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TETRACYCLIC TRITERPENOIDS FROM MELIA AZEDARACH, L.
II. 2-OXA-TRANS-BICYCLO[3,3,0]-OCTANONES

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A new euphane-type (20β-H) hydroxy ketone isolated from the bark of Melia azedarach, L. and given the name, kulinone, was shown recently to be 16-hydroxybutyrospermone, with tentative assignment of the β configuration to the hydroxy group (1).

The present paper is a report of the isolation of two companions of kulinone, herewith named kulactone, 1a, and kulolactone, 2a, and of their characterization as compounds of the novel 2-oxa-trans-bicyclo[3,3,0]-octan-3-one system.

Kulactone 1a, $C_{30}H_{44}O_3$ (M^+ 452),[1] mp. 163.0-164.5°, $[\alpha]_D$ -58°, $[\Phi]_{313m\mu}$ -2670°, $[\Phi]_{278m\mu}$-250°, $[\Phi]_{231m\mu}$ -8150°, obtained with compound 2a and kulinone from the petroleum ether extracts of the tree bark, was separated and purified by column and preparative thin-layer chromatography. Its infrared spectrum like that of kulinone, 3a, displays the bands indicative of trisubstituted alkenes (6.0, 11.9 and 12.1μ) and a 6-ring ketone (5.83μ), but in addition has a γ-lactone carbonyl band at 5.59μ. Its nuclear magnetic resonance spectrum ($CDCl_3$) shows 5 sharp 3H singlets at τ9.04, 8.97, 8.94, 8.88 and 8.74; two broadened 3H singlets at τ8.39 and 8.31 ($C{=}C{-}CH_3$); 1H multiplets at τ7.23,[2] 5.83 (-C$\underline{H}$O-), 4.9 (>C$\underline{H}$=C<) and 4.7 (>C$\underline{H}$=C<).

Compound 1a like kulinone, 3a, forms a ketal and a dinitrophenylhydrazone, and is catalytically hydrogenated under neutral conditions to a dihydro compound which resists further hydrogenation but still gives a positive tetranitromethane test. Its lactone ring can be cleaved easily by either methanolic KOH or methanolic HCl to yield the identical hydroxy ester 4, mp. 107.8-108.5°, $[\alpha]_D$ -32°. The 3-ethylene ketals of ester 4 and of 1a on reduction with $LiAlH_4$

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[1] All new compounds have been adequately characterized by ir and nmr analyses; in addition, compound 2a and those for which melting points are recorded have given satisfactory elemental analyses.

[2] This is a distinctive multiplet (See figure 1) observed in every compound of 3-oxo-Δ^7-euphene structure encountered in this work, but is not present in kulolactone, butyrospermol, 4,4-dimethylcholestan-3-one, 3-ketals, and 3-oxo-Δ^8-derivatives (prepared by isomerization of corresponding Δ^7-compounds). The signal probably is due to the 2α-equatorial proton, the Y part of an ABXY system. Experiments to confirm this, and examination of compounds of other triterpenoid structures to ascertain whether this nmr signal has diagnostic significance will be reported separately.

yield the same diol 5a, mp. 172.0-172.5°, (mp, $[\alpha]_D$, ir, nmr). Diol 5a can be selectively mesylated to a mono-mesylate which with $LiAlH_4$ is converted to kulinone* (mp, mmp, $[\alpha]_D$, ir, nmr).

These conversions indicate that (a) neither acid nor base fission of kulactone is accompanied by change of configuration at centers C-16, 17 and 20; (b) configuration of both C-17 and 20 hydrogens is β (side chain, α) (2); (c) the oxido linkage of the lactone is at C-16, and thus the only possible positions for the carbonyl group of the γ-lactone are C-13, 14 and 21. Nmr evidence indicates that the lactone carbonyl is C-21; the high field methyl signals are all clean singlets in the spectrum of kulactone, without the splitting expected for a structure with C-21 methyl. Additional evidence that the lactone carbonyl resides in the side chain, and not at one of the C-13 or 14 angular positions, is afforded by mass spectral analysis of kulactone and certain of its derivatives, and by hydrolysis studies.[3] However, with the C-21 lactone carbonyl, and the supposedly obligatory cis configuration of a lactone of this type,[4] conversion of kulactone, through the diol 5a and its 21-mono-mesylate, should yield 16-epikulinone, 3b, (1), not kulinone.

The actual result permits two interpretations: either the assignment of 16β to the hydroxy group of kulinone should be reversed, or kulactone is a trans-lactone. Initially we were inclined to accept the former alternative, even though several pieces of experimental data had indicated that kulactone was atypical,[5] but subsequent developments revealed compelling evidence favoring the latter.

The mesylate of the ketal of 4 when refluxed in collidine gave, instead of an olefin as expected, a new lactone 1b,* $C_{30}H_{44}O_3$ (M^+ 452), mp. 182.2-182.8°, $[\alpha]_D$ 0°. The ir and nmr spectra of 1b are very similar to those of kulactone. The only significant difference in the ir is the lower frequency of the carbonyl absorption (5.64μ) in 1b; and in the nmr, the chemical shift, band width and splitting pattern of the signal assigned to C-16 proton. The same lactone 1b* is formed, in addition to the hydroxy ester 4,* when compound 6 (as ketal), prepared by oxidation of 4 (as ketal), is reduced by $NaBH_4$. Lactone 1b, stable to methanolic HCl, is cleaved by base, but the product of basic hydrolysis on acidification reverts to the original lactone.[6]

On treatment with $LiAlH_4$, 1b (as ketal) is converted to diol 5b which differs from diol 5a.

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* After cleavage of the intermediary 3-ketal.

[3] The mass spectral and hydrolysis experimental results will be reported in a full paper.

[4] A trans-fused 2-oxa-bicyclo[3,3,0]-octanone is unknown, although futile attempts at synthesis have been reported (3). Recent literature contains several references to the non-existence and instability of the trans structure (4,5). Discussions on bicyclo[3,3,0]-octane systems are available (6).

[5] The high ir lactone carbonyl absorption frequency of kulactone; the ease of cleavage of the lactone under mild acidic conditions; the resistance of the cleaved product to re-lactonization.

[6] Hückel and Gelmroth (3a) obtained analogous results on the reduction of cyclopentanone-2-acetic acid methyl ester and hydrolysis of cis-1,2-cyclopentanol-acetic acid lactone.

Compounds 5a and 5b react with trityl bromide to yield different primary mono-trityl ethers, which on oxidation yield the identical (tlc, ir, nmr) 16-keto derivative 7, providing evidence that kulactone and 1b are epimeric at C-16. Comparison of the properties and reactions of the two compounds leads to assignment of the trans structure to kulactone: 16β-hydroxy-3-oxo-$\Delta^{7,24}$-euphadien-21-oic acid 21 → 16 lactone. Consequently lactone 1b is the cis compound, or 16-epikulactone. Corroboration of this assignment comes from spectral data[7] of 20-epi-16-epi-deacetyltetrahydrofusidic acid lactone, which has the precise geometry at C-13, 14, 16, 17 and 20 and the exact side chain structure of 16-epikulactone (5).

Kulolactone, 2a, $C_{30}H_{46}O_3$, amorphous, $[\alpha]_D$ -42°, $[\Phi]_{285m\mu}$ -1620°, $[\Phi]_{262m\mu}$ -920°, $[\Phi]_{230m\mu}$ -5050°; λ_{max} (CS_2) 2.7, 9.7μ (-OH), 5.58μ (γ-lactone C=O), 10.46μ (-C-O-C); nmr: 3H singlets at τ9.20, 9.05, 8.77, 6H singlet at τ9.02 (5 tertiary Me); two broadened 3H singlets at τ8.37 and 8.27; 1H triplet at τ6.53 (CHOH) and 1H multiplets at τ5.85 (-CH-O-), 4.9 (>CH=C<) and 4.7 (>CH=C<), is evidently the 3α-hydroxy derivative of kulactone, as deduced from the following: when kulactone is treated with $NaBH_4$ under mild conditions, a hydroxy derivative 2b is formed whose ir spectrum is nearly identical to that of kulolactone. The nmr spectrum of 2b differs significantly from that of 2a only in one respect; the signal due to the proton at C-3 is a broad multiplet centered at τ6.73, compatible with an axial proton assignment (4a). Both 2a and 2b are oxidized to kulactone (mp, tlc, ir).

The survival of the lactone structure under basic albeit mild conditions, as shown in the formation of compound 2b, in an apparently highly strained fused-ring system is surprising. Existence of trans lactones of natural origin in contrast to the failure to synthesize such structures in the laboratory may be rationalized on the basis of the favorable entropy of activation of enzyme-catalyzed reactions.

Kulactone, kulolactone and kulinone constitute the first group of compounds of euphane (20β-H) type to be reported from Meliaceae. In line with the suggestion (1) that kulinone might represent a variant in the proposed biogenetic pathway between euphane or tirucallane precursors and limonoid derivatives, the novel euphane lactones described here would indicate that side chain metabolism can follow oxygenation at C-16, prior to the oxidative rearrangement steps of the original proposal (7).

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[7] We thank Dr. W. O. Godtfredsen for ir and nmr spectra of this compound. This compound has a lactone carbonyl absorption at 5.64μ, and the nmr signal for the C-16 proton is nearly identical with the corresponding signal of 1b in all respects. (The C-16 H signal of 1b is merged with the C-24 H olefinic signal; however, in the 24,25-dihydro derivative of 1b the C-16 proton signal is seen clearly). The C-16 H of kulactone has a chemical shift 0.90 ppm upfield from that of the epi compound, and differs appreciably in band width and splitting pattern.

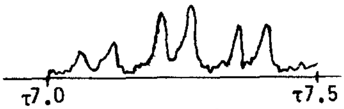
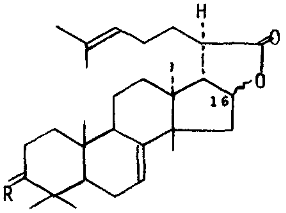
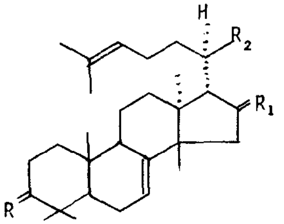


Figure 1

Partial nmr spectrum of kulinone between τ7.0 and 7.5 [100 Mc, $CDCl_3$ (TMS)]



	R	C-16
1a	=0	β-0-
1b	=0	α-0-
2a	H,α-OH	β-0-
2b	H,β-OH	β-0-



	R	R_1	R_2
3a	=0	H,β-OH	$-CH_3$
3b	=0	H,α-OH	$-CH_3$
4	=0	H,β-OH	$-COOCH_3$
5a	$-OCH_2$ $-OCH_2$	H,β-OH	$-CH_2OH$
5b	$-OCH_2$ $-OCH_2$	H,α-OH	$-CH_2OH$
6	=0	=0	$-COOCH_3$
7	$-OCH_2$ $-OCH_2$	=0	$-CH_2OC\Phi_3$

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