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THE 18α-EPIMER OF α-BOSWELLIC ACID: CONFORMATIONAL DIAGNOSIS OF TRITERPENOIDS BY ULTRAVIOLET ABSORPTION SPECTROSCOPY

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Abstract—The synthesis of 18α-α-boswellic acid is reported and the hypsochromic shift in the u v. absorption spectrum associated with the 18β→18α transformation is proposed as a diagnostic technique in conformational analysis.

PENTACYCLIC triterpenoid carboxylic acids are components of many plant gums and may occur in a plurality of isomeric forms even within the same species.[1] Thus for example, three geometrical isomers of boswellic acid have been isolated,[2,3] a fourth has been synthesized,[4] and steric variations of the orientation of the 3-hydroxyl group have been rung for both the α- and β-boswellic acids.[5,6]

On the other hand, no boswellic acid had been described which is isomeric by virtue of intracarbocyclic steric conformations. The synthesis of the 18α-epimer of α-boswellic acid (Ia) was therefore undertaken by first converting Ia, as the acetate methyl ester (Ib), to its 11-oxo-congener (Ic). Equilibration of Ic afforded the 18α-epimer (Id), hydrogenation of which removed the 11-oxo function. Confirmation of the structure of the product as an 18α-α-boswellic acid derivative was provided by dehydrogenation to the known α-boswellic acid heteroannular diene (II).

Our interest in such intracarbocyclic triterpenoid stereoisomers was initially prompted by their somewhat anomalous u.v. spectra.[7] Thus, a comparison of the locations of the absorption maxima of 18α-oleanane derivatives with those of the corresponding 18β-analogs discloses that in each case the transition from the *cis*- to the *trans*-ring D/E fusion (18β→18α) results in a hypsochromic shift of *ca.* 4 nm. This shift may therefore be used to diagnose the conformation of ring junctions if suitable vicinal functions are available. Although this approach has been once used in the elucidation of the structure of glabric acid[8] it is worthy of greater emphasis as is exemplified by the u.v. spectral maxima collected in Table 1.

It is also obvious from Table 1 that oxygenation in rings A (α-boswellic acid) or E (glycyrrhetic acid) does not affect the location of the maxima if the solvents are the same.[9]

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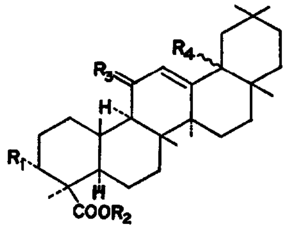

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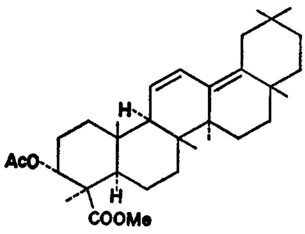

II

	R_1	R_2	R_3	R_4
Ia	OH	H	H_2	β-H
Ib	OAc	Me	H_2	β-H
Ic	OAc	Me	O	β-H
Id	OAc	Me	O	α-H
Ie	OH	H	O	α-H
If	OAc	H	O	α-H
Ig	OAc	Me	H_2	α-H
Ih	OH	Me	H_2	α-H

Moreover, such comparisons are also valid in studies of the conformation of geometric isomers. For example, if the absorption maxima of ursane derivatives are compared with those of their oleanane and 18α-oleanane analogs there is a definite affinity with the former, rather than the latter, as illustrated by the data summarized in Table 2. This further substantiates the *cis*-fusion of rings D/E in the ursane family and demonstrates the potential utility of this diagnostic tool.

TABLE 1 U V MAXIMA OF 18α AND 18β OLEANANE EPIMERS

	λ_{max} (nm)		
	18β	18α	Ref.
3β-Acetoxy-12-bromo-11-oxoolean-12-ene	269	267	10
3β-Acetoxy-12,19-dioxoolean-9(11)-ene	246	243	11
3β-Acetoxyoleana-9(11),12-diene	282	278	12, 13
3β-Acetoxy-11-oxoolean-12-ene	250	245	14, 15
3β-Acetoxy-12-oxoolean-9(11)-ene	248	242	13
3β-Acetoxy-19-oxoolean-9(11)-ene	302	298	11
3β-Acetoxy-11-oxoolean-12-en-30-oic acid	248	244	8, 11
2-Bromo-3,11-dioxoolean-12-en-30-oic acid	250	245	16
3,11-Dioxoolean-12-en-30-oic acid	250	245	16
3β-Hydroxy-11-oxoolean-12-ene	245	243	17
3β-Hydroxy-11-oxoolean-12-en-30-oic acid	248	242	8, 11
Methyl 3α-acetoxy-11-oxoolean-12-en-24-oate	248	244	(this paper)
Methyl 3β-acetoxy-11-oxoolean-12-en-28-oate	250	248	11, 12
Methyl 3β-acetoxy-11-oxoolean-12-en-30-oate	248	243	8, 18
Methyl 3β-hydroxy-11-oxoolean-12-en-30-oate	248	243	8, 11

EXPERIMENTAL

M ps were determined using a standardized N P.L thermometer Rotations were measured in $CHCl_3$ solution in a 1 dm tube at approximately 15°. U v absorption spectra were determined in ethanol solution

The phrase 'in the usual way' implies, in general, dilution with water, extraction with ether, washing consecutively with aq NaOH, water, aq HCl and aq $NaHCO_3$, followed by drying of the ethereal extract over Na_2SO_4, filtration and evaporation to dryness under reduced pressure Hydrogenations were carried

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TABLE 2. U V MAXIMA OF 18α AND 18β OLEANANE EPIMERS AND THE CORRESPONDING URSANE DERIVATIVES

	λ_{max} (nm)	Ref.
3β-Acetoxy-11-oxours-12-ene	251	19
3β-Acetoxy-11-oxoolean-12-ene	250	14, 15
3β-Acetoxy-11-oxo-18α-olean-12-ene	245	13
3β-Acetoxy-12-oxours-9(11)-ene	248	20
3β-Acetoxy-12-oxoolean-9(11)-ene	248	13
3β-Acetoxy-12-oxo-18α-olean-9(11)-ene	242	13
3β-Acetoxyursa-9(11),12-diene	282	20
3β-Acetoxyoleana-9(11),12-diene	282	12
3β-Acetoxy-18α-oleana-9(11),12-diene	278	13
Methyl 3β-acetoxy-11-oxours-12-en-28-oate	250	21
Methyl 3β-acetoxy-11-oxoolean-12-en-28-oate	250	11, 12
Methyl 3β-acetoxy-11-oxo-18α-olean-12-en-28-oate	248	13
5,8,14-Trimethyl-11-oxo-18α-novoleana-9(10),12-diene	256, 287	13
5,8,14-Trimethyl-11-oxonovursa-9(10),12-diene	258, 290	23
5,8,14-Trimethyl-11-oxo-18α-novoleana-9(10),12-dien-28-oic acid	257, 288	22
5,8,14-Trimethyl-11-oxonovursa-9(10),12-dien-28-oic acid	259, 292	23
5,8,14-Trimethyl-11-oxo-18α-novoleana-9(10),12-dien-30-oic acid	254, 287	22
3β-Acetoxy-12-bromooleana-9(11),12-diene	282	10
3β-Acetoxy-12-bromoursa-9(11),12-diene	282	10
3β-Benzoxy-12-bromoolean-12-ene	229	10
3β-Benzoxy-12-bromours-12-ene	229	10
3β-Benzoxy-12-bromo-11-oxoolean-12-ene	230, 269	10
3β-Benzoxy-12-bromo-11-oxours-12-ene	230, 269	10
2-Benzylidene-3,11-dioxoolean-12-ene	231, 255, 294	24
2-Benzylidene-3,11-dioxours-12-ene	232, 255, 293	24
3,11-Dioxoolean-12-ene	294	24
3,11-Dioxours-12-ene	293	24
3,12-Dioxoolean-9(11)-ene	248	24
3,12-Dioxours-9(11)-ene	248	24
3β-Hydroxyolean-12-ene	195	25
3β-Hydroxyurs-12-ene	196	25
Olean-2,12-diene	195	25
Ursa-2,12-diene	194	25
3-Oxoolean-12-ene	195	25
3-Oxours-12-ene	194	25
(5βH)4,23,24-Trinor-5(4→3)abeoolean-12-ene	195	25
(5βH)4,23,24-Trinor-5(4→3)abeours-12-ene	195	25

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out, at room temp., in HOAc which had been refluxed over and distilled from CrO_3. Acetylations were carried out using Ac_2O in pyridine solution at 100° for 30 min unless otherwise specified.

Methyl 3α-Acetoxy-11-oxoolean-12-en-24-oate (Ic)

A solution of methyl 3α-acetoxyolean-12-en-24-oate (3·2 g) in refluxing HOAc (150 ml) was treated with a solution of CrO_3 (3 g) in water (3 ml) and HOAc (60 ml) added dropwise during 30 min. Refluxing was continued for 1 hr and boiling water (150 ml) was added to the reaction mixture which was then allowed to stand overnight and filtered. Crystallization of the residue from methanol yielded methyl 3α-acetoxy-11-oxoolean-12-en-24-oate as plates (1·4 g), m.p. 198–199°, $[\alpha]_D$ +77° (*c*, 3·7) (Found: C, 75·1; H, 9·8. $C_{33}H_{50}O_5$ required, C, 75·2; H, 9·6%) λ_{max} at 248 nm (ϵ = 12,000).

Epimerization of Methyl 3α-Acetoxy-11-oxoolean-12-en-24-oate (Ic)

A solution of Ic (1·2 g) in 15% ethanolic KOH (120 ml) was refluxed for 70 hr and diluted with water. Extraction with ether gave an ethereal extract and an aqueous phase. Evaporation of the ethereal extract gave a residue which was acetylated using pyridine-Ac_2O. The product obtained in the usual way was crystallized from methanol to yield methyl-3α-acetoxy-11-oxo-18α-olean-12-en-24-oate (Id) as prismatic needles (300 mg), m.p. 240–242°, $[\alpha]_D$ +52° (*c*, 1·5) (Found. C, 75·0; H, 9·6. $C_{33}H_{50}O_5$ required: C, 75·2; H, 9·6%) λ_{max} at 244 nm (ϵ = 11,700) which on admixture with methyl 3α-acetoxy-11-oxoolean-12-en-24-oate, m.p. 198–199°, melted over the range 185–190°. The aqueous phase was acidified with HCl and extracted with ether. Evaporation of the ethereal solution gave a residue which crystallized from $CHCl_3$–MeOH to yield 3α-hydroxy-11-oxo-18α-olean-12-en-24-oic acid (Ie) as needles (60 mg), m.p. 310–312°, $[\alpha]_D$ +130° (*c*, 1·4). (Found: C, 76·4; H, 9·9. $C_{30}H_{46}O_4$ required: C, 76·55; H, 9·85%). Acetylation gave a product which crystallized from methanol to yield 3α-acetoxy-11-oxo-18α-olean-12-en-24-oic acid (If) as fine needles, m.p. 234–235°, $[\alpha]_D$ +63° (*c*, 1·0) (Found: C, 75·2; H, 9·3. $C_{32}H_{48}O_5$ required: C, 74·96; H, 9·4%).

Catalytic Hydrogenolysis of Methyl 3α-Acetoxy-11-oxo-18α-olean-12-en-24-oate (Id)

A solution of Id (200 mg) in HOAc (100 ml) was added to a suspension of freshly reduced Pt (from 200 mg of PtO_2) in HOAc (50 ml) and the mixture was shaken with H_2 at room temp. for 20 hr when absorption was complete. The catalyst was removed by filtration and the filtrate evaporated to dryness under reduced pressure to yield a residue which crystallized from methanol to yield methyl 3α-acetoxy-18α-olean-12-en-24-oate (Ig) as plates (150 mg), m.p. 215–216°, $[\alpha]_D$ +41° (*c*, 0·7) (Found: C, 77·2; H, 10·3. $C_{33}H_{52}O_4$ required: C, 77·3; H, 10·2%) which on admixture with methyl 3α-acetoxyolean-12-en-24-oate, m.p. 225–226°, melted over the range 188–193°. Hydrolysis of Ig using 5% methanolic KOH gave methyl 3α-hydroxy-18α-olean-12-en-24-oate (Ih) which crystallized from methanol as plates, m.p. 265–266° $[\alpha]_D$ +82° (*c*, 1·4). (Found: C, 79·0; H, 10·5. $C_{31}H_{50}O_3$ required, C, 79·1; H, 10·7%). Acetylation gave methyl 3α-acetoxy-18α-olean-12-en-24-oate, m.p. and mixed m.p. 214–215° $[\alpha]_D$ +40° (*c*, 0·8).

Dehydrogenation of Methyl 3α-Acetoxy-18α-olean-12-en-24-oate (Ig)

A solution of Ig (100 mg) in HOAc (10 ml) was refluxed with SeO_2 (100 mg) for 2 hr. The product, isolated in the usual manner, was dissolved in benzene (50 ml) and chromatographed on alumina. Elution with benzene (200 ml) gave a product which crystallized from methanol to yield methyl 3α-acetoxyoleana-11,13(18)-dien-24-oate (Ii) as fine needles (50 mg) m.p. and mixed m.p. 180–182°, $[\alpha]_D$ −69° (*c*, 0·7).