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SOME NEW METABOLITES OF *GIBBERELLA FUJIKUROI* AND THE STEREOCHEMISTRY OF (-)-KAURENE

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IN view of current interest[1-4] in the tetracyclic diterpenes we report our work on six new metabolites of *Gibberella fujikuroi*. This led independently to the stereochemistry (I) for (-)-kaurene in agreement with that recently proposed by Djerassi, Mosettig, Briggs and their co-workers.[4b] We have isolated (-)-kaurene[1,5] (m.p. 50-50.5°, $[\alpha]_D^{20}$ -80°) and the related (-)-kauranol[*6] (m.p. 214-216°, $[\alpha]_D^{22}$ -45°), the new lactones 7-hydroxykaurenolide (III) $C_{20}H_{28}O_3$ [m.p. 187-188°, $[\alpha]_D^{22}$ -25°, $\nu_{max}^{CHCl_3}$ ~3595, 3495 (OH), 1767 (γ-lactone), 1656 and 888 (=CH_2) cm^{-1}] and 7,18-dihydroxykaurenolide (IV)

[1a] L.H. Briggs, B.F. Cain, B.R. Davis and J.K. Wilmhurst, *Tetrahedron Letters* No. 8, 8 (1959);

[b] L.H. Briggs, B.F. Cain, R.C. Cambie and B.R. Davis, *Ibid.* No. 24, 18 (1960).

[2] P.K. Grant and R. Hodges, *Tetrahedron* **8**, 261 (1960); R. Henderson and R. Hodges, *Ibid.* **11**, 226 (1960).

[3] F. Dolder, H. Lichti, E. Mosettig and P. Quitt, *J. Amer. Chem. Soc.* **82**, 246 (1960).

[4a] H. Vorbruggen and C. Djerassi, *Tetrahedron Letters* No. 3, 119 (1961);

[b] C. Djerassi, P. Quitt, E. Mosettig, R.C. Cambie, P.S. Rutledge and L.H. Briggs, *J. Amer. Chem. Soc.* **83**, 3720 (1961).

[5] L.H. Briggs and R.W. Cawley, *J. Chem. Soc.* 1888 (1948).

[6] J.K. McGimpsey and J. Murray, *J. Appl. Chem.* **10**, 340 (1960).

[*] Identified by comparison with an authentic sample of (+)-kauranol, for which we are indebted to the late Dr. J. Murray.

$C_{20}H_{28}O_4$ [m.p. 211-214°, $[\alpha]_D^{24}$ -37°, $\nu_{max}^{CHCl_3}$ 3591, 3397 (OH), 1756 (γ-lactone), 1657 and 884 (=CH_2) cm^{-1}] and the anhydrides fujenal (VI) $C_{20}H_{26}O_4$* [m.p. 169-170°, $[\alpha]_D^{26}$ -74°, ν_{max} 2730 and 1725 (-CHO), 1855 and 1781 (5-ring anhydride) and 1654 (C=C) cm^{-1}] and fujenoic acid (VII) $C_{20}H_{26}O_5$ [m.p. 205-206° or 221-224°, $[\alpha]_D^{25}$ -59°, $\nu_{max}^{CHCl_3}$ 2609, 1859, 1783, 1699, 1662 and 897 cm^{-1}] from the culture filtrates of <u>G. fujikuroi</u>.

The carbon skeleton of the kaurenolides has been established by converting α-dihydro-7-hydroxykaurenolide (VIII) m.p. 142-144°, to α-dihydro-(-)-kaurene (XIV) m.p. 85-86°, $[\alpha]_D^{26}$ -33°,[5] by the following sequence which precludes epimerization at ring junctions:-

$$\begin{tikzcd}
\mathrm{VIII} \arrow[r, "CrO_3/H_2SO_4", "Me_2CO"'] & \mathrm{IX} \arrow[r, "Zn/CH_3CO_2H"] & \mathrm{X} \arrow[r, "\text{Wolff-Kishner}"] & \mathrm{XI} \arrow[dl, "1.\ CH_2N_2", "2.\ LiAlH_4"'] \\
\mathrm{XIV} & \mathrm{XIII} \arrow[l, "\text{Wolff-Kishner}"'] & \mathrm{XII} \arrow[l, "CrO_3/H_2SO_4"', "Me_2CO"] &
\end{tikzcd}$$

The infra-red spectrum of the keto-lactone (IX), m.p. 264° dec., ν_{max}^{Nujol} 1773 (γ-lactone) and 1702 (6-ring C=O) cm^{-1}, showed that the hydroxyl group in 7-hydroxykaurenolide is secondary and attached to a 6-membered ring whilst NMR spectra and other data suggested that 7-hydroxykaurenolide and 7,18-dihydroxykaurenolide differed only in that the latter contained a hydroxymethyl group in place of a methyl group in the former.

Lithium aluminium hydride reduction of 7,18-dihydroxykaurenolide monotosylate [shown to be (V)], and of (III) gave the same triol (XVII), m.p. 207-210° or 216-218°, thus confirming this relationship and showing that the $-CH_2OH$ group must be located at either C-4 or C-10. Oxidation of 7,18-dihydroxykaurenolide with $8N.CrO_3/H_2SO_4$ in acetone gave the acid (XX)

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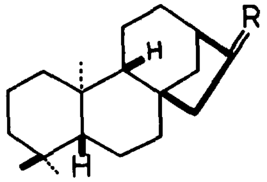
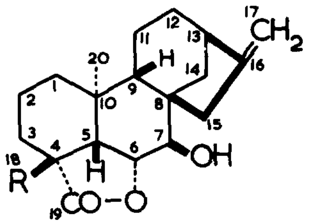
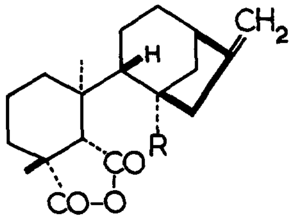
* First isolated and characterized by P.J. Curtis, J.F. Grove and A. Morrison, personal communication.



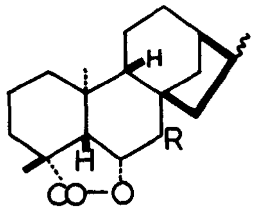
I $R=CH_2$
II $R=O$



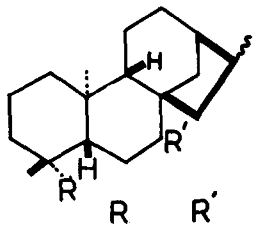
III $R=Me$
IV $R=CH_2OH$
V $R=CH_2OTs$



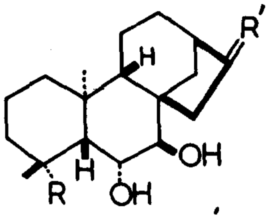
VI $R=CHO$
VII $R=CO_2H$



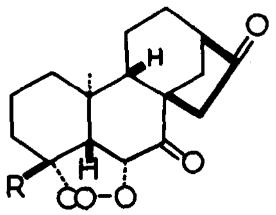
VIII $R=H, OH$
IX $R=O$



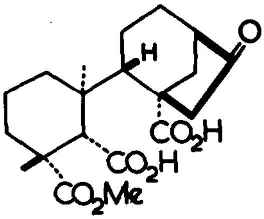
	R	R′
X	CO_2H	O
XI	CO_2H	H_2
XII	CH_2OH	H_2
XIII	CHO	H_2
XIV	Me	H_2
XV	CH_2OH	H,OH
XVI	CO_2Me	O



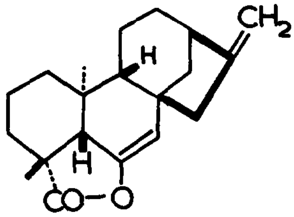
	R	R′
XVII	CH_2OH	CH_2
XVIII	CO_2Me	O
XIX	CO_2Me	H, Me



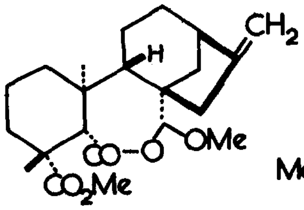
XX $R=CO_2H$
XXI $R=H$
XXII $R=CO_2Me$



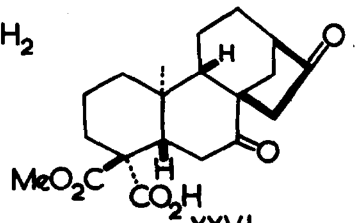
XXIII



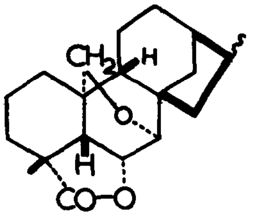
XXIV



XXV



XXVI



XXVII

which readily decarboxylated giving (XXI), m.p. 273-276°, $\nu_{max}^{CHCl_3}$ 1789 (γ-lactone), 1749 (5-ring C=O) and 1727 (6-ring C=O) cm^{-1}. Since the secondary hydroxyl group common to both kaurenolides is in ring B (see below), (XX) cannot be a β-keto acid, and to explain the decarboxylation both the $-CH_2OH$ and the lactone carbonyl group must be placed at C-4. The other end of the γ-lactone ring can then be attached to either C-2 or C-6.

Degradation of (III) by ozonolysis followed by mild alkaline hydrolysis and methylation of the product gave the diol (XVIII) m.p. 205-209°. Oxidation of (XVIII) with $8N.CrO_3/H_2SO_4$ in acetone gave, <u>inter alia</u>, the dicarboxylic acid (XXIII), m.p. 172-173° dec. then 215°, and a gummy diosphenol which can only be derived from 6,7-diol because its ultra-violet spectra (λ_{max}^{EtOH} 281 mμ ε 9,400; $\lambda_{max}^{EtOH-NaOH}$ 333-337 mμ) show[7] that the olefinic double bond is exocyclic and tetrasubstituted. Furthermore the formation of the enol-lactone (XXIV; m.p. 205-206°, ν_{max}^{Nujol} 1793, 1693, 1655, 871 and 826 cm^{-1}) on treatment of the tosylate of (III) with collidine is stereochemically improbable[8] from a 19 ⟶ 2-lactone. Hence 7-hydroxykaurenolide and 7,18-dihydroxykaurenolide are assigned the 19 ⟶ 6-lactone structures (III) and (IV) respectively.

Treatment of fujenal with methanol at 160° for 4 days gave the methyl ester pseudoester (XXV), m.p. 190°, which on ozonolysis, hydrolysis and oxidation afforded the dicarboxylic acid (XXIII) previously obtained from (III). Consequently fujenal has been assigned structure (VI) and since oxidation of fujenal gave fujenoic acid, the latter has structure (VII).

We have confirmed that (-)-kaurene nor-ketone[1b] (II) shows a positive Cotton effect similar to that of phyllocladene nor-ketone[9] so that the

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[7] <u>cf</u>. L. Dorfmann, <u>Chem. Rev.</u> <u>53</u>, 83 (1953).

[8] <u>cf</u>. W. Cocker, B.E. Cross, S.R. Duff, J.T. Edward and T.F. Holley, <u>J. Chem. Soc.</u> 2540 (1953).

[9] C. Djerassi, M. Cais and L.A. Mitscher, <u>J. Amer. Chem. Soc.</u> <u>81</u>, 2386 (1959).

absolute configuration of the C-15, C-16 bridge is β. Of the eight possible configurations involving C-5, C-9 and C-10 one is that of phyllocladene[1,2,10] leaving seven possibilities - four A/B *cis* and three A/B *trans* - to be considered for (-)-kaurene.

The orientation of the lactone carbonyl was determined in two ways. Firstly, either the C-19 hydroxymethyl in (XV), derived from the lactone carbonyl group, or the C-18 hydroxymethyl in (IV) must be axial. On lithium aluminium hydride reduction of the ditosylate of (XV) and the monotosylate (V) under identical conditions the former gave (XII) by hydrolysis at C-19 whilst the latter was hydrogenolysed at C-18. By analogy with, for example, voucapenic and vinhatacoic acid[11] derivatives it is concluded that in the kaurenolides the lactone carbonyl is axial. Secondly, the acids (XX) and (XXVI) - the carboxyl group of the latter being derived from the lactone of (XX) by hydrogenolysis of (XXII) with zinc and acetic acid - have pK_{H_2O} values of 2.81 and 4.36 respectively showing that (XXVI) has the more hindered carboxyl group.

Mild alkaline hydrolysis of β-dihydro-7-hydroxykaurenolide (VIII), m.p. 226-228°, followed by methylation gave the diol methyl ester (XIX) in 95% yield; however, similar treatment of the 7-epimer, m.p. 128-129°, of VIII, prepared by sodium borohydride reduction of (IX), gave only 60% of the corresponding diol methyl ester and 30% of the 7-keto-ester (XVI). Dehydration under these conditions strongly suggested a *trans* diaxial arrangement of the hydrogen atom at 7 and the hydroxyl group at 6 in the 7-epi-alcohols. Hence in 7-hydroxykaurenolide itself the 6- and 7-oxygen substituents are both axial and ring B has a chair conformation. This conclusion was supported when it was found that (i) the rate of elimination

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[10] R.B. Turner and K.H. Ganshirt, *Tetrahedron Letters* No. 7, 231 (1961).

[11] F.E. King, D.H. Godson and T.J. King, *J. Chem. Soc.* 1117 (1955).

of p-toluenesulphonic acid from the 7- and 7-epi-tosylates with collidine showed little difference, i.e. in neither case is the relationship between the ester group and the α-hydrogen atom diaxial and trans, and (ii) the diol (XVIII) was stable to periodate whilst its 7-epimer reacted readily. Furthermore, the keto-ester (XVI) showed a strong positive Cotton effect (amplitude +124°) in agreement with the octant rule[12] whilst the keto-lactone (IX) showed a small negative effect suggesting that the lactone comes axially into a negative octant on closing and is therefore α-oriented.

Lead tetraacetate oxidation of the 7-epi-alcohol (VIII) gave as a minor product an ether, (XXVII) in which as shown by the NMR spectrum the methyl group at C-10 had reacted, ring B being forced into a boat.[13] Hence the angular methyl group must lie on the same side of the molecule (α) as the 7-epi-hydroxyl group.

The four A/B *cis* formulations preclude a diaxial lactone whilst of the three A/B *trans* structures only one, viz. 5β, 9β, 10α, permits ring B to exist as a chair. Hence we conclude that 7-hydroxykaurenolide and (-)-kaurene have the absolute configurations (III) and (I) respectively.

Supporting evidence for the structures and absolute stereochemistry assigned to these compounds will be published in full.

We thank Mr. J.F. Grove and our colleagues for helpful discussions.

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[12] W. Moffitt, R.B. Woodward, A. Moscowitz, W. Klyne and C. Djerassi, *J. Amer. Chem. Soc.* **83**, 4013 (1961).

[13] *cf*. H. Immer, M.L. Mihailovic, J. Schaffner, D. Arigoni and O. Jeger, *Experientia* **16**, 530 (1960); D. Dvornik and O.E. Edwards, *Tetrahedron* **14**, 54 (1961).