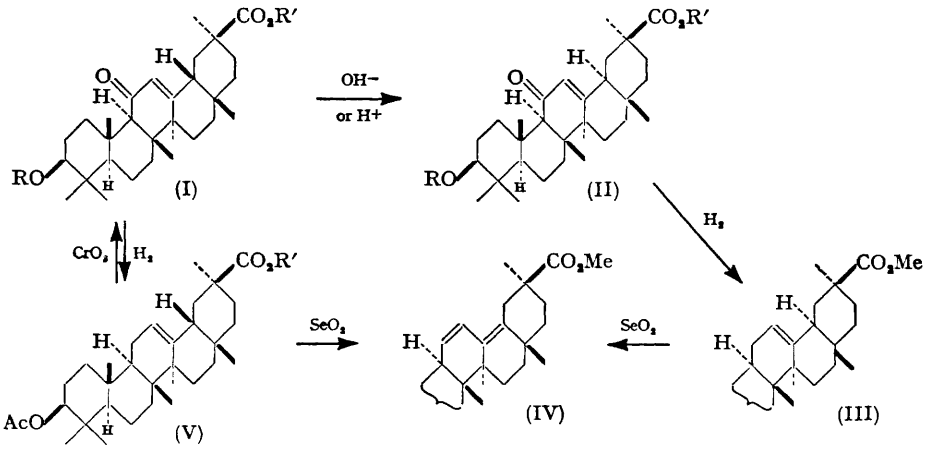
Triterpenoids. Part XLII. The Configuration of the Carboxyl Group in Glycyrrhetic Acid.*

By J. M. Beaton and F. S. Spring.

[Reprint Order No. 6311.]

18α-Glycyrrhetic acid (II; R = R′ = H) has been prepared and characterised. A comparison of the rates of alkaline hydrolysis of methyl glycyrrhetate (I; R = H, R′ = Me) and methyl 18α-glycyrrhetate (II; R = H, R′ = Me) shows that the carboxyl group in glycyrrhetic acid is axially bound and therefore β-orientated.†

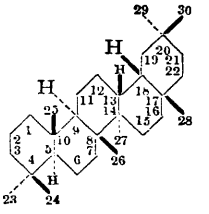
The constitution of glycyrrhetic acid was established by the elegant researches of Ruzicka, Jeger, and their collaborators (Ruzicka and Cohen, *Helv. Chim. Acta*, 1937, **20**, 804; Ruzicka, Leuenberger, and Schellenberg, *ibid.*, p. 1271; Ruzicka and Marxer, *ibid.*, 1939, **22**, 195; Ruzicka and Jeger, *ibid.*, 1942, **25**, 775; Ruzicka, Jeger, and Winter, *ibid.*, 1943, **26**, 265; Ruzicka, Jeger, and Ingold, *ibid.*, p. 2278). The stereochemistry of the acid, apart from the configuration of the carboxyl group, is disclosed by its conversion (Ruzicka and Marxer, *loc. cit.*) into β-amyrin, the stereochemistry of which has been fully elucidated mainly by Barton and Holness (*J.*, 1952, 78; cf. Barton, *J.*, 1953, 1027). The experiments described in the present paper establish that the carboxyl group in glycyrrhetic acid is β-orientated and so lead to the complete definition shown in (I; R = R′ = H).



Prolonged treatment of methyl glycyrrhetate with concentrated alkali gives an acid different from, and isomeric with, glycyrrhetic acid. The isomeric acid is also obtained by heating a solution of glycyrrhetic acid in acetic acid containing concentrated hydrochloric acid. It has been characterised by the preparation of its acetate, its methyl ester, and its methyl ester acetate. Like glycyrrhetic acid, the isomer shows the characteristic

* Part XLI, *J.*, 1955, **3072**.

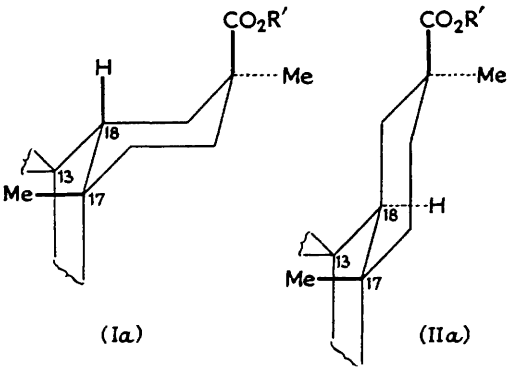
† We suggest that the numbering of the oleanane carbon skeleton should now be extended to that shown opposite. The α-carbon atoms attached to $C_{(4)}$ and $C_{(20)}$ are given the lower numbers, 23 and 29 respectively, and the β-carbon atoms attached at the same points are given the higher numbers, 24 and 30 respectively. This conforms with the numbering hitherto used for 23- and 24-substituted oleanane derivatives (Vogel, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1951, **34**, 2321). This system being used, the proof given in the present paper that the carboxyl group in glycyrrhetic acid is β-orientated leads to the systematic name 3β-hydroxy-11-oxo-olean-12-en-30-oic acid for this compound and so does not necessitate a change from previous practice.



ultraviolet absorption of an αβ-unsaturated ketone. The behaviour of the analogously constituted methyl 11-oxo-oleanolate acetate (Barton and Holness, *loc. cit.*) and 11-oxo-olean-12-enyl benzoate (Budziarek, Manson, and Spring, *J.*, 1951, 3336) with concentrated alkali is a *prima facie* reason for assuming that the isomeric acid differs from glycyrrhetic acid only in the configuration at $C_{(18)}$ and that the configuration at $C_{(9)}$ in the two acids is the same. A proof that the isomeric acid is 18α-glycyrrhetic acid (II; R = R′ = H) was obtained by hydrogenolysis of the methyl ester acetate (II; R = Ac, R′ = Me) which yielded the 11-deoxo-compound (III); oxidation of this with selenium dioxide gave the methyl 11 : 13(18)-dienolate acetate (IV) previously obtained by similar oxidation of methyl deoxoglycyrrhetate acetate (V; R′ = Me) (Bilham, Kon, and Ross, *J.*, 1942, 535; Ruzicka and Jeger, *loc. cit.*; Barton and Brooks, *J.*, 1951, 257).

It is possible that variations observed in the constants of glycyrrhetic acid and its derivatives, such as those which led Voss, Klein, and Sauer (*Ber.*, 1937, **70**, 122; cf. Ruzicka, Furter, and Leuenberger, *Helv. Chim. Acta*, 1937, **20**, 312) to postulate the existence of α- and β-glycyrrhetic acids, may in part be due to the formation of mixtures of glycyrrhetic and 18α-glycyrrhetic acid.

Comparative hydrolyses of methyl glycyrrhetate and 18α-glycyrrhetate show that the former is much more hindered than the latter. For example, the 18α-ester with boiling 3% alcoholic potassium hydroxide gives a 91·5% yield of the 18α-acid in 2 hours, while methyl glycyrrhetate gives only a 5% yield of glycyrrhetic acid, the remainder being unchanged ester. In our opinion, this proves that the carboxyl groups of glycyrrhetic and of 18α-glycyrrhetic acids are respectively axial and equatorial. This means that the carboxyl group of glycyrrhetic acid (I*a*) is β-orientated, the change to 18α-glycyrrhetic acid (II*a*) leading to a conformation in which the β-carboxyl group is equatorial.



(I*a*) (II*a*)

It has been reported that oxidation of deoxoglycyrrhetic acid acetate (V; R′ = H) with chromic acid gives a neutral and an acidic product in approximately equal proportions. The acidic product was identified as glycyrrhetic acid acetate (I; R′ = H; R = Ac). The neutral compound was formulated as a saturated keto-lactone and its formation was used as a proof of the close proximity of the double bond and the carboxyl group in deoxoglycyrrhetic acid (Ruzicka and Marxer, *loc. cit.*). The formation of a saturated keto-lactone from (V; R′ = H) is, on steric considerations, remarkable and the oxidation of deoxoglycyrrhetic acid acetate was therefore re-examined. We have been unable to obtain the saturated keto-lactone, the oxidation giving glycyrrhetic acid acetate in high yield as sole product. The reason for this discrepancy, in our view, is that it is difficult completely to extract glycyrrhetic acid acetate from ether with either sodium hydrogen carbonate or with sodium carbonate—the latter (" soda ") was used in the original experiment; rapid and complete extraction requires the use of caustic alkali. After extraction of an ethereal solution of the reaction product with sodium carbonate solution, we obtained a " neutral " fraction which was in fact glycyrrhetic acid acetate; a comparison of the constants of glycyrrhetic acid acetate and the " saturated keto-lactone " reported

by Ruzicka and Marxer (and shown below), together with our experience, shows that these compounds are identical.

Glycyrrhetic acid acetate	$C_{32}H_{48}O_5$, m. p. 322—325°, $[\alpha]_D$ +141°
" Saturated keto-lactone "	$C_{32}H_{48}O_5$, m. p. 319—322° (sinters 308°), $[\alpha]_D$ + 134°

Experimental

Specific rotations were measured in $CHCl_3$ and ultra-violet absorption spectra in EtOH.

18α-*Glycyrrhetic Acid* (II; R = R′ = H).—(*a*) A mixture of methyl glycyrrhetate (I; R = H, R′ = Me) (10 g.) and potassium hydroxide (400 g.) in water (200 c.c.) and ethanol (1800 c.c.) was refluxed for 120 hr. The solution was diluted with water (2 l.), then acidified with concentrated hydrochloric acid, and the precipitated solid collected. Repeated crystallisation from chloroform–methanol yielded 18α-*glycyrrhetic acid* (3·8 g.) as rectangular plates, m. p. 331—335°, $[\alpha]_D$ + 98° ± 4° (*c*, 0·13, 0·12), $\lambda_{max.}$ 2420 Å (ε 12,200). The acid is sparingly soluble in chloroform (Found: C, 76·7; H, 10·1. $C_{30}H_{46}O_4$ requires C, 76·55; H, 9·85%). (*b*) A solution of glycyrrhetic acid (1·5 g.) in acetic acid (50 c.c.) containing concentrated hydrochloric acid (10 c.c.) was heated on the steam-bath for 2 hr., during which a small amount of crystals separated. Water was added and the product crystallised repeatedly from chloroform–methanol to give 18α-glycyrrhetic acid (0·6 g.) as plates, m. p. 330—335° (no depression).

18α-*Glycyrrhetic Acid Acetate* (II; R = Ac, R′ = H).—18α-Glycyrrhetic acid (0·65 g.) was heated with pyridine and acetic anhydride on the steam-bath for 1½ hr. The product crystallised from chloroform–methanol, to give 18α-*glycyrrhetic acid acetate* (0·50 g.) as triangular plates, m. p. 321—323°, $[\alpha]_D$ + 91° (*c*, 1·9), $\lambda_{max.}$ 2430 Å (ε 11,900) (Found: C, 75·2; H, 9·6. $C_{32}H_{48}O_5$ requires C, 75·0; H, 9·4%).

Methyl 18α-*Glycyrrhetate* (II; R = H, R′ = Me).—Diazomethane in ether was added to a suspension of 18α-glycyrrhetic acid (1·0 g.) in methanol (200 c.c.) until the solid dissolved and a yellow colour persisted. After 1 hr., acetic acid was added and the mixture evaporated under reduced pressure. The residue crystallised from chloroform–methanol, to give *methyl* 18α-*glycyrrhetate* (0·75 g.) as needles, m. p. 267—268°, $[\alpha]_D$ +95° (*c*, 1·7), $\lambda_{max.}$ 2440 Å (ε 11,300) (Found: C, 77·0; H, 10·2. $C_{31}H_{48}O_4$ requires C, 76·8; H, 10·0%).

Methyl 18α-*Glycyrrhetate Acetate* (II; R = Ac, R′ = Me).—A solution of 18α-glycyrrhetic acid acetate (350 mg.) in ether (100 c.c.) was treated with diazomethane in ether. The product, isolated in the usual way and crystallised from chloroform–methanol, gave *methyl* 18α-*glycyrrhetate acetate* as plates, m. p. 254—255° (softening at 245°), $[\alpha]_D$ +87° (*c*, 1·4), $\lambda_{max.}$ 2430 Å (ε 12,000) (Found: C, 75·2; H, 9·5. $C_{33}H_{50}O_5$ requires C, 75·2; H, 9·6%).

Comparative Hydrolyses of Methyl Glycyrrhetate (I; R = H, R′ = Me) *and Methyl* 18α-*Glycyrrhetate* (II; R = H, R′ = Me).—A solution of the ester (200 mg.) in aqueous-methanolic potassium hydroxide (100 c.c.) was refluxed for 2 hr. The solution was diluted with water and extracted repeatedly with ether, so yielding a neutral fraction of unchanged ester. Acidification of the alkaline solution with hydrochloric acid, followed by ether extraction, gave the acid fraction:

Concn. (%) of alkali	1	3	5 *
Acid (%) from: Me glycyrrhetate	0	5	37
Me 18α-glycyrrhetate	28·5	91·5	98

* The methyl ester acetates were used in this case and the refluxing period was 2½ hr.

The acid fraction from the hydrolysis of methyl 18α-glycyrrhetate by 3% alcoholic potassium hydroxide crystallised from chloroform–methanol, to give 18α-glycyrrhetic acid as plates, m. p. 331—335°, $[\alpha]_D$ +100° ± 4° (*c*, 0·12).

Hydrogenolysis of Methyl 18α-*Glycyrrhetate Acetate* (II; R = Ac, R′ = Me).—A solution of the keto-ester (500 mg.) in glacial acetic acid (150 c.c.) was shaken with platinum and hydrogen until absorption was complete (*ca.* 36 hr.). The product, isolated in the usual way and crystallised from chloroform–methanol, yielded *methyl* 11-*deoxo*-18α-*glycyrrhetate acetate* (III) as plates (460 mg.), m. p. 242—243°, $[\alpha]_D$ +69° (*c*, 1·9), ε at 2060 Å = 2700 (Found: C, 77·7; H, 10·5. $C_{33}H_{52}O_4$ requires C, 77·3; H, 10·2%). It gives a yellow colour with tetranitromethane.

Oxidation of Methyl 11-*Deoxo*-18α-*Glycyrrhetate Acetate* (III) *with Selenium Dioxide*.—A mixture of the methyl ester (300 mg.) in acetic acid (30 c.c.) was added to a suspension of selenium dioxide (300 mg.) in water (0·5 c.c.), and the mixture refluxed for 15 min., then

filtered. The filtrate was refluxed with zinc dust (*ca.* 1·5 g.) for 5 min. The product, isolated in the usual manner, crystallised from chloroform–methanol, to give methyl 3β-hydroxyoleana-11 : 13(18)-dien-30-oate acetate (IV) (235 mg.) which after recrystallisation from the same solvent had m. p. 234—235°, $[\alpha]_D$ − 34° (*c*, 2·2), $\lambda_{max.}$ 2410, 2500, and 2590 Å (ε 28,500, 32,200, and 19,800). A specimen prepared from methyl 11-deoxoglycyrrhetate acetate had m. p. 234—235° (no depression), $[\alpha]_D$ − 34° (*c*, 1·8).

We thank the Carnegie Trust for the Universities of Scotland for the award of a scholarship (to J. M. B.), and Dr. A. C. Syme and Mr. Wm. McCorkindale for the microanalyses.

THE ROYAL TECHNICAL COLLEGE, GLASGOW. [*Received, April 7th*, 1955.]