

1060.344

PATENT SPECIFICATION

NO DRAWINGS

Inventors: JOHN CAMERON TURNER and WILLIAM ALAN McFARLANE DAVIES

1060.344



Date of filing Complete Specification (under Section 3 (3) of the Patents Act 1949) Jan. 14, 1966.

Application Date: Feb. 11, 1965.

Application Date: May 6, 1965.

Application Date: Oct. 7, 1965.

Complete Specification Published: March 1, 1967.

© Crown Copyright 1967.

No. 5891/65.

No. 19063/65.

No. 42551/65.

Index at acceptance:—C2 C(1Q2, 1Q6B2, 1Q7A, 1Q8A, 1Q9A, 1Q9B, 1Q9D1, 1Q11G, 2B46C3, 2B46G5, 2B47A3, 2B47B3, 2B47C3, 2B47G1, 2B47G2, 2B47G5, 2B47G6, 2B47G7, 3A8A4, 3A8B2, 3A8C6, 3A8K, 3A12A4A, 3A12A4C, 3A12B6, 3A12C4, 3A14C3, 3A14C8A)

Int. Cl.:—C 07 c 103/86, C 07 d 41/00, C 07 d 51/70, C 07 d 87/28

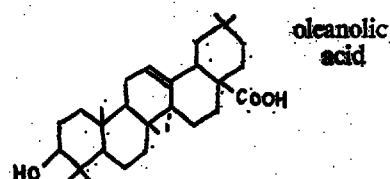
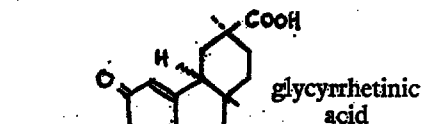
COMPLETE SPECIFICATION

New Derivatives of Glycyrrhetic and Oleanolic Acids

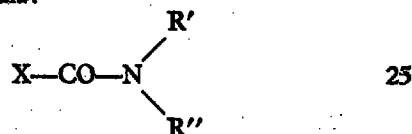
We, BIOREX LABORATORIES LIMITED, of 47—51, Exmouth Street, Rosebery Avenue, London, E.C.1., a British Company, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with new derivatives of glycyrrhetic and oleanolic acids and with the preparation thereof. The new derivatives according to the present invention have been found to possess interesting pharmaceutical properties, such as an excellent anti-inflammatory action and a low toxicity.

The two parent acids on which the new compounds are based have the following structural formulae:



sent invention can be represented by the general formula:—



wherein R' and R'', which may be the same or different, are hydrogen atoms or unsubstituted or substituted alkyl, cycloalkyl, aralkyl or aryl radicals or can be joined together to form, with the nitrogen atom to which they are attached, a heterocyclic radical, which may contain further hetero atoms, such as nitrogen, oxygen or sulphur atoms, and which may be substituted, and X is the acyl residue of 18 α - or 18 β -glycyrrhetic or of oleanolic acid, the hydroxyl group of which may be acylated with a mono- or polycarboxylic acid, any carboxylic acid groups therein being either in the free acid form or in the salt form, or X is the acyl residue of 3-keto-18 α - or 18 β -glycyrrhetic acid or of 3-keto-oleanolic acid. 30

When R and R' are alkyl radicals, they preferably contain up to 6 carbon atoms (e.g. methyl, ethyl, propyl, isopropyl, butyl and hexyl radicals). When R and R' are cycloalkyl radicals, they preferably contain 4—8 carbon atoms (e.g. cyclobutyl, cyclohexyl and cyclooctyl). When R and R' are aralkyl radicals, they are preferably C₁—C₄ alkyl radicals bearing a benzene ring (e.g. benzyl and ethyl-benzene radicals). When R and R' are aryl radicals, they are preferably phenyl radicals, which may be substituted by, for example, carboxylic acid or esterified carboxylic acid groups, halogen atoms or alkyl or halo- 55

The new compounds according to the pre-

[Price 4s. 6d.]

alkyl radicals. When R and R' are joined to form a ring, this ring preferably contains 4—8 carbon atoms and possibly also a sulphur, oxygen or nitrogen atom or an alkyl-substituted nitrogen atom (e.g. a heptamethylene, piperazine, N-methyl piperazine, or morpholine ring).

Examples of acids with which the 3-hydroxyl group may be esterified are preferably aliphatic mono- and dicarboxylic acids containing up to 20 carbon atoms, such as acetic acid, propionic acid, butyric acid, malonic acid, maleic acid, lauric acid, stearic acid and succinic acid.

In order to prepare the new compounds according to the present invention, and 3-hydroxyl group of the parent acid is first protected by acylation with a monocarboxylic acid, for example, by reacting with an appropriate acid anhydride or acid halide, the carboxylic acid group in the acyl compound so obtained or in the corresponding 3-keto acid then converted into an acid halide group, preferably an acid chloride group, for example by reaction with thionyl chloride, the acid halide so obtained thereafter reacted with an amine of the general formula R'.NH.R'', in which R' and R'' have the same meanings as above, and then, if desired, the acyloxy group hydrolysed to liberate the hydroxyl group which can, if desired, again be acylated with a mono- or polycarboxylic acid.

The following Examples are given for the purpose of illustrating the present invention:—

EXAMPLE 1.

30 g. 3-O-acetyl-18 β -glycyrrhetic acid chloride and 60 g. cyclohexylamine are heated at 80° C. for 1 hour and the reaction mixture then cooled and poured into 50 cc. petroleum ether. The solid product obtained is filtered off and recrystallised, first from methanol and then from aqueous dimethyl formamide. There are obtained 10 g. 3-O-acetyl-18 β -glycyrrhetic acid cyclohexylamide in the form of a white, odourless powder melting at 264—265° C.; $[\alpha]_D^{25} = +133 \pm 1^\circ$ (c.=1% in chloroform).

In an analogous manner, there can also be prepared 3 - O - acetyl - 18 β - glycyrrhetic acid piperazinamide; m.p. 273—274° C.

EXAMPLE 2.

20 g. 3 - O - acetyl - 18 β - glycyrrhetic acid chloride and 50 g. heptamethylene-imide are heated at 100° C. for 1 hour and the reaction mixture cooled and 300 cc. petroleum ether added thereto. The product obtained is filtered off and recrystallised several times from aqueous ethanol. There are obtained about 6 g. 3 - O - acetyl - 18 β - glycyrrhetic acid heptamethylene-imide in the form of white, odourless needles having a melting point of 249.5—250° C.; $[\alpha]_D^{25} = +122 \pm 1^\circ$ (c.=1% in chloroform).

EXAMPLE 3.

35 g. 3 - O - acetyl - 18 β - glycyrrhetic acid chloride are dissolved in 200 cc. diethylamine and the solution left at room temperature for 1 hour. The reaction mixture is then poured into a large volume of water and the precipitated solid product filtered off and recrystallised, first from methanol and then from methanol-ethyl acetate (4:1). There are obtained 15 g. 3 - O - acetyl - 18 β - glycyrrhetic acid di-ethylamide in the form of white, odourless needles melting at 228—229° C.; $[\alpha]_D^{20} = +117.5 \pm 1^\circ$ (c.=1% in chloroform).

EXAMPLE 4.

3 - O - lauroyl - 18 α - glycyrrhetic acid is converted into the corresponding acid chloride by heating in benzene with a large excess of thionyl chloride, the benzene and excess thionyl chloride distilled off in a vacuum and the last traces of thionyl chloride removed by redissolving the product in dry benzene and again evaporating. The acid chloride obtained is used as such without further purification.

2.5 equivalents of N-methyl-piperazine are added to a benzene solution of this acid chloride and the solution boiled for 20 minutes. After cooling, N-methyl-piperazine hydrochloride formed as a by-product is filtered off, the filtrate concentrated to a small volume and the residue allowed to crystallise. For purification, the product is recrystallised from methanol to give a 30—40% yield of 3 - O - lauroyl - 18 α - glycyrrhetic acid N - methyl - piperazinamide in the form of white, odourless powder melting at 159—160° C.; $[\alpha]_D^{20} = +47.5 \pm 1^\circ$ (c.=1% in chloroform).

In an analogous manner, there is obtained 3 - O - lauroyl - 18 β - glycyrrhetic acid N - methyl - piperazinamide, which can be purified by recrystallisation from petroleum ether and then from hexane; m.p. 105—105.5° C., $[\alpha]_D^{25} = +105 \pm 1^\circ$ (c.=1% in chloroform).

EXAMPLE 5.

18 g. 18 β -glycyrrhetic acid anthranilide prepared as in Example 13 in 150 cc. dry pyridine were heated for 9 hours at 100° C. with 12.2 g. succinic anhydride. A little water was added to the hot reaction mixture, to decompose any anhydrides formed, followed by 200 cc. ethanol. 400 cc. 50% hydrochloric acid and 200 cc. water were then added and the solid product obtained filtered off and washed with water and then dried to give 21 g. of crude product. After several recrystallisations from ethanol, there are obtained 16 g. 3 - O - (β - carboxy - propionyl) - 18 β - glycyrrhetic acid anthranilide containing alcohol of crystallisation. Upon heating, this alcohol of crystallisation is lost at about 200° C. and the compound melts at 265—266° C.;

$[\alpha]_D^{20} = +124 \pm 1^\circ$ (c.=1% in chloroform as the alcoholate).

From this anthranilide, there can be prepared, in known manner, the corresponding disodium salt; $[\alpha]_D^{20} = +166 \pm 1^\circ$ (c.=1% in water).

EXAMPLE 6.

Starting from 3 - keto - glycyrrhetic acid chloride and N - methyl - piperazine, using the method described in Example 1, there is prepared 3 - keto - glycyrrhetic acid N - methyl piperazinamide.

EXAMPLE 7.

3 - O - acetyl - 18 β - glycyrrhetic acid chloride (prepared by boiling a mixture of acetyl glycyrrhetic acid and thionyl chloride for at least 30 minutes and then removing excess thionyl chloride) is heated at 80° C. for one hour with a fourfold excess of N-methyl-piperazine. The reaction mixture is then poured into cold water and the reaction product which separates is filtered off, washed with cold water and dried. After recrystallisation from dichloromethane - petroleum ether and then from absolute alcohol, pure 3 - O - acetyl - 18 β - glycyrrhetic acid N - methyl - piperazinamide is obtained in a yield of about 50% of the theoretical yield; m.p. 243—245° C.; $[\alpha]_D^{20} = +120 \pm 1^\circ$ (c.=1% in chloroform).

EXAMPLE 8.

9 g. of the 3 - O - acetyl - 18 β - glycyrrhetic acid N - methyl - piperazinamide obtained as in Example 7 are heated for 2 hours at 60° C. in 200 ml. 50% aqueous alcohol containing 10 g. potassium hydroxide. The reaction mixture is then poured into cold water and the precipitated reaction product filtered off, washed with water and dried. After recrystallisation from aqueous dimethyl formamide, there are obtained 5 g. 18 β - glycyrrhetic acid N-methyl-piperazinamide; m.p. 252—253° C.; $[\alpha]_D^{20} = +140 \pm 1^\circ$ (c.=1% in chloroform).

EXAMPLE 9.

Acetyl 18 β - glycyrrhetic acid chloride is heated at about 80° C. for 30 minutes with a fourfold excess of *m*-trifluoromethyl-aniline. The reaction mixture is then poured into dilute hydrochloric acid and the precipitated reaction product filtered off, washed first with dilute hydrochloric acid and then with water and dried. After recrystallisation from aqueous ethanol, pure 3 - O - acetyl - 18 β - glycyrrhetic acid *m*-trifluoromethyl-anilide is obtained in a yield of about 70% of the theoretical yield; m.p. 262—263° C., $[\alpha]_D^{20} = +166 \pm 1^\circ$ (c.=1% in chloroform).

EXAMPLE 10.

15 g. acetyl oleanolic acid chloride and 25 g. methyl anthranilate are well mixed together

and heated for 40 minutes at 170—180° C. After cooling, the reaction mixture is dissolved in ether and extracted several times with dilute hydrochloric acid and then with water. After evaporation of the combined ether extracts, there is obtained a crude product which is purified by recrystallisation from aqueous ethanol. There are thus obtained 15 g. 3 - O - acetyl - oleanolic acid *o* - carbo - methoxy - anilide; m.p. 216—217° C.; $[\alpha]_D^{20} = +32 \pm 1^\circ$ (c.=1% in chloroform).

EXAMPLE 11.

13 g. 3 - O - acetyl - oleanolic acid *o* - carbo - methoxy - anilide and 7 g. potassium hydroxide are dissolved in 170 ml. 80% warm aqueous ethanol and heated for 2 hours at 50—60° C. The solution is then acidified with dilute hydrochloric acid and the precipitated product filtered off, washed with water and dried. The product is purified by recrystallisation from aqueous ethanol. There are thus obtained 8 g. oleanolic acid *o* - carboxy - anilide; m.p. 232—234° C.; $[\alpha]_D^{20} = +35 \pm 4^\circ$ (c.=0.2% in chloroform).

EXAMPLE 12.

15 g. acetyl - 18 β - glycyrrhetic acid chloride (prepared by boiling a mixture of acetyl-18 β -glycyrrhetic acid and thionyl chloride for at least 30 minutes and then removing excess thionyl chloride) is heated at 100° C. for 1 hour with 75 ml. pyridine and 15 g. anthranilic acid. The reaction mixture is cooled to room temperature and acidified and the solid product filtered off and recrystallised from aqueous acetic acid to give 10.3 g. of the 3 - O - acetyl - anthranilide of 18 β - glycyrrhetic acid which has a melting point above 350° C.

EXAMPLE 13.

10.3 g. of the 3 - O - acetyl - anthranilide of 18 β - glycyrrhetic acid obtained as in Example 12 are dissolved in 50% aqueous methanol containing 6 g. sodium hydroxide and the reaction mixture maintained at 50° C. for 3 hours. Acidification of the reaction mixture resulted in the precipitation of the anthranilide of 18 β - glycyrrhetic acid which is isolated and purified by recrystallisation from aqueous dimethyl formamide. The yield is 8 g. and the compound has a melting point of about 355° C.; $E_{1\text{ cm}}^{1\%} = 439 \pm 5$ at 253 $m\mu$ in methanol containing 4% 1N sodium hydroxide solution.

EXAMPLE 14.

20. g. acetyl - 18 β - glycyrrhetic acid chloride, 30 g. methyl *p*-aminobenzoate and 25 ml. pyridine are heated for 2 hours at a bath temperature of 130° C. and the cooled reaction mixture then added to 300 ml. ether and 100 ml. chloroform. The solution obtained is washed with dilute hydrochloric acid and

then with water. The organic layer is separated and dried over anhydrous sodium sulphate, the solution evaporated to dryness and the residue recrystallised first from aqueous alcohol and then from acetone-ether to give 17 g. of the 3 - 0 - acetyl - *p* - carbomethoxy - anilide of 18 β -glycyrrhetic acid which has a melting point of 282—283° C.; $[\alpha]_D = 200 \pm 1^\circ$ (c=1% in chloroform).

EXAMPLE 15.

15 g. of the 3 - 0 - acetyl - *p* - carbomethoxy - anilide of 18 β - glycyrrhetic acid obtained as in Example 14 are finely ground and warmed for 2 hours at 50° C. with 300 ml. ethanol and 50 ml. 20% potassium hydroxide solution. After allowing to cool to room temperature and leaving to stand for some time, the reaction mixture is acidified and diluted with water to give a solid product which is isolated and recrystallised from aqueous acetic acid to give 11 g. of the *p*-carboxy-anilide of 18 β -glycyrrhetic acid with a melting point of about 355° C.; $[\alpha]_D = +215 \pm 4^\circ$ (c.=0.2% in chloroform).

EXAMPLE 16.

A mixture of 20 g. acetyl-18 β -glycyrrhetic acid chloride and 25 ml. morpholine is heated for 1 hour at a bath temperature of 100° C. The reaction mixture is then cooled and diluted with water and the precipitated solid isolated by filtration and recrystallisation from aqueous ethanol to give 19 g. of the 3-0-acetyl-morpholine of 18 β -glycyrrhetic acid with a melting point of 252—254° C.; $[\alpha]_D = +129 \pm 1^\circ$ (c.=1% in chloroform). Further recrystallisation did not result in any change of the melting point.

EXAMPLE 17.

17 g. of the 3-0-acetyl-morpholine of 18 β -glycyrrhetic acid obtained as in Example 16 are mixed with 300 ml. ethanol and 12 g. sodium hydroxide in 15 ml. water, heated to 50° C. for a few minutes to give a clear solution and the temperature then maintained at 30—40° C. for 2 hours. A crystalline precipitate begins to separate out after about 30 minutes. The reaction mixture is thereafter diluted with water and the solid product which separates is filtered off and recrystallised from aqueous alcohol to give 13.5 g. of the pure morpholine of 18 β -glycyrrhetic acid which has a melting point of 243—245° C.; $[\alpha]_D = +141 \pm 1^\circ$ (c.=1% in chloroform).

The present invention also includes within its scope pharmaceutical compositions containing one or more of the new compounds in admixture with a solid or liquid carrier. These pharmaceutical compositions can be administered orally or parenterally.

Solid compositions for oral administration include compressed tablets, pills, dispersible powders and granules. In such solid composi-

tions, at least one active compound according to the present invention is admixed with at least one inert diluent, such as calcium carbonate, starch, alginic acid or lactose. The compositions may also comprise, as is normal practice, additional substances other than inert diluents, for example, lubricating agents, such as magnesium stearate.

Liquid compositions for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs containing inert diluents commonly used in the art, such as water and liquid paraffin. Besides inert diluents, such compositions may also comprise adjuvants, such as wetting and suspension agents and sweetening and flavour agents.

The compositions according to the present invention, for oral administration, include capsules of absorbable material, such as gelatine, containing at least one of the active substances according to the present invention, with or without the addition of diluents or excipients.

Preparations according to the present invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions or emulsions. Examples of non-aqueous solvents or suspending media include propylene glycol, polyethylene glycol, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. These compositions may also contain adjuvants, such as wetting, emulsifying and dispersing agents. They may be sterilised, for example, by filtration through bacteria-retaining filters, by incorporation into the compositions of sterilising agents, by irradiation or by heating. They may also be produced in the form of sterile solid compositions, which can be dissolved in sterile water or some other sterile injectable medium immediately before use.

The percentage of active ingredient in the compositions of the present invention may be varied, it being necessary that it should constitute a proportion such that a suitable dosage for the desired therapeutic effect shall be obtained. In general, the preparations of the present invention should be administered, in the case of oral administration, to give 25 to 750 mg. of active substance per day and, in the case of parenteral administration, 10 to 500 mg. of active substance per day.

The following Examples illustrate pharmaceutical compositions according to the present invention:—

EXAMPLE 18.

200 mg. tablets are prepared containing:

3 - 0 - acetyl - 18 β - glycyrr -		
hetic acid - N - methyl -		
piperazinamide	50 mg	
starch	145 mg	
magnesium stearate	5 mg.	125

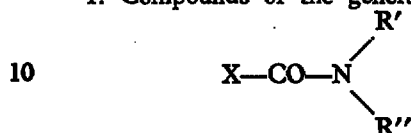
EXAMPLE 19.

200 mg. tablets are prepared containing:

3 - O - acetyl - 18 β - glycyrrhetic acid morpholide	50 mg
starch	100 mg.
lactose	45 mg
magnesium stearate	5 mg.

WHAT WE CLAIM IS:—

1. Compounds of the general formula:—



wherein R' and R'', which may be the same or different, are hydrogen atoms or unsubstituted or substituted alkyl, cycloalkyl, aralkyl or aryl radicals or can be joined together to form, with the nitrogen atom to which they are attached, a heterocyclic radical, which may contain further hetero atoms, and X is the acyl residue of 18 α - or 18 β -glycyrrhetic acid or of oleanolic acid, the hydroxyl group of which may be acylated with a mono- or polycarboxylic acid, any carboxylic acid groups therein being either in the free acid form or in the salt form, or X is the residue of 3-keto-18 α - or 18 β -glycyrrhetic acid or of 3-keto-oleanolic acid.

2. 3 - O - acetyl - 18 β - glycyrrhetic acid cyclohexylamide.

3. 3 - O - acetyl - 18 β - glycyrrhetic acid piperazinamide.

4. 3 - O - acetyl - 18 β - glycyrrhetic acid heptamethylene - imide.

5. 3 - O - acetyl - 18 β - glycyrrhetic acid diethylamide.

6. 3 - O - lauroyl - 18 α - glycyrrhetic acid N - methyl - piperazinamide.

7. 3 - O - lauroyl - 18 β - glycyrrhetic acid N - methyl - piperazinamide.

8. 3 - O - (β - carboxy - propionyl) - 18 β - glycyrrhetic acid anthranilide.

9. Disodium 3 - O - (β - carboxy - propionyl) - 18 β - glycyrrhetic acid anthranilide.

10. 3 - keto - glycyrrhetic acid N - methyl - piperazinamide.

11. 3 - O - acetyl - 18 β - glycyrrhetic acid N - methyl - piperazinamide.

12. 18 β - glycyrrhetic acid N - methyl - piperazinamide.

13. 3 - O - acetyl - 18 β - glycyrrhetic acid *m*-trifluoromethyl - anilide.

14. 3 - O - acetyl - oleanolic acid *o* - carbomethoxy - anilide.

15. Oleanolic acid *o* - carboxy - anilide.

16. 3 - O - acetyl - 18 β - glycyrrhetic acid anthranilide.

17. 18 β - glycyrrhetic acid anthranilide.

18. 3 - O - acetyl - 18 β - glycyrrhetic acid *p* - carbomethoxy - anilide.

19. 18 β - glycyrrhetic acid *p* - carboxy - anilide.

20. 3 - O - acetyl - 18 β - glycyrrhetic acid morpholide.

21. 18 β - glycyrrhetic acid morpholide.

22. Process for the preparation of compounds of the general formula given in claim 1, wherein the hydroxyl group of 18 α - or 18 β -glycyrrhetic acid or of oleanolic acid is first acylated with a monocarboxylic acid and the acyl compound thus obtained or 3-keto-18 α - or 18 β -glycyrrhetic acid or 3-keto-oleanolic acid converted into the corresponding acid halide which is then reacted with an amine of the general formula R'.NH.R'', in which R' and R'' have the same meanings as in claim 1, and, if desired, the acyloxy group hydrolysed to liberate the hydroxyl group which can, if desired, again be acylated with a mono- or polycarboxylic acid.

23. Process according to claim 22, wherein the acylation is carried out with the use of an acid anhydride or acid halide.

24. Process according to claim 22 or 23, wherein the carboxylic acid group present in the acylated compound is converted into the corresponding acid chloride by reaction with thionyl chloride.

25. Process for the preparation of compounds of the general formula given in claim 1, substantially as hereinbefore described and exemplified.

26. Compounds of the general formula given in claim 1, whenever prepared by the process according to any of claims 22 to 25.

27. Pharmaceutical compositions containing at least one compound of the general formula given in claim 1, in admixture with a solid or liquid pharmaceutical carrier.

H. A. L. VENNER,
Chartered Patent Agent,
Rugby Chambers,
2, Rugby Street,
London, W.C.1.
Agent for the Applicants.

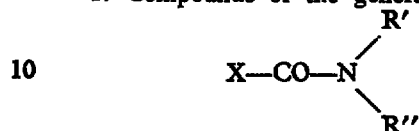
EXAMPLE 19.

200 mg. tablets are prepared containing:

3 - 0 - acetyl - 18 β - glycyrrhetinic acid morpholide	50 mg
5 starch	100 mg.
lactose	45 mg
magnesium stearate	5 mg.

WHAT WE CLAIM IS:—

1. Compounds of the general formula:—



wherein R' and R'', which may be the same or different, are hydrogen atoms or unsubstituted or substituted alkyl, cycloalkyl, aralkyl or aryl radicals or can be joined together to form, with the nitrogen atom to which they are attached, a heterocyclic radical, which may contain further hetero atoms, and X is the acyl residue of 18 α - or 18 β -glycyrrhetic acid or of oleanolic acid, the hydroxyl group of which may be acylated with a mono- or polycarboxylic acid, any carboxylic acid groups therein being either in the free acid form or in the salt form, or X is the residue of 3-keto-18 α - or 18 β -glycyrrhetic acid or of 3-keto-oleanolic acid.

2. 3 - 0 - acetyl - 18 β - glycyrrhetic acid cyclohexylamide.

3. 3 - 0 - acetyl - 18 β - glycyrrhetic acid piperazinamide.

4. 3 - 0 - acetyl - 18 β - glycyrrhetic acid heptamethylene - imide.

5. 3 - 0 - acetyl - 18 β - glycyrrhetic acid diethylamide.

6. 3 - 0 - lauroyl - 18 α - glycyrrhetic acid N - methyl - piperazinamide.

7. 3 - 0 - lauroyl - 18 β - glycyrrhetic acid N - methyl - piperazinamide.

8. 3 - 0 - (β - carboxy - propionyl) - 18 β - glycyrrhetic acid anthranilide.

9. Disodium 3 - 0 - (β - carboxy - propionyl) - 18 β - glycyrrhetic acid anthranilide.

10. 3 - keto - glycyrrhetic acid N - methyl - piperazinamide.

11. 3 - 0 - acetyl - 18 β - glycyrrhetic acid N - methyl - piperazinamide.

12. 18 β - glycyrrhetic acid N - methyl - piperazinamide.

13. 3 - 0 - acetyl - 18 β - glycyrrhetic acid *m* - trifluoromethyl - anilide.

14. 3 - 0 - acetyl - oleanolic acid *o* - carbomethoxy - anilide.

15. Oleanolic acid *o* - carboxy - anilide.

16. 3 - 0 - acetyl - 18 β - glycyrrhetic acid anthranilide.

17. 18 β - glycyrrhetic acid anthranilide.

18. 3 - 0 - acetyl - 18 β - glycyrrhetic acid *p* - carbomethoxy - anilide.

19. 18 β - glycyrrhetic acid *p* - carboxy - anilide.

20. 3 - 0 - acetyl - 18 β - glycyrrhetic acid morpholide.

21. 18 β - glycyrrhetic acid morpholide.

22. Process for the preparation of compounds of the general formula given in claim 1, wherein the hydroxyl group of 18 α - or 18 β -glycyrrhetic acid or of oleanolic acid is first acylated with a monocarboxylic acid and the acyl compound thus obtained or 3-keto-18 α - or 18 β -glycyrrhetic acid or 3-keto-oleanolic acid converted into the corresponding acid halide which is then reacted with an amine of the general formula R'.NH.R'', in which R' and R'' have the same meanings as in claim 1, and, if desired, the acyloxy group hydrolysed to liberate the hydroxyl group which can, if desired, again be acylated with a mono- or polycarboxylic acid.

23. Process according to claim 22, wherein the acylation is carried out with the use of an acid anhydride or acid halide.

24. Process according to claim 22 or 23, wherein the carboxylic acid group present in the acylated compound is converted into the corresponding acid chloride by reaction with thionyl chloride.

25. Process for the preparation of compounds of the general formula given in claim 1, substantially as hereinbefore described and exemplified.

26. Compounds of the general formula given in claim 1, whenever prepared by the process according to any of claims 22 to 25.

27. Pharmaceutical compositions containing at least one compound of the general formula given in claim 1, in admixture with a solid or liquid pharmaceutical carrier.

H. A. L. VENNER,
Chartered Patent Agent,
Rugby Chambers,
2, Rugby Street,
London, W.C.1.
Agent for the Applicants.

