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1α, 19-DIHYDROXY-16α-(-)-KAURAN-17-OIC ACID

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The configuration of the grayanotoxin skeleton (1) may be rationalised as arising by a Wagner-Meerwein rearrangement of a 1α-hydroxy-(-)-kaurane. The validity of such a process has been demonstrated recently in the triterpene series (2). Hitherto, no 1-hydroxy-(-)-kaurane derivatives have been reported and we now wish to describe evidence for such a structure.

Further separation of the diterpene acids of Ricinocarpus stylosus (3) has given a dihydroxy-acid (I), $C_{20}H_{32}O_4$,* m.p. 259-260°, $[\alpha]_D^{24}$ -56° (ethanol). The acid is methylated readily under Fischer-Speier conditions and the ester easily saponified, indicating an unhindered acid group. The primary and secondary hydroxyl groups of (I) are oxidised by prolonged treatment with 8N.CrO_3/H_2SO_4 in acetone to the keto-diacid (III), $C_{20}H_{28}O_5$, m.p. 257-259°, $[\alpha]_D^{25}$ -176° (ethanol), ($\lambda_{max.}^{EtOH}$ 295 mμ, ε 31).

The N.M.R. spectra** of the methyl ester of (I) and the diacetate (II), $C_{24}H_{36}O_6$, m.p. 147-149°, $[\alpha]_D^{24}$ -40° (chlf.) suggested a kaurane nucleus (3b) for (I) with an axial 4-CH_2OH group, a 16-carboxyl group and a secondary equatorial hydroxyl function. In particular the diacetate (II) showed its methylene quartet, due to the axial 4-CH_2OAc group, centered at 5.94τ

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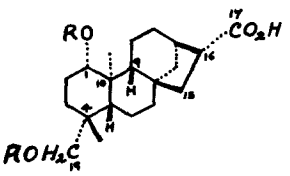
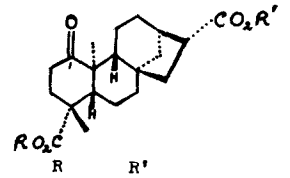
* Satisfactory analyses were obtained for all compounds described in this paper.

** N.M.R. spectra were measured at 60 mc/sec for $CDCl_3$ or $CHCl_3$ solutions containing Me_4Si as internal standard.

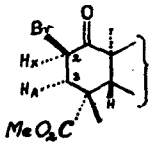


I R = H

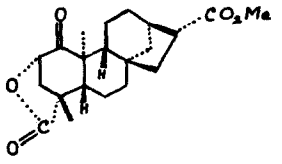
II R = Ac



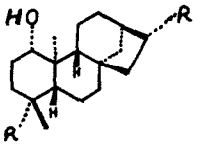
	R	R'
III	H	H
IV	CH_3	CH_3
V	H	CH_3



VI



VII

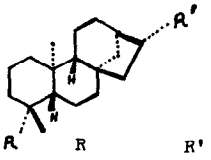


VIII R = CH_2OH

IX R = CH_2OTs

X R = CH_2SCH_2Ph

XI R = CH_3



	R	R'
XII	CO_2Me	CO_2Me
XIII	CH_2OH	CO_2Me
XIV	CH_3	CH_3
XV	CH_2OAc	CH_2OAc
XVI	CO_2H	CO_2Me

(J = 11 c.p.s.) characteristic of this group (3). The secondary equatorial acetoxyl group showed its axial-H as a triplet at 5.42τ ($W_{\frac{1}{2}}$ = 14 c.p.s.).*

Absence of a β-ketoacid function in (III) followed from its failure to decarboxylate in refluxing pyridine or at the melting point. Wolff-Kischner reduction of (III) and methylation gave dimethyl 16α-(-)-kauran-17,19-dioate (XII) of established configuration (3). Similarly, the ketodimethyl ester (IV), $C_{22}H_{32}O_5$, m.p. 139-140°, $[\alpha]_D^{24}$ -165° (chlf.), ($\nu_{max.}^{CS_2}$ 1732 and 1707 cm^{-1}) was converted to its ethylene thioketal, $C_{24}H_{36}O_4S_2$, m.p. 161-162°, which gave (IV) with hydrochloric acid in hot methanol-dioxan and (XII) by desulphurization with Raney nickel.

Monobromination of the ketodiester (IV) in acetic acid gave the equatorial bromoketone (VI), $C_{22}H_{31}O_5Br$, m.p. 207-208°, $[\alpha]_D^{25}$ -140° (chlf.), ($\lambda_{max.}^{EtOH}$ 292 mμ, ε 31; $\nu_{max.}^{CS_2}$ 1734 cm^{-1}). The N.M.R. spectrum of (IV) showed quartets (175, 181, 188 and 194 c.p.s.) and (324, 330, 337 and 343 c.p.s.) centered at 6.92τ and 4.44τ due to the A and X protons of an AEX system, which were assigned to the 3α- and 2α-hydrogens respectively. The observed splittings in the quartets correspond well with those in analogous systems (4,5). In the kaurane skeleton an AEX pattern for the axial-H of the α-bromoketone can only arise from a 2-bromo-1-ketone or a 2-bromo-3-ketone. Evidence described above eliminates the latter possibility and this is supported by the non-identity of the triol (VIII), $C_{20}H_{34}O_3$, m.p. 165-166°, $[\alpha]_D^{24}$ -24° (ethanol), obtained from (I) by reduction of its methyl ester with $LiAlH_4$, with the known 16α-(-)-kauran-3α,17,19-triol (6) and by the failure of (I) to form an ethylidene derivative and the absence of any intramolecularly hydrogen bonded hydroxyl in the infrared spectrum (CS_2) of the methyl ester of (I) (7).

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* Half-height widths were measured at maximum resolution.

Treatment of the α-bromoketone (VI) with refluxing sym-collidine gave a mixture from which was isolated a small proportion of the γ-lactone (VII), $C_{21}H_{28}O_5$, m.p. 244-245°, $[\alpha]_D^{24}$ -96° (chlf.). The infrared (CS_2) carbonyl absorptions at 1800 (γ-lactone), 1739 (ester) and 1725 (ketone) cm^{-1} are as expected for this system (8). The formation of a γ-lactone requires a 1:4-relation of the carbonyl to the carboxyl group. The N.M.R. spectrum of (VII) showed the 2-H as a multiplet at 5.35τ.

TABLE I

Chemical Shifts (τ values) of Methyl Groups in Kaurane Derivatives

Compound	Substituents		4-Methyl	10-Methyl
	4-Axial	1		
XIII	CH_2OH	H	9.04	9.01
Methyl Ester of I	CH_2OH	OH(α)	9.07	8.91
XIV*	CH_3	H	9.15, 9.19	8.99
XI*	CH_3	OH(α)	9.19, 9.20	8.88
XV	CH_2OAc	H	9.06	8.97
II	CH_2OAc	OAc(α)	9.06	8.79
XVI	CO_2H	H	8.77	9.07
V	CO_2H	=O	8.68	8.64
XII	CO_2Me	H	8.83	9.18
IV	CO_2Me	=O	8.78	8.78
VII	CO_2R	=O	8.76	8.49

* 16α-Methyl, 9.09 (doublet, J = 7 c.p.s.)

Other evidence consistent with oxygenation at the 1-position lies in the N.M.R. methyl signals of the various compounds (Table I) as compared with analogous kaurane compounds lacking 1-substitution (3b). In particular, the deshielding of the 10-methyl by the 1-ketone is similar to that observed in the 1-ketosteroids (9). The γ-lactone (VII) has its 10-methyl deshielded still further by the lactone ring. These results (Table I) confirm the previous assignments (3b) of the methyl signals in 16α-(-)-kaurane (XIV) and its derivatives.

Prolonged oxidation of the methyl ester of (I) with 8N.CrO_3/H_2SO_4 in acetone gave the ketoacid-methyl ester (V), $C_{21}H_{30}O_5$, m.p. 196-198°, $[\alpha]_D^{24}$ -165° (chlf.), ($\nu_{max.}^{CS_2}$ 1736, 1707 and 1698 cm^{-1}). The acid had a pK^*_{mcs} value (10) of 7.50 which has been decreased by the 1-ketone dipole from that observed (8.52) for (XVI) (3).

Partial tosylation of the triol (VIII) gave the ditosylate (IX), $C_{34}H_{46}O_7S_2$, m.p. 158-159° (decomp.), $[\alpha]_D^{24}$ -30° (chlf.). Treatment of (IX) with sodium benzylmercaptide in dimethylformamide at 100° (3) gave the dibenzylthioether (X) which was desulphurized with Raney nickel to give 16α-(-)-kauran-1α-ol (XI), $C_{20}H_{34}O$, m.p. 129-130°, $[\alpha]_D^{24}$ -42° (chlf.). The α-configuration at the 1-position in these compounds is based on the N.M.R. pattern of the axial 1-H in the diacetate (II), the triacetate of the triol (VIII), $C_{26}H_{40}O_6$, m.p. 101-102°, $[\alpha]_D^{24}$ -27° (chlf.), and the kauranol (XI). In the triacetate of (VIII) and in (XI) the 1-H appears as triplets centered at 5.45τ and 6.70τ respectively with half-height widths of 14.5 c.p.s. and 16.5 c.p.s. respectively.

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