381. *Triterpenoids. Part XLIX.* The Constitution of the Ester $C_{33}H_{46}O_7$ obtained by Oxidation of Methyl Glycyrrhetate Acetate.*

By GEORGE BROWNLIE and F. S. SPRING.

The formula (I) † proposed by McKean and Spring for the acetate $C_{32}H_{46}O_5$ (O_5 acetate) obtained by the oxidation of some β-amyrin acetate derivatives is supported by a study of the analogous ester, $C_{33}H_{46}O_7$ (IX), obtained from methyl glycyrrhetate acetate.

MCKEAN and SPRING [1] suggested that the constitution of the acetate, $C_{32}H_{46}O_5$ (O_5 acetate), obtained in high yield by the oxidation of several β-amyrin derivatives, is represented by (I).† This proposal is supported by the behaviour of the O_5 acetate with methanolic potassium hydroxide when an αβ-unsaturated lactone ester, $C_{31}H_{48}O_5$, formulated as (II),‡ is obtained, vigorous alkaline hydrolysis of which gives an amorphous acid characterised

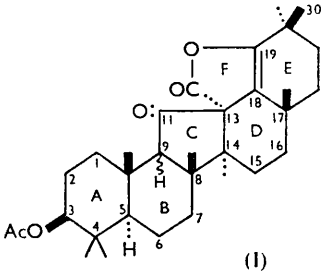
* Part XLVIII, *J.*, 1956, 1377.

† The configuration at $C_{(13)}$ shown in (I) is suggested in this paper.

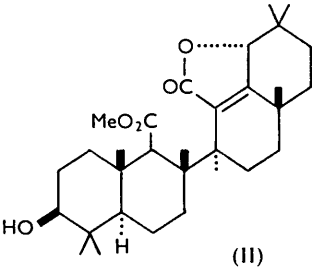
‡ The configurations at $C_{(9)}$ and $C_{(18)}$ (or $C_{(19)}$) in (II), (III), and (IV) are discussed later in this paper.

[1] McKean and Spring, *J.*, 1954, 1989.

as the crystalline saturated dimethyl-oxo-ester, $C_{32}H_{52}O_6$, represented by (III). The expression (I) affords a satisfactory interpretation of the conversion of the O_5 acetate into a hydroxy-diketone, $C_{29}H_{46}O_3$ (IV), the formation of which is attributed to hydrolysis of the 3-acetate and the βγ-unsaturated lactone groups with spontaneous decarboxylation of the resulting β-oxo-acid (IV*a*). A possible mechanism for the conversion of oleanane derivatives into the O_5 acetate, attributed to R. B. Woodward, has been outlined by Yates and Stout.[2]



(I)



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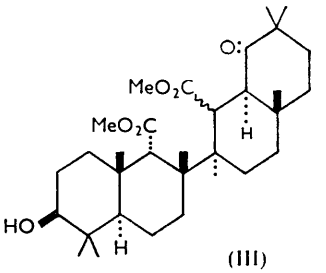

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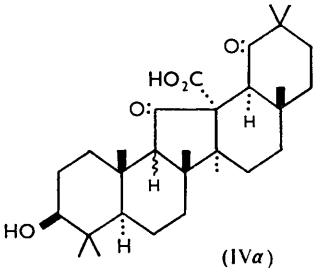
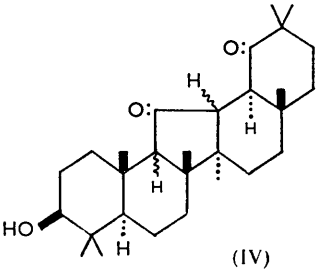


(IV*a*)



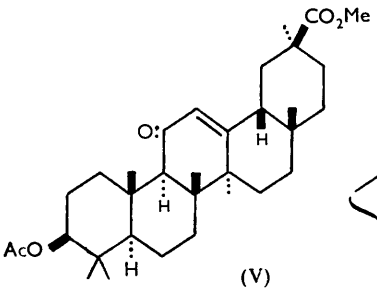
(IV)

Oxidation of methyl glycyrrhetate acetate (V) [3] with selenium dioxide gives an ester, $C_{33}H_{46}O_7$, previously prepared by Jeger, Norymberski, and Ruzicka [4] from methyl 3β-acetoxyoleana-11 : 13(18)-dien-30-oate (VI) and methyl 3β-acetoxyolean-13(18)-en-30-oate (VII) by oxidation with chromic acid and by oxidation of methyl 3β-acetoxy-11-oxo-oleana-12 : 18-dien-30-oate (VIII) with selenium dioxide. The ester, $C_{33}H_{46}O_7$, resembles the O_5 acetate in giving a faint yellow colour with tetranitromethane and in its ultraviolet absorption which shows a broad band near 2300 Å (ε 4400). These properties, its molecular formula, and the methods by which it is prepared support the view that it has a structure analogous to that of the O_5 acetate and this view is confirmed by the reactions described below; if the O_5 acetate is correctly represented by (I), the ester, $C_{33}H_{46}O_7$, from glycyrrhetic acid is (IX).

Treatment of the ester $C_{33}H_{46}O_7$ (IX) with methanolic potassium hydroxide or with methanolic sodium methoxide gives, in good yield, a crystalline acid, $C_{31}H_{46}O_7$. In addition to a carboxyl group, this compound contains a methoxycarbonyl and a hydroxyl group and it was characterised by the preparation of an acetate dimethyl ester, $C_{34}H_{50}O_8$ In addition, the acid, $C_{31}H_{46}O_7$, contains an αβ-unsaturated lactone group as shown by the absorption spectrum ($\lambda_{max.}$ 2240 Å; ε 11,000) and by a positive Legal test. These properties and its method of formation show that it is an analogue of the αβ-unsaturated lactone ester (II) obtained from the O_5 acetate and that its formula is to be derived from that of (II) by the replacement of the 30-methyl by a carboxyl group. We prefer the formula (X) rather than that of the isomer in which $C_{(30)}$ is a methoxycarbonyl group and $C_{(11)}$ a carboxyl group because the methyl ester (II) is the major product obtained by treatment of the O_5 acetate with methanolic potassium hydroxide. On the assumption that ring E in the derived acetate dimethyl ester (X*a*) has the chair conformation, the 30-methoxycarbonyl

[2] Yates and Stout, *J. Amer. Chem. Soc.*, 1954, **76**, 5112.
[3] Beaton and Spring, *J.*, 1955, 3126.
[4] Jeger, Norymberski, and Ruzicka, *Helv. Chim. Acta*, 1944, **27**, 1532.

group is equatorial and, in analogy with the behaviour of methyl 18α-glycyrrhetate,[3] relatively easy hydrolysis of this group is expected; treatment of the acetate dimethyl ester (X*a*) with 4% alcoholic potassium hydroxide regenerates the monomethyl ester (X). In our opinion, the stability to alkali of the methoxycarbonyl group in both (II) and (X)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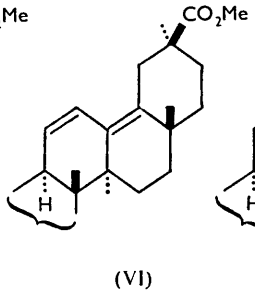
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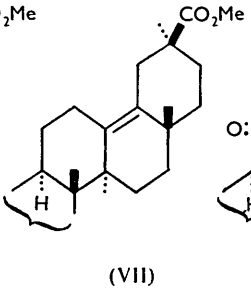
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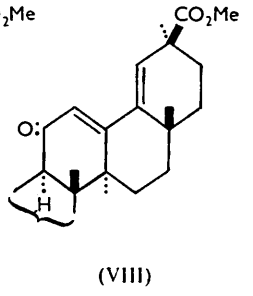
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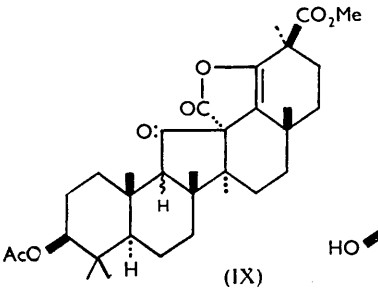
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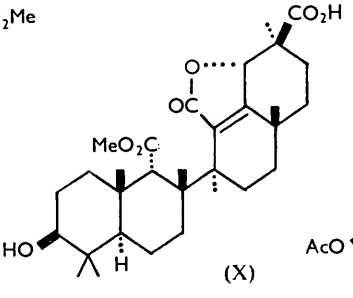
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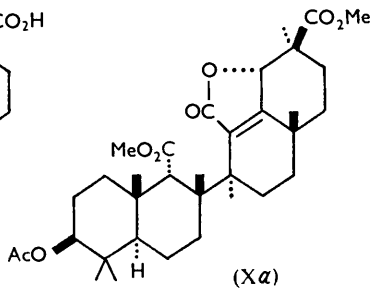
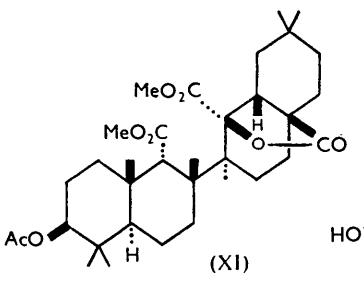

(X*a*)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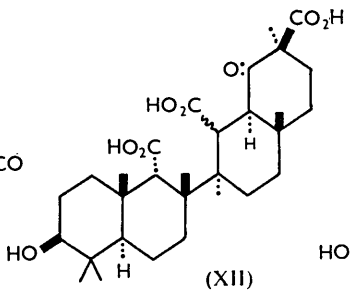
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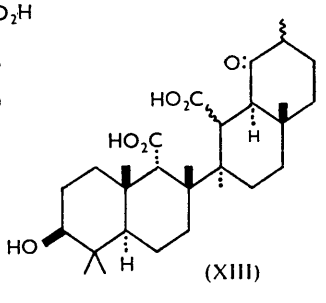
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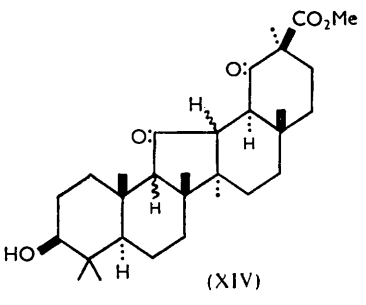
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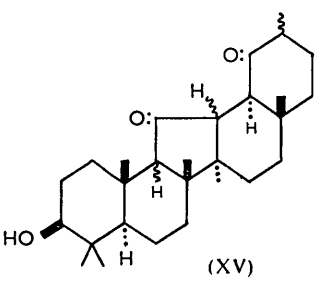
(XV)

shows that it is axially bound and that this is the more stable of the two possible arrangements at $C_{(9)}$. The $C_{(9)}$-axial ester (XI) derived from oleanolic acid is known to be more stable than its C_9-epimer.[5]

An attempt was made to confirm the formula (X) for the acid, $C_{31}H_{46}O_7$, by alkaline

[5] Gutmann, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1951, **34**, 1154; Barton, *Chem. and Ind.*, 1953, 664.

hydrolysis using forcing conditions in the hope that the saturated oxo-dicarboxylic acid (XIII) would be formed *via* the unstable oxo-tricarboxylic acid (XII). The attempt was not conclusive because the acid product is not crystalline and does not give crystalline derivatives. Proof of the proximity of the enol lactone and the methoxycarbonyl group in the O_7 ester was obtained by hydrolysis of this compound with aqueous-alcoholic alkali, a crystalline hydroxy-diketone, $C_{28}H_{44}O_3$, being isolated in good yield. The infrared absorption of the hydroxy-diketone (XV), which was characterised as its acetate $C_{30}H_{46}O_4$, contains bands at 1720 (5-ring ketone) and at 1702 cm.$^{-1}$ (6-ring ketone), values in good agreement with those observed [1] for the higher homologue (IV). In each case the 5-ring carbonyl band is at a lower frequency than usual. The formation of the saturated hydroxy-diketone (XV) from the O_7 ester proves that the unsaturated lactone group in the latter is derived from the enol form of a 19-oxo-oleanane derivative and supports the formula (I) for the O_5 acetate.

In our opinion, the lactone-carbonyl group in the O_5 acetate is α-oriented because only this arrangement will allow the junction of the two fragments A/B and D/E/F through a methylene group bridging $C_{(9)}$ and $C_{(13)}$ with either α- or β-configuration at $C_{(9)}$. The configuration at $C_{(9)}$ in the O_5 acetate is the more stable arrangement because the compound is recovered unchanged after prolonged treatment with mineral acid.[6] Although we have given reasons for the view that the 9-methoxycarbonyl groups in (II) and (X) are α-orientated, it does not follow that the 9-hydrogen atoms in the parents (I) and (IX) [1] are β-orientated, since inversion at $C_{(9)}$ may accompany, precede, or follow methanolysis of the 11 : 13 bond. As stated above, if ring E in the lactone (X) has the chair conformation, the carboxyl group (β) is equatorial, a conclusion supported by the ease of hydrolysis of the corresponding ester; it follows that the 19-hydrogen atom in the lactones (II) and (X) is β-orientated since the equatorial $C_{(19)}$-bond must be part of the unsaturated lactone ring. We provisionally represent the 18-hydrogen atom in (XV) and (IV) as α-orientated because of the relative ease with which the 30-methoxycarbonyl group in (IX) is hydrolysed by aqueous alkali, a property which suggests that in the intermediate (XIV) the methoxycarbonyl group is equatorial. This allocation is provisional because hydrolysis of the methoxycarbonyl group may be facilitated by the neighbouring carbonyl group.

Experimental.

Specific rotations were measured in $CHCl_3$ solution in a 1-dm. tube at room temperature, and ultraviolet absorption spectra were measured in EtOH.

Ester, $C_{33}H_{46}O_7$ (IX).—A solution of methyl glycyrrhetate acetate (m. p. 300—302°, $[\alpha]_D$ +147°; 15 g.) in glacial acetic acid (400 c.c.) was refluxed with selenium dioxide (15 g.) for 24 hr. After filtration, the solution was again treated with selenium dioxide (15 g.) and refluxed for 24 hr. The product was isolated in the usual way and crystallised from chloroform–methanol, to give the ester (7·0 g.) as needles m. p. 288—290°, $[\alpha]_D$ + 2·4° (*c* 3·5), $\lambda_{max.}$ 2260 Å (ε 440) (Found : C, 71·7; H, 8·4. Calc. for $C_{33}H_{46}O_7$: C, 71·4; H, 8·4%). Jeger *et al.*[4] give m. p. 285—286°, $[\alpha]_D$ +4°, + 2·6° for this compound.

Acid, $C_{31}H_{46}O_7$ (X).—(*a*) A solution of the ester, $C_{33}H_{46}O_7$ (2·5 g.), in 5% methanolic potassium hydroxide was refluxed for 3 hr. The product was separated into neutral and acid fractions in the usual way. The neutral fraction is described below. Crystallisation of the acid fraction from acetone–light petroleum gave the *acid*, $C_{31}H_{46}O_7$, m. p. 206—208°, $[\alpha]_D$ −2°, −1·7° (*c* 2·0, 5·0), $\lambda_{max.}$ 2240 Å (ε 11,000) (Found : C, 70·1; H, 9·0; OMe, 6·1. $C_{30}H_{43}O_6{\cdot}OCH_3$ requires C, 79·2; H, 8·7; OMe, 5·85%). The acid does not give a colour with tetranitromethane.

(*b*) A solution of the ester, $C_{33}H_{46}O_7$ (1 g.), in methanolic sodium methoxide (50 c.c. of methanol; 2 g. of sodium) was refluxed for 5½ hr. The product was separated into acid and neutral fractions in the usual way; the latter is described below. The acid fraction (730 mg.) crystallised from acetone–light petroleum as needles, m. p. and mixed m. p. 206—208°, $[\alpha]_D$ −2·2° (*c* 4·0).

Acetate Dimethyl Ester $C_{34}H_{50}O_8$ (X*a*).—The acid, $C_{31}H_{46}O_7$ (250 mg.), in pyridine (5 c.c.) and acetic anhydride (5 c.c.) was kept at 100° for 2 hr. The acetylated product was isolated in the usual way and its solution in ether treated at 16° with an excess of diazomethane and

[6] Mower, Green, and Spring, *J.*, 1944, 256.

kept overnight. The neutral product crystallised from acetone–light petroleum, to give the *acetate dimethyl ester* as needles, m. p. 204—205°, $[\alpha]_D$ −1·4° (*c* 4·0), $\lambda_{max.}$ 2230 Å (ε 12,700) [Found : C, 69·4; H, 8·7; OMe, 10·8. $C_{32}H_{44}O_6(OCH_3)_2$ requires C, 69·6; H, 8·6; OMe, 10·8%]. A mixture with the acid, $C_{31}H_{46}O_7$, had m. p. 183—195°. A solution of the acetate dimethyl ester (800 mg.) and potassium hydroxide (1 g.) in 80% aqueous methanol (25 c.c.) was heated under reflux for 13 hr. The solution was diluted with water, then extracted with ether, and the extract evaporated. A negligible amount of neutral fraction was obtained. The acid fraction was isolated in the usual way and crystallised from acetone–light petroleum, to give the acid, $C_{31}H_{46}O_7$ (X) (750 mg.), as needles, m. p. and mixed m. p. 206—208°, $[\alpha]_D$ −2° (*c* 2·0).

Conversion of the O_7 *Ester* (IX) *into the Hydroxy-diketone*, $C_{28}H_{44}O_3$ (XV).—(*a*) Aqueous potassium hydroxide (33%; 30 c.c.) was added to a solution of the O_7 ester (2 g.) in methanol (170 c.c.), and the solution refluxed for 8 hr. After dilution with water, the neutral fraction was isolated by ether-extraction and crystallised from methanol, to give the *hydroxy-diketone* (800 mg.) as needles, $[\alpha]_D$ +124° (*c* 1·5) (Found : C, 78·4, 78·3; H, 10·4, 10·4. $C_{28}H_{44}O_3$ requires C, 78·45; H, 10·35%). It does not give a colour with tetranitromethane. The hydroxy-diketone separates in a solvated form, m. p. 125—130°, from methanol. On drying in a high vacuum, or on sublimation, the unsolvated form has m. p. 173—175°.

The hydroxy-diketone was heated with acetic anhydride and pyridine at 100° for 1½ hr. The *acetate diketone* crystallised from methanol as needles, m. p. 171—173° (after sublimation in a vacuum), $[\alpha]_D$ +119° (*c* 1·0) (Found : C, 76·8; H, 9·85. $C_{30}H_{46}O_4$ requires C, 76·55; H, 9·85%).

(*b*) The neutral fractions obtained during the preparation of the acid, $C_{31}H_{46}O_7$ [methods (*a*) and (*b*)] were crystallised from aqueous methanol from which the hydroxy-diketone separates as needles (i) (350 mg.) m. p. 125—130° (170—173° after drying in a vacuum), $[\alpha]_D$ +126° (*c* 0·9), (ii) m. p. 125—130° (171—173°, after drying in a vacuum), $[\alpha]_D$ +125° (*c* 1·2).

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