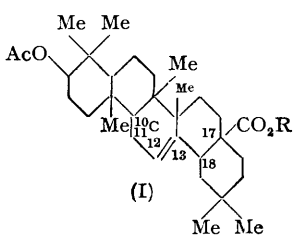
84. *Triterpene Resinols and Related Acids. Part XXV.* Ketoisooleanolic Acid and* isoOleanolic Acid.

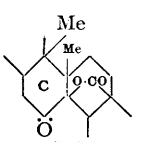
By L. C. McKean, William Manson, and F. S. Spring.

The αβ-unsaturated keto-acid obtained by hydrolysis of acetylketo-oleanolic lactone (II) is shown to be acetyl-12-keto-olean-10-enolic acid (V; R = H), and the methyl ester (V; R = Me) of this acid is shown to be identical with the product obtained by bromination of methyl acetyldihydro-keto-oleanolate (IV). Catalytic reduction of this ester gives methyl acetylolean-10-enolate (XII; R = Me) isomeric with methyl acetyloleanolate (methyl acetylolean-12-enolate) (I; R = Me), with methyl acetylmorolate (methyl acetylolean-18-enolate) (XV), and with methyl δ-acetyloleanolate [methyl acetylolean-13(18)-enolate] (XIII; R = Me).

Acetylketo*iso*oleanolic acid was prepared by Kitasato (*Acta Phytochim.*, 1935, **8**, 315) by treatment of acetylketo-oleanolic lactone (II) with hydrogen bromide in acetic acid, and later by Ruzicka, Cohen, Furter, and Sluys-Veer (*Helv. Chim. Acta*, 1938, **21**, 1735) by treatment of the lactone (II), which can be obtained by several routes from acetyloleanolic acid (I; R = H), with hydrogen bromide in ethanol. Acetylketo*iso*oleanolic acid was



(I)



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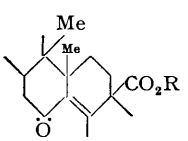

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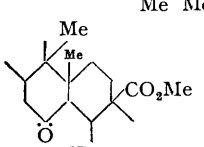

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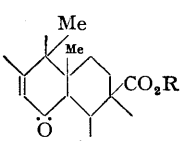

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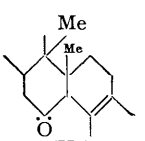
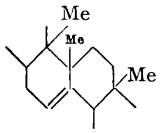


(VI)

* Part XXIV, *J.*, 1951, 3336.

provisionally represented by the formula (III; R = H) by Ruzicka *et al.* (*loc. cit.*), and this formula received support from the behaviour of the acid on treatment with boiling quinoline, an isomeric neutral compound being obtained, presumably by lactonisation between the carboxyl group and the double bond.

According to Picard, Sharples, and Spring (*J.*, 1939, 1045) methyl acetylketo*iso*-oleanolate can be prepared from methyl acetyloleanolate (I; R = Me) by oxidation to methyl acetyldihydroketo-oleanolate (IV) (Ruzicka and Cohen, *Helv. Chim. Acta*, 1937, **20**, 804) followed by bromination of the last. Bromination of β-amyranonyl acetate (VIII) which differs from methyl acetyldihydroketo-oleanolate (IV) solely in the nature of the attachment at $C_{(17)}$ and which is obtained by oxidation of β-amyrin acetate (VII), gives *iso*-β-amyrenonyl acetate which has been shown to be 2-acetoxyolean-10-en-12-one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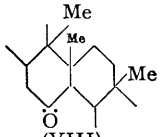
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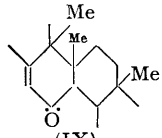
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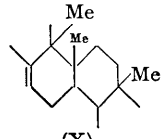

(X)

(IX) (Budziarek, Johnston, Manson, and Spring, *J.*, 1951, 3019). By analogy the structure of methyl acetylketo*iso*oleanolate will be (V; R = Me). Of the alternative formulæ (III; R = H) and (V; R = H) for acetylketo*iso*oleanolic acid, the latter is not in harmony with the behaviour of the acid when treated with quinoline. The formation, under these conditions, of an isomeric lactone requires that the carboxyl group and ethylenic linkage of acetylketo*iso*oleanolic acid be relatively close to each other (probably βγ- or γδ-unsaturated acid). On the other hand, comparison of the optical rotations of the corresponding oleanolic acid and β-amyrin derivatives (see table) supports the view that *iso*-β-amyrenonyl acetate (IX) and acetylketo*iso*oleanolic acid differ only in the nature of the substituent attached to $C_{(17)}$, *i.e.*, that acetylketo*iso*oleanolic acid is acetyl-12-keto-

β-Amyrin acetate (VII)	+81°[1]	Acetyloleanolic acid (I; R = H)	+75°[1]
		Methyl acetyloleanolate (I, R = Me)	+70°[1]
β-Amyranonyl acetate (VIII)	−15°[2]	Methyl acetyldihydroketo-oleanolate (IV)	−11°[3]
iso-β-Amyrenonyl acetate (IX)	+61°[2]	Acetylketo*iso*oleanolic acid	+61°[4]

[1] Elsevier, " Encyclopædia of Organic Chemistry," 1940, Vol. XIV, pp. 533, 540. [2] Budziarek, Johnston, Manson, and Spring (*loc. cit.*). [3] Picard and Spring, *J.*, 1940, 1387; Ruzicka and Cohen, *loc. cit.*; Dietrich and Jeger, *Helv. Chim. Acta*, 1950, **33**, 711. [4] Ruzicka, Cohen, Furter, and Sluys-Veer, *loc. cit.*

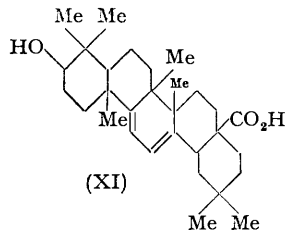
olean-10-enolic acid (V; R = H). With the object of deciding between the alternative formulæ (III; R = H) and (V; R = H), acetylketo*iso*oleanolic acid was re-examined.

Treatment of acetylketo-oleanolic lactone (II) with hydrogen bromide in ethanol, under the conditions described in the Experimental section, gave the hitherto undescribed keto*iso*oleanolic acid and not the acetyl derivative. Acetylation of this acid gave acetyl-keto*iso*oleanolic acid, the physical constants of which are in good agreement with those observed by Ruzicka, Cohen, Furter, and Sluys-Veer (*loc. cit.*) for the product obtained directly from the alcoholic hydrogen bromide reaction mixture. The specific rotation (+47°) of the acetylketo*iso*oleanolic acid obtained by Kitasato (*loc. cit.*) by treatment of acetylketo-oleanolic lactone with hydrogen bromide in acetic acid is in good agreement with the value observed by us for keto*iso*oleanolic acid (+45°) but markedly different from that of the acetylketo*iso*oleanolic acid obtained by us (+61°) and by Ruzicka, Cohen, Furter, and Sluys-Veer (*loc. cit.*) (+61°). Esterification of acetylketo*iso*oleanolic acid with diazomethane gave methyl acetylketo*iso*oleanolate. Since a direct comparison of the methyl acetylketo*iso*oleanolate obtained by bromination of methyl acetyldihydroketo-oleanolate with that obtained by the action of hydrogen bromide on acetylketo-oleanolic lactone was not made by Picard, Sharples, and Spring (*loc. cit.*), the possibility existed that the two materials, although similar, are distinct, the ester obtained by the bromination route being methyl 12-keto-olean-10-enolate (V; R = Me), and that obtained from acetyl-keto-oleanolic lactone (II) the isomeric methyl 12-keto-olean-13(18)-enolate (III; R = Me). We have now proved the identity by a direct comparison and confirmed it by hydrolysis

of methyl acetylketo*iso*oleanolate, obtained by the bromination route, to methyl keto*iso*-oleanolate identical with a specimen obtained by methylation of keto*iso*oleanolic acid:

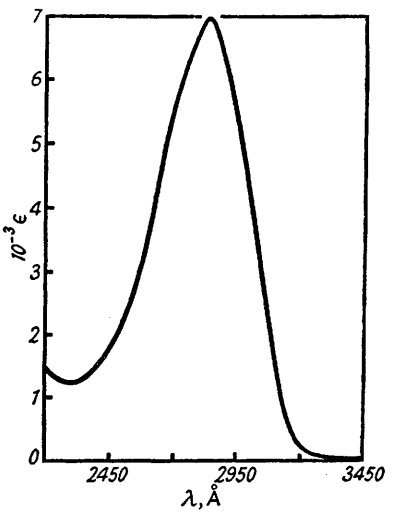
	From (IV):		From (II):	
	m. p.	$[\alpha]_D$	m. p.	$[\alpha]_D$
Methyl acetylketo*iso*oleanolate	208—209°	+57°	207—208°	+56°
Methyl keto*iso*oleanolate	233	+42	232—233	+40

Reduction of keto*iso*oleanolic acid with sodium amalgam gives a hydroxy-dienoic acid which is almost certainly identical with the dehydro*iso*oleanolic acid obtained by a similar reduction of acetylketo*iso*oleanolic acid by Kitasato (*loc. cit.*). The hydroxy-dienoic acid exhibits an intense light-absorption maximum (Fig.) at 2830 Å, which shows that the acid is olean-10 : 12-dienolic acid (XI) and consequently that acetylketo*iso*oleanolic acid is acetyl-12-keto-olean-10-enolic acid (V; R = H) and not acetyl-12-keto-olean-13(18)-enolic acid (III; R = H). Acetylketo*iso*oleanolic acid sublimes unchanged in a vacuum at 250°. This pronounced stability to heat is in accord with formula (V; R = H) but not with formula (III; R = H); the $\beta\gamma$-unsaturated acid (III; R = H) would be expected to lose carbon dioxide when heated, to give the nor-β-amyrenonyl acetate (VI).



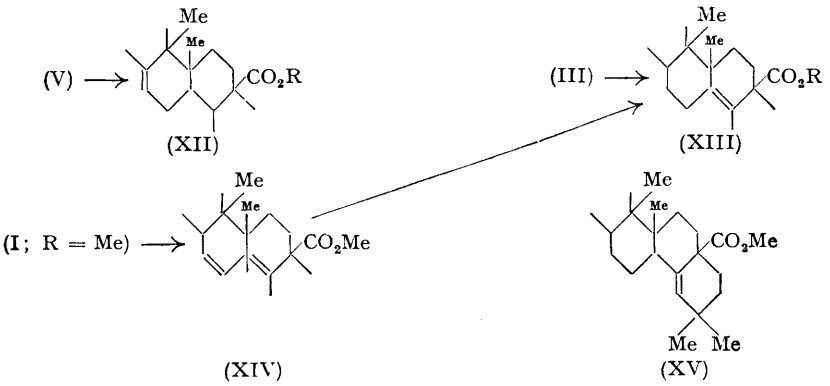
(XI)

The formation of an isomeric lactone from acetyl keto*iso*oleanolic acid by treatment with quinoline requires comment. We have made several attempts to prepare this lactone, the majority of which were unsuccessful. In one case, however, a very small yield of a neutral product was obtained, the melting point and crystalline form of which were similar to those observed by Ruzicka, Cohen, Furter, and Sluys-Veer (*loc. cit.*). Although this neutral compound was not available in sufficient quantity for a detailed study, it exhibits a light-absorption maximum at 2570 Å (ε = 14 000) and does not give a colour with tetranitromethane in chloroform. Whatever the nature of this neutral product, the presence therein of a strongly absorbing chromophore shows that it has not been produced from acetylketo*iso*oleanolic acid by simple additive interaction of carboxyl group and double bond, and its formation does not indicate a necessarily close proximity of these two functions in acetylketo*iso*oleanolic acid.



The preferred formula (V; R = H) for acetylketo*iso*oleanolic acid has been confirmed by an independent method. Clemmensen reduction of acetylketo*iso*oleanolic acid gives acetyl*iso*oleanolic acid (Ruzicka, Cohen, Furter, and Sluys-Veer, *loc. cit.*). Analogously, reduction of *iso*-β-amyrenonyl acetate (IX) by the Clemmensen method (Budziarek, Johnston, Manson, and Spring, *loc. cit.*) or by catalytic means (Jeger and Ruzicka, *Helv. Chim. Acta*, 1945, **28**, 209) gives 2-acetoxyolean-10-ene (X). If acetylketo*iso*oleanolic acid is acetyl-12-keto-olean-10-enolic acid (V; R = H), acetyl*iso*oleanolic acid is acetylolean-10-enolic acid (XII; R = H). If, on the other hand, acetylketo*iso*oleanolic acid is acetyl-12-keto-olean-13(18)-enolic acid (III; R = H), acetyl*iso*oleanolic acid will be acetylolean-13(18)-enolic acid (XIII; R = H), a formulation used without title in Elsevier's "Encyclopædia of Organic Chemistry" (1940, Vol. XIV, p. 543). The last formula assumes not only that (III; R = H) is a valid representation of acetylketo*iso*-oleanolic acid but that Clemmensen reduction of the αβ-unsaturated keto-acid has proceeded without migration of the double bond. Support for this last assumption is to be found in the stability of δ-amyrin acetate [2-acetoxyolean-13(18)-ene] to mineral acid (Ruzicka and Jeger, *Helv. Chim. Acta*, 1941, **24**, 1236). Methyl acetylolean-13(18)-enolate

(methyl δ-acetyloleanolate) (XIII; R = Me) has been prepared by an unambiguous method from methyl acetyloleanolate (I; R = Me) by oxidation with selenium dioxide to methyl acetylolean-11 : 13(18)-dienolate (XIV) followed by catalytic reduction of the latter (Jeger, Norymberski, and Ruzicka, *Helv. Chim. Acta*, 1944, **27**, 1532; Barton and Brooks,



J., 1951, 257). We find that catalytic reduction of methyl acetylketo*iso*oleanolate gives methyl acetyl*iso*oleanolate which differs from methyl δ-acetyloleanolate [methyl acetyl-olean-13(18)-enolate] (XIII; R = Me), thus proving that acetylketo*iso*oleanolic acid is not acetyl-12-keto-olean-13(18)-enolic acid (III; R = H). We conclude that methyl acetyl*iso*oleanolate is methyl acetylolean-10-enolate (XII; R = Me) and that it is a third double-bond isomer of methyl acetyloleanolate (methyl acetylolean-12-enolate) (I; R = Me), the other two being methyl acetylmorolate (methyl acetylolean-18-enolate) (XV) (Barton and Brooks, *loc. cit.*) and methyl δ-acetyloleanolate [methyl acetylolean-13(18)-enolate] (XIII; R = Me).

Experimental

M. p.s are corrected, and rotations were measured in chloroform at room temperature in a 1-dm. tube.

Treatment of Acetylketo-oleanolic Lactone with Hydrogen Bromide.—The lactone (1 g.) in ethanol (50 c.c.) was saturated with dry hydrogen bromide, and the solution refluxed for 30 minutes. The mixture was again saturated with hydrogen bromide and refluxed for 30 minutes. After cooling to room temperature the mixture was saturated with hydrogen bromide, kept overnight, and then diluted with water. The mixture was extracted with ether, the extract washed with 3% aqueous sodium hydroxide, and the alkaline solution washed with ether before acidification with dilute hydrochloric acid. The precipitated solid was collected by means of ether, and the ethereal solution washed with water, dried ($MgSO_4$), and evaporated. The solid residue (0·8 g.) was crystallised from methanol–chloroform, to give *12-keto-olean-10-enolic acid* as prisms, m. p. 320° (decomp.), $[\alpha]_D$ +45° (*c*, 1·14) (Found: C, 76·8; H, 10·2. $C_{30}H_{46}O_4$ requires C, 76·55; H, 9·9%). Light absorption in ethanol: Max. at 2490 Å, ε = 10 000.

Methyl 12-keto-olean-10-enolate was obtained by esterification of the acid with ethereal diazomethane. The neutral product separated from methanol–chloroform as fine needles, m. p. 232—233°, $[\alpha]_D$ +40° (*c*, 0·53) (Found: C, 77·0; H, 10·2. Calc. for $C_{31}H_{48}O_4$: C, 76·8; H, 10·0%). Light absorption in ethanol: Max. at 2500 Å, ε = 10 900. Kitasato (*Acta Phytochim.*, 1936, **9**, 43) gives m. p. 216°, $[\alpha]_D$ +25·7°, for this ester.

Acetyl-12-keto-olean-10-enolic acid was obtained by acetylation of 12-keto-olean-10-enolic acid with acetic anhydride in pyridine. Crystallisation of the product from methanol–chloroform gave the acetate as prisms, m. p. 328° (decomp.), $[\alpha]_D$ +61° (*c*, 1·00) (Found: C, 74·6; H, 9·7. Calc. for $C_{32}H_{48}O_5$: C, 74·9; H, 9·5%). Ruzicka, Cohen, Furter, and Sluys-Veer (*loc. cit.*) give m. p. 328—330°, $[\alpha]_D$ +61°, and Kitasato (*loc. cit.*) gives m. p. 324—330°, $[\alpha]_D$ +46·6°, for the acetyl-acid.

Methyl acetyl-12-keto-olean-10-enolate was obtained by acetylation of methyl 12-keto-olean-10-enolate with pyridine and acetic anhydride. It separated from methanol as plates, m. p.

207—208°, $[\alpha]_D$ +56° (*c*, 0·88) (Found: C, 75·5; H, 9·7. Calc. for $C_{33}H_{50}O_5$: C, 75·2; H, 9·6%).

Bromination of Methyl Acetyldihydroketo-oleanolate.—Methyl acetyldihydroketo-oleanolate (13 g.) in acetic acid (850 c.c.) was treated with a few drops of 48% aqueous hydrobromic acid, and then with a solution of bromine in acetic acid (5%; 85·5 c.c.) at 40°. The solution was kept at room temperature overnight before being heated on the steam-bath for 30 minutes. The solution was then poured into water, and the precipitated solid collected, washed with water, dried *in vacuo*, and crystallised from methanol, to give methyl acetyl-12-keto-olean-10-enolate (8·5 g.) as plates, m. p. 208—209°, $[\alpha]_D$ +57° (*c*, 1·06) (Found: C, 75·2; H, 9·7. Calc. for $C_{33}H_{50}O_5$: C, 75·2; H, 9·6%). A mixture with the specimen (m. p. 207—208°) obtained from acetylketo-oleanolic lactone had m. p. 207·5—209°. Methyl acetyl-12-keto-olean-10-enolate crystallises from methanol as either plates or prismatic needles according to the concentration of the solution, the two forms being interchangeable.

Hydrolysis of methyl acetyl-12-keto-olean-10-enolate, obtained by the bromine route, with % ethanolic potassium hydroxide for 2 hours followed by crystallisation from aqueous methanol gave methyl 12-keto-olean-10-enolate as needles, m. p. 233°, $[\alpha]_D$ +42° (*c*, 0·95) (Found: C, 77·1; H, 10·1. Calc. for $C_{31}H_{48}O_4$: C, 76·8; H, 10·0%). A mixture of the ester with the hydroxy-ester (m. p. 232—233°) from acetylketo-oleanolic lactone had m. p. 233°.

Methyl Acetylolean-10-enolate.—Methyl acetyl-12-keto-olean-10-enolate (1 g.) in stabilised glacial acetic acid (75 c.c.) was shaken with hydrogen in the presence of platinum (0·4 g.) at room temperature and atmospheric pressure for 2 days, during which the equivalent of approx. 2 mols. of hydrogen was absorbed. The solution was filtered, the filtrate diluted with water, and the crystalline solid, m. p. 172—177°, separating collected. After two recrystallisations from methanol–chloroform the product had m. p. 172—177° and showed an absorption maximum in ethanol at 2830 Å (ε = 880). The solid (0·47 g.) was dissolved in light petroleum (b. p. 60—80°; 100 c.c.) and chromatographed on activated alumina (Grade II; 15 × 2 cm.). Light petroleum (b. p. 40—60°; 620 c.c.) and light petroleum–benzene (4 : 1; 100 c.c.) eluted a solid (235 mg.), m. p. 184—187°, crystallisation of which from methanol–chloroform gave *methyl acetylolean-10-enolate* as needles, m. p. 191·5—192·5°, $[\alpha]_D$ +52°, +52° (*c*, 0·84; 0·40) (Found: C, 77·4; H, 10·4. $C_{33}H_{52}O_4$ requires C, 77·3; H, 10·2%). Methyl acetylolean-10-enolate gives a yellow colour with tetranitromethane in chloroform; it does not show selective absorption in the ultra-violet region.

After the column had been washed with light petroleum–benzene (4 : 1; 500 c.c.), benzene (200 c.c.) eluted a solid (42 mg.), m. p. 191—196°, $\lambda_{max.}$ 2830 Å ($\varepsilon \simeq 1500$). This fraction was not obtained pure but probably contained an appreciable quantity of methyl acetylolean-10 : 12-dienolate.

Methyl olean-10-enolate was obtained by treatment of methyl acetylolean-10-enolate (100 mg.) with boiling ethanolic potassium hydroxide (5%; 10 c.c.) for 2 hours. Crystallisation of the product from methanol–chloroform yielded the ester as needles, m. p. 213—214°, $[\alpha]_D$ +41° (*c*, 0·93) (Found: C, 79·1; H, 11·0. $C_{31}H_{50}O_3$ requires C, 79·1; H, 10·7%).

Treatment of Acetyl-12-keto-olean-10-enolic Acid with Quinoline.—Acetyl-12-keto-olean-10-enolic acid (0·30 g.) in quinoline (50 c.c.) was heated for 2 hours at 250—255°. The solution was poured into dilute hydrochloric acid (7%; 250 c.c.), and the mixture extracted with ether. The ethereal extract was washed successively with dilute hydrochloric acid, sodium hydroxide solution, and water, and dried ($MgSO_4$). Removal of the solvent gave a dark brown residue (46 mg.), which after being washed with a little methanol was crystallised from methanol, yielding needles, m. p. 278—281°; a mixture with acetylketo-oleanolic lactone (m. p. 280—282°) had m. p. 262—270°. Light absorption in ethanol: Max. at 2570 Å, ε = 14 200.

Acidification of the alkaline washings of the ethereal extract, followed by crystallisation of the product from methanol–chloroform, gave acetyl-12-keto-olean-10-enolic acid (0·24 g.) as prisms, m. p. 316—319° (decomp.).

Olean-10 : 12-dienolic Acid.—12-Keto-olean-10-enolic acid (1·2 g.) was heated under reflux in ethanol (90%; 100 c.c.) with sodium amalgam (3%; 70 g.) for 3 hours. The cold mixture was filtered, then acidified with dilute hydrochloric acid, and the precipitated solid extracted with ether. The extract was washed with water, dried ($MgSO_4$), and evaporated. The residue was crystallised from methanol, to give olean-10 : 12-dienolic acid as prisms, m. p. 293—295°, $[\alpha]_D$ +202° (*c*, 0·78) (Found: C, 79·2; H, 10·2. Calc. for $C_{30}H_{46}O_3$: C, 79·2; H, 10·2%). Light absorption in ethanol: Max. at 2830 Å, ε = 7000. Kitasato (*loc. cit.*) gives m. p. 295—300°, $[\alpha]_D$ +206·8°, for the sodium amalgam reduction product from acetylketo*iso*oleanolic acid. Purification of the acid was extremely difficult and, although the m. p. remained unaltered

after each crystallisation, the specific rotation and the intensity of the ultra-violet absorption maximum increased slightly; lack of material did not permit the crystallisations to be continued until constant values were obtained. Both values are probably somewhat low, a comment which likewise applies to those for the methyl ester.

Methyl olean-10 : 12-dienolate was obtained by esterification of the acid with ethereal diazomethane. It separates from methanol as needles, m. p. 194—196°, $[\alpha]_D$ +203° (*c*, 0·92). Light absorption in ethanol: Max. at 2840 Å, $\varepsilon = 6800$. Kitasato (*loc. cit.*) gives m. p. 198° for the methyl ester of the acid obtained by sodium amalgam reduction of acetylketo*iso*oleanolic acid.

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