or diluent, or other inert solvents, for example paradioxan, may be used in addition in order to bring about complete dissolution of the reactants. For the purpose of accelerating the alcoholysis it is preferably performed at a raised temperature, if necessary, in a sealed vessel under superatmospheric pressure and/or under an inert gas, for example nitrogen.

Some of the methyl reserpates esterified in the 18-position with organic sulphonic acids used as starting materials are the subject-matter of copending application No. 46383/64 (Serial No. 999,397). They may be prepared by methods known *per se*. For example, a methyl reserpate may be reacted with an organic sulphonic acid halide, particularly an unsubstituted or substituted benzenesulphonyl halide, such as 3- or 4-nitro-benzenesulphonyl chloride or 4-bromo-benzenesulphonyl chloride, in the presence of a base, especially a tertiary organic nitrogen base, such as pyridine or collidine. For this esterification the above-mentioned base may also serve simultaneously as diluent or solvent, or, if necessary, other inert solvents may be added. The reaction is usually performed with cooling or at room temperature preferably with the exclusion of moisture.

New and particularly suitable starting materials are methyl 18-O-R'-reserpates in which R' stands for a halogeno- or nitro-benzenesulphonyl radical, and their salts, particularly those in which R' represents a mono-bromo- or mono-nitro-benzenesulphonyl radical, and their acid addition salts.

In view of the fact that several asymmetrical carbon atoms are concerned in the formation of the new compounds, the latter may be present in the form of mixtures of racemates, pure racemates or as optical antipodes.

Mixtures of racemates of the starting or end products may be separated in a known manner into pure racemates on the basis of physico-chemical differences, for example by fractional crystallization.

Racemic starting or end products may also be resolved into the optical antipodes by known methods, for example as follows: The racemic bases dissolved in a suitable inert solvent are reacted with an optically active acid and the resulting salts are separated, for example on the basis of their different solubilities, into diastereoisomers from which the antipodes of the new bases may be liberated by the action of an alkaline agent. Especially usual optically active acids are the D- and L-forms of tartaric acid, di-*o*-toluyl-tartaric acid, malic acid, mandelic acid, camphor-sulphonic acid or quinic acid. Optically active forms of the above compounds may also be obtained by using biochemical methods. The starting materials are preferably, however, in the configuration which corresponds to that of the reserpine obtained from plants of the Rauwolfia type, that is to say they belong to the laevorotatory series.

Depending on the methods used, the new compounds are obtained in the free form or in the form of their salts. For example, basic, neutral, acid or mixed salts may be obtained, if desired also hemi-, mono-, sesqui- or poly-hydrates thereof. The salts of the new compounds may be converted into the free bases in a manner known *per se*, for example by reaction with a basic agent, for example aqueous ammonia, moist silver oxide or an ion exchange resin. The free bases may be converted into acid addition salts of inorganic or organic, therapeutically useful acids, if desired, in the presence of a suitable solvent or diluent. Acids of the above type are, for example, mineral acids, such as hydrochloric acid, hydrobromic acid, sulphuric or phosphoric acids, nitric acid or perchloric acid, or aliphatic, alicyclic, aromatic or heterocyclic carboxylic or sulphonic acids, such as formic, acetic, propionic, oxalic, succinic, glycollic, lactic, malic, tartaric, citric, maleic, hydroxymaleic, dihydroxymaleic or pyruvic acid; phenylacetic, benzoic, para-amino-benzoic, anthranilic, para-hydroxy-benzoic, salicylic or para-amino-salicylic acid; ~~toluenesulphonic, naphthalenesulphonic~~ hydroxyethanesulphonic or ethylenesulphonic acid; toluenesulphonic, naphthalenesulphonic acids or sulphanilic acid; methionine, tryptophan, lysine or arginine; as well as ascorbic acid.

The above-mentioned, new bases and their physiologically tolerable salts may be used as medicaments, for example in the form of pharmaceutical preparations which contain these compounds in admixture or conjunction with a pharmaceutical, organic or inorganic, solid or liquid carrier, suitable for enteral, for example oral, or parenteral administration. As carriers there may be

used substances which do not react with the new compounds, such, for example, as water, gelatine, lactose, starches, magnesium stearate, talc, vegetable oils, benzyl alcohol, gums, polyalkyleneglycols, cholesterol and any other known carriers for medicaments. The pharmaceutical preparations may be, for example in the form of tablets, dragees, capsules or in liquid form as solutions, suspensions or emulsions. The pharmaceutical preparations may be sterilized and/or contain auxiliaries, such as preserving, stabilizing, wetting or emulsifying agents, salts for modifying the osmotic pressure or buffers. They may also contain other therapeutically valuable substances.

The pharmaceutical preparations for enteral, for example oral, administration, such as tablets, capsules or pills, contain preferably 0.0001-0.02 gram of the new compounds per dosage unit. A content of active ingredient of 0.0005 to 0.01 gram per dosage unit is particularly favourable, for example for tablets.

Solutions for parenteral administration contain preferably 0.0001 to 0.02 gram/cc of the new compounds. Especially suitable injections solutions are those with a content of active ingredient of 0.001 to 0.01 gram/cc.

The above-mentioned compounds may also be used in veterinary medicine with ordinary feedstuffs or carriers.

Our Specification No. 28120/61 (Serial No. 999,394) describes and claims animal feed and drink preparations, some of which preparations contain the ethers of the present invention.

The following Examples illustrate the invention. The temperatures are given in degrees Centigrade.

Example 1

A mixture of 1.9 grams of methyl 18-O-(4-bromo-benzene-sulphonyl)-reserpate, 0.36 gram of triethylamine and 240 ml of methanol is sealed in a thick-walled hydrogenation bottle after squirting with nitrogen. The reaction mixture is heated on a steam-bath for 21 hours; the light yellow solution is evaporated, the residue is extracted into methylene chloride, and the organic solution is washed with a 5 per cent aqueous sodium carbonate solution and subsequently with a saturated aqueous sodium chloride solution, and is then dried and evaporated to yield a tan solid, which is muddled with diethyl ether. The latter is dissolved in a 1:2-mixture of benzene and cyclohexane, the solution is passed through charcoal, and the filtrate is evaporated to a small volume, whereupon crystallization occurs. The resulting methyl 18-epi-O-methyl-reserpate melts at 241-244°C (with decomposition).

The starting material used in the above reaction may be prepared as described in Specification No. 46383/64 (Serial 999,397).

Example 2

To a solution of 6.35 grams of methyl 18-epi-O-methyl-reserpate in 100 ml of acetone is added a solution of 1.4 ml of concentrated hydrochloric acid in 16 ml of acetone. A gel-like material precipitates immediately, which on scratching becomes crystalline. The mixture is chilled in an ice-bath for thirty minutes, the solid material is filtered off and washed with cold acetone to yield the desired methyl 18-epi-O-methyl-reserpate hydrochloride, melting point 239-242°C (with decomposition).

Example 3

A mixture of 3.17 grams of methyl 18-O-(4-bromo-benzene-sulphonyl)-reserpate, 0.6 gram of triethylamine and 240 ml of absolute ethanol is heated in a sealed vessel on a steam bath for five days while maintaining a nitrogen atmosphere and stirring. The solvent is then evaporated under reduced pressure, the residue is dissolved in methylene chloride, and the solution is washed twice with a five per cent aqueous solution of sodium carbonate and once with a saturated aqueous solution of sodium chloride. The organic solution is dried, the solvent is evaporated, the residue is triturated with diethyl ether, and the organic solvent is evaporated to leave crude methyl 18-epi-O-ethyl-reserpate. The crude product is recrystallized several times from a mixture of benzene and cyclohexane and melts finally at 229-230°C (with decomposition); $[\alpha]_D^{26} = -27°$ (chloroform).

Example 4

To a solution of 0.88 gram of methyl 18-epi-O-ethyl-reserpate in 15 ml of acetone is added a solution of 0.2 ml of concentrated hydrochloric acid in 2.2 ml of acetone. A crystalline product is obtained on scratching; the slurry is chilled and the methyl 18-epi-O-ethyl-reserpate hydrochloride is obtained in white plates, which are filtered off and washed with cold acetone, melting point 233-235°C (with decomposition).

Example 5

A mixture of 5.56 grams of methyl 18-O-(4-bromo-benzene-sulphonyl)-reserpate, 0.90 gram of triethylamine and 250 ml of *n*-propanol is refluxed in a nitrogen atmosphere for 95 hours. After evaporating the solvent the reaction mixture is worked up as shown in Example 3 to yield the desired methyl 18-epi-O-*n*-propyl-reserpate which melts at 223-225° (with decomposition) after recrystallization from a mixture of benzene and cyclohexane; $[\alpha]_D^{29} = -26°$ (chloroform).

Example 6

A total of 0.91 gram of methyl 18-epi-O-*n*-propyl-reserpate is dissolved in 25 ml

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of 0.1 N aqueous hydrochloric acid; the solution is frozen and lyophilized to yield the semicrystalline methyl 18-epi-O-*n*-propyl-reserpate hydrochloride, which crystallizes as the dihydrate, melting point 213-223°C (with decomposition).

Example 7

A mixture of 5.56 grams of methyl 18-O-(4-bromo-benzene-sulphonyl)-reserpate, 0.9 gram of triethylamine and 240 ml of isopropanol is heated for thirteen days in a sealed vessel at 100°C while stirring. The reaction mixture is worked up as shown in Example 3 to yield the methyl 18-epi-O-isopropyl-reserpate, which melts at 225-229°C (with decomposition) after recrystallization from a mixture of benzene and cyclohexane, $[\alpha]_D^{24} = -23°$ (chloroform).

The hydrochloride, which is prepared according to the lyophilization procedure of Example 6, crystallizes with 1½ moles of water, melting point 224-228°C (with decomposition).

Example 8

A mixture of 0.1 gram of methyl 18-O-(4-nitro-benzene-sulphonyl)-reserpate, 0.02 gram of triethylamine and 25 ml of methanol is heated at 100°C in a sealed vessel for 17½ hours; the reaction mixture is worked up as shown in Example 3 to yield the methyl 18-epi-O-methyl-reserpate, melting point 239-241°C (with decomposition). The product is identical with the compound described according to the procedure of Example 1.

The starting material may be prepared as described in Specification No. 46383/64 (Serial 999,397).

Example 9

A mixture of 18.0 grams of methyl 18-O-(3-nitro-benzene-sulphonyl)-reserpate, 1440 ml of ethanol and 3.6 grams of triethylamine is refluxed for about 40 hours. After decolorizing with charcoal the solution is taken to dryness under reduced pressure, the residue is dissolved in 200 ml of methylene chloride, the organic solution is washed with two portions of 100 ml of a five per cent aqueous sodium carbonate solution and then with 200 ml of a saturated aqueous sodium chloride solution. The aqueous washings are extracted with 50 ml of methylene chloride, the organic solutions are combined, dried over sodium sulphate and evaporated to dryness under reduced pressure. The residue is recrystallized by dissolving it in 170 ml of hot isopropanol and chilling over night to 0-5°C. The resulting methyl 18-epi-O-ethyl-reserpate is filtered off, washed with cold isopropanol and dried, melting point 220-223°C. The compound is identical with the product obtained according to the procedure of Example 3.

The starting material may be prepared as described in Specification No. 46383/64 (Serial 999,397).

Example 10

To a solution of 1.82 grams of methyl 18-epi-O-*n*-propyl-reserpate and 0.5 gram of maleic acid in about 40 ml of acetone is added about 50 ml of diethyl ether. On scratching, the desired methyl 18-epi-O-*n*-propyl-reserpate maleate hemihydrate crystallizes in large plates, melting point 196-198°C (with decomposition).

In an analogous manner there is obtained the methyl 18-epi-O-ethyl-reserpate maleate hemihydrate, melting point 195-197°C (with decomposition).

Example 11

To a solution of 4.57 grams of methyl 18-epi-O-*n*-propyl-reserpate in about 130 ml of ethyl acetate is added while stirring a precooled solution of 0.5 gram of sulphuric acid (97 per cent) in 2 ml of ethyl acetate. The reaction mixture is stirred at −10°C to 0°C for one hour and then allowed to stand at −10°C overnight. The desired methyl 18-epi-O-*n*-propyl-reserpate hemisulphate monohydrate is filtered off, washed with cold ethyl acetate and dried at 60°C and under a pressure of 20 mm, melting point 202-207°C (with decomposition).

Example 12

A mixture of 3.17 grams of methyl 18-O-(4-bromo-benzene-sulphonyl)-reserpate and 200 ml of methanol in a sealed bottle after being flushed with nitrogen is placed on a steam bath; the mixture is stirred and heated for 45 hours. The solvent is evaporated under reduced pressure, the residue is dissolved in methylene chloride, and the organic solution is washed with a 5 per cent aqueous solution of sodium carbonate and then with a saturated aqueous solution of sodium chloride, dried and evaporated. The reddish-brown solid crystallizes on stirring with a small amount of diethyl ether, the crystalline material is filtered off after chilling to yield the pale-tan crude methyl 18-epi-O-methyl-reserpate, which yields the pure product in white filaments, melting point 236-238°C (with decomposition) after recrystallization from isopropanol using charcoal, and which is identical with the product obtained according to the procedure described in Example 1.

Example 13

A mixture of 2.0 grams of methyl 18-O-methane-sulphonyl-reserpate, 0.5 gram of triethylamine and 120 ml of methanol is placed in a pressure flask, which is then flushed with nitrogen and sealed. The mixture is heated on a steam bath for twenty days; the solvents are evaporated under reduced pressure and the residue is dissolved in methylene chloride. The organic solution is washed twice with a five per cent aqueous solution of sodium carbonate and once with a saturated aqueous sodium

chloride solution, then filtered through a diatomaceous earth preparation and evaporated under reduced pressure. The residue is dissolved in 25 ml of hot benzene, the solution is filtered, the filtrate is clarified with charcoal and diluted with 75 ml of cyclohexane and then cooled. The crystalline methyl 18-epi-O-methyl-reserpate, melting point 230-233°C, precipitates and is collected; the product is identical with the compound obtained according to the procedure of Example 1, $[\alpha]_D^{25} = -37°$ (chloroform).

The starting material may be prepared by adding 2.12 grams of methane sulphonyl chloride and 45 ml of pyridine to a solution of 6 grams of methyl reserpate in 105 ml of pyridine while cooling in an ice bath, allowing the mixture to stand at room temperature for three days and diluting it with 750 ml of a 2.5 per cent aqueous sodium hydrogen carbonate solution. The resulting methyl 18-O-methane-sulphonyl-reserpate is recrystallized from a mixture of methanol and methylene chloride, melting point 244-245°C.

Example 14

The methyl 18-epi-O-R-reserpates of the present invention and physiologically acid addition salts thereof may be used in the form of pharmaceutically acceptable preparations. For example, tablets containing 0.0005 gram of methyl 18-epi-O-methyl-reserpate hydrochloride as the active ingredient may be prepared as follows (for 20,000 tablets):

Ingredients	
methyl 18-epi-O-methyl reserpate hydrochloride	10.0 grams
Lactose, spray dried	2675.0 grams
Corn starch	300.0 grams
Magnesium stearate	15.0 grams
	3000.0 grams

The methyl 18-epi-O-methyl-reserpate hydrochloride is triturated with the corn starch and forced through a No. 60 sieve; the tools and the sieve are rinsed with a small amount of lactose. The remainder of the lactose and the magnesium stearate are passed through a No. 20 screen, placed in a mixer and the triturate is added. The mass is mixed together for twenty minutes, and the mix is compressed into tablets weighing 0.150 gram, using 9/32 inch die, standard concave punches, uppers bisected, lowers plain.

Example 15

Tablets containing 0.001 gram of methyl 18-epi-O-*n*-propyl-reserpate maleate as the active ingredient may be prepared as follows (for 11,000 tablets):

Ingredients	
methyl 18-epi-O-*n*-propyl-reserpate maleate	11.00 grams
Corn starch	82.50 grams
Lactose, spray dried	1548.25 grams
Magnesium stearate	8.25 grams
	1650.00 grams

The methyl 18-epi-O-*n*-propyl-reserpate maleate is triturated with the corn starch. The magnesium stearate is blended with 100 grams of lactose. All powders are passed through a No. 30 mesh screen, mixed for 30 minutes in a mixer, and then compressed into tablets weighing 0.15 gram using 9/32 inch concave punches, upper bisected and lower with a monogram.

Example 16

Tablets containing 0.0005 gram of methyl 18-epi-O-*n*-propyl-reserpate maleate as the active ingredient are prepared as follows (for 3000 tablets):

Ingredients	
methyl 18-epi-O-*n*-propyl-reserpate maleate	1.50 grams
Corn starch	22.50 grams
Lactose, spray dried	423.75 grams
Magnesium stearate	2.25 grams
	450.00 grams

The methyl 18-epi-O-*n*-propyl-reserpate maleate is triturated with the corn starch. The magnesium stearate is blended with 50 grams of lactose. All powders are passed through a No. 30 mesh screen, mixed for 30 minutes in a mixer, and then compressed into tablets weighing 0.15 gram using 9/32 inch concave punches, upper bisected and lower with a monogram.

Example 17

An injectable solution containing 0.005 gram/ml of methyl 18-epi-O-methyl-reserpate hydrochloride as the active ingredient may be prepared as follows (for 120 ml):

Ingredients	
methyl 18-epi-O-methyl-reserpate hydrochloride	0.600 gram
Sodium acetate, anhydrous	0.720 gram
Acetic acid, glacial	0.510 gram
Fe III-ethylenediamine tetra-acetate	0.012 gram
Thiourea	0.120 gram
Water for injection, q.s.	120.000 ml

The ingredients with the exception of methyl 18-epi-O-methyl-reserpate hydrochloride are dissolved in 110 ml of water. Nitrogen gas is bubbled through the solution and the active compound is dissolved therein. Sufficient water is added to complete the volume of 120 ml, the solution is filtered, and 5 ml portions are filled into 5 ml clear grass ampoules which are sterilized after sealing at 110°C for thirty minutes.

Example 18

An injectable solution containing 0.005 gram/ml of methyl 18-epi-O-*n*-propyl-reserpate sulphate as the active ingredient

may be prepared as follows (for 3000 ml):

Ingredients

methyl 18-epi-O-*n*-propyl-reserpate sulphate	15.0 grams
Sodium chloride	24.6 grams
Thiourea	3.0 grams
Water for injection q.s.	3000.0 ml

Nitrogen is passed for 15 minutes through 3500 ml of boiling water. The thiourea, methyl 18-epi-O-*n*-propyl-reserpate sulphate and the sodium chloride is dissolved in 2800 ml of the hot nitrogen-treated water. After cooling the volume is brought to 3000 ml, and the solution is filtered through a medium porosity sintered glass filter. The filling tube and the amber ampoules are flushed with nitrogen, and the latter are filled with 2.2 ml of the solution, sealed and sterilized at 115.5°C for thirty minutes.

WHAT WE CLAIM IS:—

1. A process for the manufacture of a methyl 18-epi-O-R-reserpate, in which R represents an alkyl group containing 1 to 3 carbon atoms, or a salt thereof, wherein a methyl reserpate esterified in the 18-position with an organic sulphonic acid, or a salt thereof, is subjected to alcoholysis with an alkanol of the formula R-OH in which R has the meaning given above, and, if desired, a resulting base is converted into a salt thereof or a resulting salt is converted into the corresponding base.

2. A process as claimed in claim 1, wherein a methyl 18-O-sulphonyl-reserpate or a salt thereof is used as starting materials in which the organic radical of the sulphonyl group is a substituted or unsubstituted hydrocarbon radical.

3. A process as claimed in claim 1 or claim 2, wherein a methyl 18-O-R_1-reserpate or a salt thereof is used as starting material in which R_1 represents a benzenesulphonyl radical.

4. A process as claimed in any one of claims 1 to 3, wherein a methyl 18-O-R_1-reserpate or a salt thereof is used as starting materials in which R_1 represents a nitro- or halogeno-benzenesulphonyl radical.

5. A process as claimed in any one of claims 1 to 4, wherein the alcoholysis is carried out in the presence of a base of medium strength as catalyst.

6. A process as claimed in claim 5, wherein a tri-lower alkylamine is used as catalyst.

7. A process as claimed in any one of claims 1 to 6, wherein the starting material is present in the configuration which corresponds to that of the reserpine obtained from plants of the Rauwolfia type.

8. A process for the manufacture of a new ether as claimed in any one of claims 1 to 7 conducted substantially as described in any one of Examples 1 to 13 herein.

9. A compound obtained by the process claimed in any one of claims 1 to 8.

10. A methyl 18-epi-O-R-reserpate in which R represents an alkyl radical containing 1 to 3 carbon atoms or a salt thereof.

11. Methyl 18-epi-O-methyl-reserpate or an acid addition salt thereof.

12. Methyl 18-epi-O-ethyl-reserpate or an acid addition salt thereof.

13. Methyl 18-epi-O-*n*-propyl-reserpate or an acid addition salt thereof.

14. Methyl 18-epi-O-isopropyl-reserpate or an acid addition salt thereof.

15. The hydrochloride of a compound claimed in any one of claims 10 to 14.

16. The maleate of a compound claimed in any one of claims 10 to 14.

17. The sulphate of a compound claimed in any one of claims 10 to 14.

18. The laevorotatory antipode of a compound claimed in any one of claims 10 to 17.

19. A new compound as claimed in claim 10 and described in any one of the Examples herein.

20. A pharmaceutical preparation which comprises a base as claimed in any one of claims 10 to 19 in admixture or conjunction with a pharmaceutically suitable carrier.

21. A pharmaceutical preparation which comprises a physiologically tolerable salt as claimed in any one of claims 10 to 19 in admixture or conjunction with a pharmaceutically suitable carrier.

22. A pharmaceutical preparation having the composition substantially as described in any one of Examples 14 to 18 herein.

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Berwick-upon-Tweed: Printed for Her Majesty's Stationery Office by The Tweeddale Press Ltd.—1965.
Published at The Patent Office, 25 Southampton Buildings, London, W.C.2 from which copies may be obtained.

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may be prepared as follows (for 3000 ml):

Ingredients

methyl 18-epi-O-*n*-propyl-reserpate sulphate	15.0 grams
Sodium chloride	24.6 grams
Thiourea	3.0 grams
Water for injection q.s.	3000.0 ml

Nitrogen is passed for 15 minutes through 3500 ml of boiling water. The thiourea, methyl 18-epi-O-*n*-propyl-reserpate sulphate and the sodium chloride is dissolved in 2800 ml of the hot nitrogen-treated water. After cooling the volume is brought to 3000 ml, and the solution is filtered through a medium porosity sintered glass filter. The filling tube and the amber ampoules are flushed with nitrogen, and the latter are filled with 2.2 ml of the solution, sealed and sterilized at 115.5°C for thirty minutes.

WHAT WE CLAIM IS:—

1. A process for the manufacture of a methyl 18-epi-O-R-reserpate, in which R represents an alkyl group containing 1 to 3 carbon atoms, or a salt thereof, wherein a methyl reserpate esterified in the 18-position with an organic sulphonic acid, or a salt thereof, is subjected to alcoholysis with an alkanol of the formula R-OH in which R has the meaning given above, and, if desired, a resulting base is converted into a salt thereof or a resulting salt is converted into the corresponding base.

2. A process as claimed in claim 1, wherein a methyl 18-O-sulphonyl-reserpate or a salt thereof is used as starting materials in which the organic radical of the sulphonyl group is a substituted or unsubstituted hydrocarbon radical.

3. A process as claimed in claim 1 or claim 2, wherein a methyl 18-O-R_1-reserpate or a salt thereof is used as starting material in which R_1 represents a benzenesulphonyl radical.

4. A process as claimed in any one of claims 1 to 3, wherein a methyl 18-O-R_1-reserpate or a salt thereof is used as starting materials in which R_1 represents a nitro- or halogeno-benzenesulphonyl radical.

5. A process as claimed in any one of claims 1 to 4, wherein the alcoholysis is carried out in the presence of a base of medium strength as catalyst.

6. A process as claimed in claim 5, wherein a tri-lower alkylamine is used as catalyst.

7. A process as claimed in any one of claims 1 to 6, wherein the starting material is present in the configuration which corresponds to that of the reserpine obtained from plants of the Rauwolfia type.

8. A process for the manufacture of a new ether as claimed in any one of claims 1 to 7 conducted substantially as described in any one of Examples 1 to 13 herein.

9. A compound obtained by the process claimed in any one of claims 1 to 8.

10. A methyl 18-epi-O-R-reserpate in which R represents an alkyl radical containing 1 to 3 carbon atoms or a salt thereof.

11. Methyl 18-epi-O-methyl-reserpate or an acid addition salt thereof.

12. Methyl 18-epi-O-ethyl-reserpate or an acid addition salt thereof.

13. Methyl 18-epi-O-*n*-propyl-reserpate or an acid addition salt thereof.

14. Methyl 18-epi-O-isopropyl-reserpate or an acid addition salt thereof.

15. The hydrochloride of a compound claimed in any one of claims 10 to 14.

16. The maleate of a compound claimed in any one of claims 10 to 14.

17. The sulphate of a compound claimed in any one of claims 10 to 14.

18. The laevorotatory antipode of a compound claimed in any one of claims 10 to 17.

19. A new compound as claimed in claim 10 and described in any one of the Examples herein.

20. A pharmaceutical preparation which comprises a base as claimed in any one of claims 10 to 19 in admixture or conjunction with a pharmaceutically suitable carrier.

21. A pharmaceutical preparation which comprises a physiologically tolerable salt as claimed in any one of claims 10 to 19 in admixture or conjunction with a pharmaceutically suitable carrier.

22. A pharmaceutical preparation having the composition substantially as described in any one of Examples 14 to 18 herein.

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