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Chemical Studies on Pentacyclic Triterpenes. IV* Determination of the Configuration of the 2-Acetyl Group in Methyl 2ξ-Acetoxy-20β-hydroxyursonate

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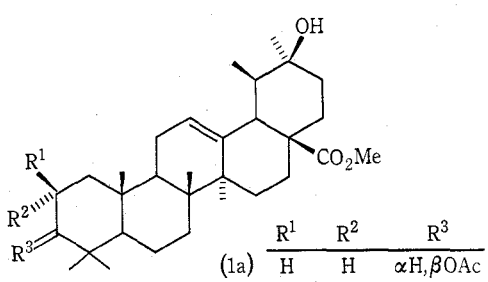
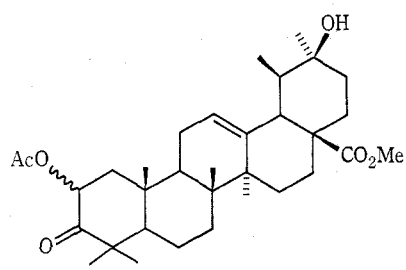
Abstract

The acetoxyl group at position 2 in methyl 2ξ-acetoxy-20β-hydroxyursonate isolated from the ether extract of defatted apple peels was shown by chemical reactions to possess the α (equatorial) configuration.

Apple peels which are the main source of ursolic acid contain two other triterpene acids also; these can be isolated from the ether extract of the defatted peels as their methyl ester acetates. Their structures were determined[1,2] as methyl 3β-acetoxy-20β-hydroxyursolate (1a) and methyl 2ξ-acetoxy-20β-hydroxyursonate (2). The acetoxyl group at position 2 in compound (2) was left without assigning its configuration. Thus, it seems essential to determine the configuration of this acetoxyl group.



	R^1	R^2	R^3
(1a)	H	H	αH,βOAc
(1b)	H	H	αH,βOH
(1c)	H	H	O
(1d)	H	OAc	O
(1e)	OAc	H	O



(2)

The present work explains the chemical methods by which the configuration of the 2-acetoxyl group has been assigned as α (equatorial). Methyl 3β-acetoxy-20β-hydroxyursolate (1a), which is associated with compound (2) in peels, on hydrolysis with ethanolic potassium hydroxide gave methyl 20β-hydroxyursolate (1b), and this on oxidation with chromium trioxide–pyridine, afforded methyl 20β-hydroxyursonate (1c). Preparation of the two acetates isomeric at position 2, (1d) and (1e), from compound

* Part III, *Indian J. Chem.*, in press.

[1] Lawrie, W., McLean, J., and El-Garby Younes, M., *Chem. Ind.* (London), 1966, 1720.
[2] Lawrie, W., McLean, J., and El-Garby Younes, M., *J. Chem. Soc.*, 1967, 851.

(1c) was performed as follows: The 2α-acetate isomer (1d) in which the acetoxyl group possesses the equatorial configuration was prepared according to the procedure described by Henbest *et al.*,[3] in which methyl 20β-hydroxyursonate (1c) in acetic acid was stirred at 25° with lead tetraacetate with boron trifluoride–ether complex as a catalyst. Chromatography of the reaction product gave methyl 2α-acetoxy-20β-hydroxyursonate (1d), as the only isolable acetoxy ketone, identical in all respects with the natural compound. For further confirmation, the other isomer (2β-acetate), which is considered to be less stable than the 2α one, should be prepared, and this was done according to the method described by Halsall *et al.*,[4] in which they acetoxylated 3-oxo 4,4-dimethyl steroids at the 2-position. Methyl 20β-hydroxyursonate (1c) in acetic acid was heated at 100° for 4 h with lead tetraacetate, followed by chromatography on deactivated alumina, to afford two epimeric 2-acetates of melting points 248–249° and 268–270° respectively. The acetate of m.p. 248–249° is identical in all respects with both the natural compound and the compound prepared previously. The other epimer which has m.p. 268–270° is different from the natural compound; this indicates that the acetoxyl group at position 2 may possess the β (equatorial) configuration with ring A in a flexible conformation.[4] The only structure which permits the acetoxyl group to have an axial conformation and yet not interact with the 4- and 10-methyl groups, is that with the acetoxyl group in the α-configuration and with ring A in a boat form with C 1 and C 4 at the bow and stern. Thus, it can be concluded that the natural compound (2) isolated from apple peels is methyl 2α-acetoxy-20β-hydroxyursonate as shown by structure (1d).

Experimental

Rotations were measured in chloroform solution at room temperature. Infrared spectra were conducted as Nujol mulls unless otherwise stated on a Unicam SP300G grating spectrometer, while ultraviolet spectra were done in ethanol on a Unicam SP800 spectrometer. All melting points were uncorrected.

Methyl 20β-Hydroxyursolate (1b)

Methyl 3β-acetyl-20β-hydroxyursolate (1a; 1·5 g), isolated previously[1] from apple peels, was refluxed for 4 h with ethanolic potassium hydroxide (5%; 25 ml). Dilution with water, then extraction with ether and working up through ether as usual gave methyl 20β-hydroxyursolate (1b) (1·4 g; from MeOH) as colourless needles, m.p. 220–223°, $[\alpha]_D$ +57° (*c*, 0·5) (lit.[2] m.p. 220–225°, $[\alpha]_D$ +56·7°); ν_{max} 3500 and 3405 cm^{-1} (shoulder) (OH), 1720 cm^{-1} (methyl ester). Acetate absorption was absent.

Methyl 20β-Hydroxyursonate (1c)

Methyl 20β-hydroxyursolate (1·4 g) in pyridine (30 ml) was added to a solution of chromium trioxide (1·5 g) in pyridine (30 ml) and the mixture left overnight at room temperature. Dilution with water, extraction with ether and working up through ether as usual gave *methyl 20β-hydroxyursonate* (1c) (1·1 g; from MeOH–$CHCl_3$) as colourless needles, m.p. 241–243°, $[\alpha]_D$ +69° (*c*, 0·6); ν_{max} 3510 (OH) and 1710 cm^{-1} (C=O); λ_{max} 276, log ε 1·52 (Found: C, 76·3; H, 10·2. $C_{31}H_{48}O_4$ requires C, 76·8; H, 9·9%).

Methyl 2α-Acetoxy-20β-hydroxyursonate (1d)

A solution of methyl 20β-hydroxyursonate (0·5 g) in benzene (50 ml) and lead tetraacetate (0·6 g) was stirred at 25° with boron trifluoride–ether complex (1 ml) under nitrogen gas. After 2·5 h the

[3] Henbest, H. B., Hones, D. N., and Slatter, G. P., *J. Chem. Soc.*, 1961, 4472.
[4] Chaudhry, G. R., Halsall, T. G., and Jones, E. R., *J. Chem. Soc.*, 1961, 2725.

starch–iodide test for lead tetraacetate was negative. Extraction with ether, and working up as usual, afforded a yellowish gum, showing mainly one spot on a t.l.c. plate. Its infrared spectrum indicated the presence of acetate group. The gum was chromatographed on deactivated alumina (20 g) from light petroleum. Elution with light petroleum–benzene (1 : 4) gave methyl 20β-hydroxyursonate (70 mg; $CHCl_3$–MeOH) as colourless needles (identified by m.p. and m.m.p.), while continued elution with benzene–ether (9 : 1) afforded methyl 2α-acetoxy-20β-hydroxyursonate (0·3 g) as colourless needles (MeOH–$CHCl_3$), m.p. 246–248°, $[\alpha]_D$ +92·5° (*c*, 0·9); λ_{max} 279, logε, 1·26; ν_{max} 3484 (OH), 1742, 1258 (α-acetoxy ketone), 1721 cm^{-1} (methyl ester). (*The natural compound*[1,2] has m.p. 248–249°, $[\alpha]_D$ +95·2°.) No depression in m.p. was observed on admixture.

Methyl 2β-Acetoxy-20β-hydroxyursonate[4]

A solution of methyl 20β-hydroxyursonate (0·5 g), lead tetraacetate (1·0 g) and acetic acid (8 ml) was heated at 100° for 4 h. Most of the solvent was removed under reduced pressure and the resulting viscous mass was treated with $NaHCO_3$ solution (10%) and then extracted with benzene. Working up through benzene as usual afforded a residue (0·4 g), which was adsorbed from light petroleum on deactivated alumina (30 g). Elution with light petroleum–benzene (1 : 9) and then with benzene afforded a mixture of the two isomeric acetates as colourless needles (0·26 g), which could not be separated by column or by thin-layer chromatography. The mixture of the acetates was then fractionally crystallized from methanol–chloroform to give a less soluble and a more soluble fraction. The former fraction was recrystallized thrice to afford colourless needles of pure methyl 2α-acetoxy-20β-hydroxyursonate (70 mg), identical in all respects (m.p., i.r. and specific rotation) with both the natural compound and with the compound prepared in the previous experiment. The more soluble fraction was freed from the solvent and recrystallized thrice from methanol to afford pure *methyl 2β-acetoxy-20β-hydroxyursonate* (80 mg) as colourless needles, m.p. 268–270°, $[\alpha]_D$ +126° (*c*, 0·9); ν_{max} 3501 (OH), 1750, 1233 (α-acetoxy ketone), 1715 cm^{-1} (methyl ester); λ_{max} 289, logε 1·42 (Found: C, 73·4; H, 9·5. $C_{33}H_{50}O_6$ requires C, 73·0; H, 9·3%).

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