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STRUCTURES OF KOKZEYLANOL AND KOKZEYLANONOL TWO NEW NATURAL TRI- AND TETRA- OXYGENATED D:A-FRIEDO-OLEANANES

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Abstract: Kokzeylanol and kokzeylanonol obtained from Kokoona zeylanica have been shown to be 6β,27-dihydroxy-D:A-friedo-olean-3-one (1) and 6β,27-dihydroxy-D:A-friedo-oleana-3,21-dione (2), respectively by the deoxygenation of their 27-acetoxy derivatives using Lithium-ethylene diamine reduction coupled with spectroscopic and irradiation methods. Kokzeylanonol represents the first tetraoxygenated D:A-friedo-oleanane isolated from a natural source.

Recent reports from this laboratory dealt with the application of an irradiation method[1] and triphenyl tinhydride deoxygenation of the derived thiobenzoates[2] in the structure elucidation of some novel 27-hydroxy-D:A-friedo-olean-21-ones and 6β-hydroxy-D:A-friedo-oleananes isolated from Kokoona zeylanica Thwaites (Celastraceae). We herein report the application of $Li\text{-}(CH_2NH_2)_2$ deoxygenation[3] of sterically hindered primary alcohol function in the structure determination two new 27-hydroxyfriedelanes, kokzeylanol and kokzeylanonol obtained from the same plant; latter being the first example of a tetraoxygenated D:A-friedo-oleanane and is significant as polyoxygenated triterpenes are reported to exhibit anti-tumour activity.[4] This also constitutes the first report of the application of metal-amine reduction to deoxygenate primary alcohols. The methods known hitherto for this purpose are cumbersome and/or lead to rearranged products.[5,6]

Spectroscopic evidence suggests that kokzeylanol[7] is a D:A-friedo-oleanane triterpene containing oxo, hydroxymethine and hydroxymethyl groups [(ν 3610, 3490 and 1714 cm^{-1}; δ, 3.50 (1H, m, $W_{\frac{1}{2}}$ 18 Hz), 4.08 (2H, br s); m/z 427 (100%, M^+-CH_2OH)[1]] ; and kokzeylanonol is a D:A-friedo-oleanane with two oxo, a hydroxymethine and a hydroxymethyl function [(ν 3490, 1722 and 1714 cm^{-1}; δ, 3.50 (1H, m, $W_{\frac{1}{2}}$ 18 Hz), 4.10 (2H, br s); m/z 441 (45%, M^+-CH_2OH)]. The steric crowding around the hydroxymethyl group in both compounds is apparent from the

^{1}H-n.m.r. spectra of their acetates which show a clear dd (J 13 Hz). In order to relate kokzeylanol (1) and kokzeylanonol (2) to known D:A-friedo-oleananes, a deoxygenation procedure applicable to both primary and secondary alcohol functions was required. Presence of oxo groups ruled out the possible use of conventional Huang-Minlon reduction.[5,6] Triphenyltin hydride reduction previously employed by us to deoxygenate 6β-hydroxy- and 21β-hydroxy-friedelanes[2] having secondary alcohol groups, when attempted on 27-thiobenzoyloxyfriedelane (6) afforded 27-benzyloxyfriedelane (7) and not the deoxygenated product (friedelan). However, reduction of the derived acetate (5) by Barton's procedure,[3] but employing Li-$(CH_2NH_2)_2$ proved to be the method of choice as exemplified by successful deoxygenation of several triterpene acetates bearing both primary and secondary alcohol functions (see Table).

Li-$(CH_2NH_2)_2$ reduction of kokzeylanol diacetate (3), m.p. 250-252°C, followed by oxidation (CrO_3-pyridine) furnished friedelin, and similar treatment of kokzeylanonol diacetate (4), m.p. 270-272°C, gave friedelan-3,21-dione (11)[1] (see Scheme). Kokzeylanol (1) has also been related to friedelan-3,6-dione (10) and the relationship between the two natural products was shown by Huang-Minlon reduction of both giving 6β,27-dihydroxyfriedelane (12), m.p. 282-284°C, identical with an authentic sample.[1] The foregoing evidence suggest that kokzeylanol is 6β,27-dihydroxy-D:A-friedo-oleanan-3-one (1) and kokzeylanonol is 6β,27-dihydroxy-D:A-friedo-oleana-3,21-dione (2).

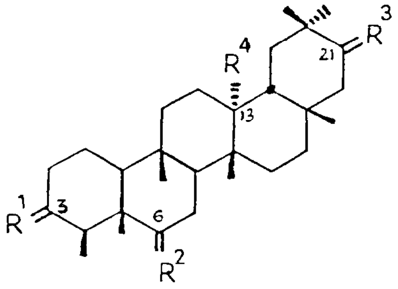
TABLE. Li-$(CH_2NH_2)_2$ reduction of triterpene acetates

Triterpene acetate	Product(s) (% Yield)[a]
27-Acetoxyfriedelane	Friedelan (65); 27-Hydroxyfriedelane (30)
6-Acetoxyfriedelan-3-one (Zeylanol acetate)	Friedelin[b] (75)
Kokzeylanol diacetate	Friedelin[b] (60)
Kokzeylanonol diacetate	Friedelan-3,21-dione[b] (40)

[a] Reductions were carried out by heating a mixture of the triterpene acetate (50 mg), lithium (100 mg) and dry ethylene diamine (10 ml) under reflux in an atmosphere of nitrogen for 30 mins. Usual work-up (Ref. 3) afforded the product(s).

[b] Product obtained after oxidation with CrO_3-pyridine at 25°C, for 12 h.

The presence of 21-oxo and 27-hydroxy functions in kokzeylanonol (2) was further confirmed by the irradiation[1,8] (125 W for 12 h, in refluxing dry dioxan) of the $NaBH_4$ reduction product (13) yielding 3β,6β,27-trihydroxy-E-secofriedel-19-ene-21-carbaldehyde (14)[7], m.p. 130-132°C (60% yield), formed by intramolecular γ-H abstraction within the biradical produced by α-cleavage and 3β,6β,27-trihydroxy-21,22-bisnor-E-secofriedel-16,19-diene (15), m.p. 98-100°C (30% yield), formed by Norrish type II process from (14).



(1) R^1 = O; R^2 = β-OH, α-H; R^3 = H_2; R^4 = CH_2OH

(2) R^1 = R^3 = O; R^2 = β-OH, α-H; R^4 = CH_2OH

(3) R^1 = O; R^2 = β-OAc, α-H; R^3 = H_2; R^4 = CH_2OAc

(4) R^1 = R^3 = O; R^2 = β-OAc, α-H; R^4 = CH_2OAc

(5) R^1 = R^2 = R^3 = H_2; R^4 = CH_2OAc

(6) R^1 = R^2 = R^3 = H_2; R^4 = $CH_2OC(=S)Ph$

(7) R^1 = R^2 = R^3 = H_2; R^4 = CH_2OCH_2Ph

(8) R^1 = R^2 = O; R^3 = H_2; R^4 = CHO

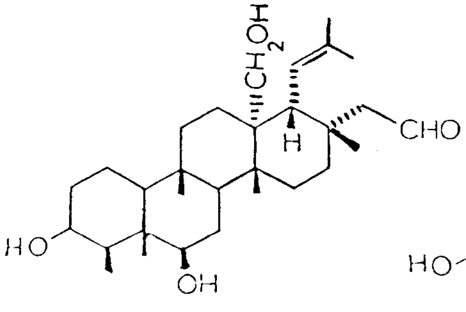
(9) R^1 = R^2 = OH,H; R^3 = H_2; R^4 = CHO

(10) R^1 = R^2 = O; R^3 = H_2; R^4 = Me

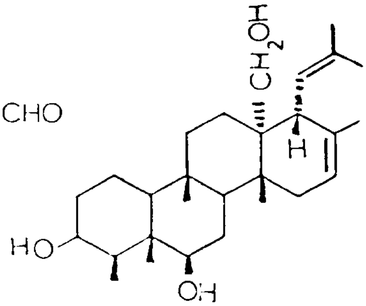
(11) R^1 = R^3 = O; R^2 = H_2; R^4 = Me

(12) R^1 = R^3 = H_2; R^2 = β-OH, α-H; R^4 = CH_2OH

(13) R^1 = R^2 = β-OH, α-H; R^3 = O; R^4 = CH_2OH



(14)



(15)

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$$\begin{tikzcd}
 & (\underline{8}) \arrow[r, "\mathrm{iv}"] & (\underline{9}) \arrow[r, "\mathrm{v,\ iii}"] & (\underline{10}) \\
(\underline{3}) \arrow[d, "\begin{array}{l}\mathrm{ii}\\ \mathrm{iii}\end{array}"] & \begin{array}{c}(\underline{1})\\ \text{m.p. } 282\text{-}284^{\circ}\text{C}\\ (\alpha)_D\ \ -0.8^{\circ}\end{array} \arrow[l, "\mathrm{i}"'] \arrow[u, "\mathrm{iii}"] \arrow[r, "\mathrm{v}"] & (\underline{12}) & \begin{array}{c}(\underline{2})\\ \text{m.p. } 314\text{-}316^{\circ}\text{C}\\ (\alpha)_D\ +86.8^{\circ}\end{array} \arrow[l, "\mathrm{v}"'] \arrow[d, "\mathrm{i}"] \\
\text{Friedelin} & & (\underline{11}) & (\underline{4}) \arrow[l, "\mathrm{ii}", "\mathrm{iii}"']
\end{tikzcd}$$

SCHEME. i, Ac_2O, pyridine; ii, $Li\text{-}(CH_2NH_2)_2$, reflux, 30 mins; iii, CrO_3, pyridine, 25°C; iv, $NaBH_4$, CH_3OH, 25°C, 10 mins; v, $NH_2NH_2.H_2O$ (98-100%), $(CH_2OH)_2$, KOH, 150-160°C for 3 hr and 210°C for 4 hr.

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7. For physical data, see Scheme. The composition of all new compounds was confirmed by elemental analysis and/or high resolution mass spectrometry; structural assignments are based on i.r., ^{1}H-n.m.r. and in some cases ^{13}C-n.m.r. spectroscopic evidence.
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