546. *New Metabolites of* Gibberella fujikuroi. *Part III.*[1] *The Structure of 7-Hydroxykaurenolide.*

By B. E. Cross, R. H. B. Galt, and J. R. Hanson.

Stepwise deoxygenation of 7-hydroxykaurenolide gives (−)-kaurane. On the basis of this relationship and other evidence the structure of 7-hydroxykaurenolide has been determined. The absolute configurations of 7-hydroxykaurenolide and (−)-kaurene have been shown to be 6α,7β-dihydroxy-(−)-kaur-16-en-19-oic acid 19→6α-lactone (II) and (XIX; R = :CH_2), respectively.

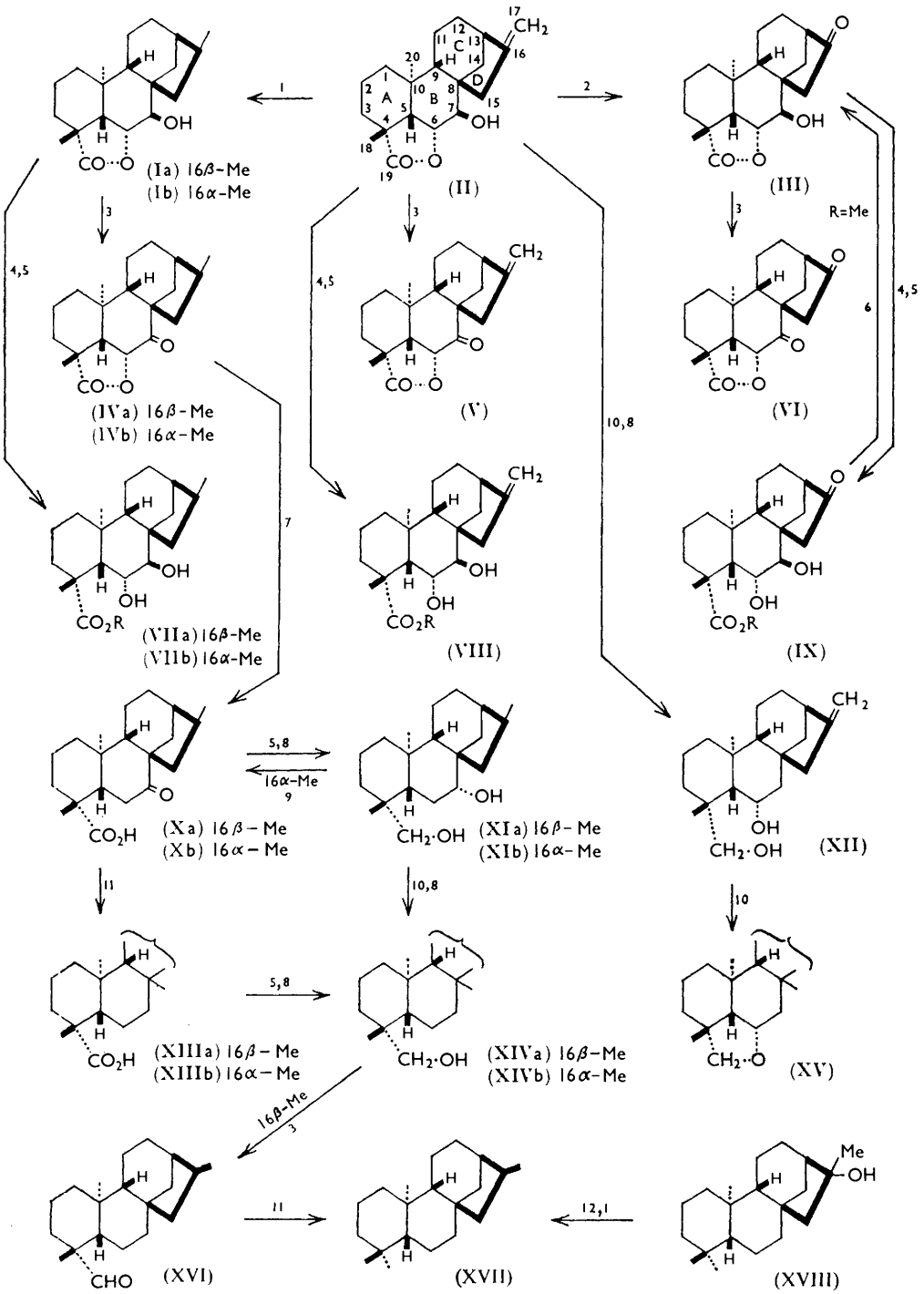
The isolation of a number of new C_{20} metabolites of *Gibberella fujikuroi* which include 7-hydroxy-, 7,18-dihydroxy-, and 7,16,18-trihydroxy-kaurenolide, fujenal, and fujenoic acid has been described in Part II,[1] and evidence for their structures and absolute configurations has been briefly reported.[2] The structures of these metabolites have all been related [2,3] to that of 7-hydroxykaurenolide which is therefore the key compound in this series. The present paper describes the work on 7-hydroxykaurenolide.

7-Hydroxykaurenolide (II), $C_{20}H_{28}O_3$, occurs in polymorphic forms both having m. p. 187—188°, $[\alpha]_D^{22}$ −25°, but with distinct infrared spectra as Nujol mulls. In chloroform solution both forms gave identical spectra showing absorption attributed to hydroxyl (3595 and 3495 cm.$^{-1}$), γ-lactone (1765 cm.$^{-1}$), and exocyclic methylene (1656 and 888 cm.$^{-1}$) groups. Nuclear magnetic resonance spectroscopy revealed the presence of two tertiary methyl groups (singlets at τ 9·13 and 8·72). On hydrogenation 7-hydroxykaurenolide took up one mol. of hydrogen and gave a mixture of epimers which on chromatography and fractional crystallisation gave pure β-dihydro-7-hydroxykaurenolide (Ib), $C_{20}H_{30}O_3$, m. p. 226—228°. Separation of the more soluble α-dihydro-epimer (Ia) was difficult and the best samples contained 5—10% of the β-dihydro-compound. However, it is believed that the degradation products of α-dihydro-7-hydroxykaurenolide described below are pure compounds with the exception of the 7-keto-compound (IVa) which is known to contain a small amount of the 16-epimer. With perbenzoic acid 7-hydroxykaurenolide gave a single monoepoxide, $C_{20}H_{28}O_4$; α-dihydro-7-hydroxykaurenolide showed only weak absorption in the ultraviolet region, at 200 mμ. 7-Hydroxykaurenolide is therefore tetracarbocyclic.

The methylene group was shown to be exocyclic to a 5-membered ring by ozonolysis of 7-hydroxykaurenolide to formaldehyde (0·6 mol.) and the nor-ketone, $C_{19}H_{26}O_4$ (III), which in chloroform solution showed $\nu_{max.}$ 1772 (γ-lactone) and 1740 cm.$^{-1}$ (cyclopentanone). With 5% sulphuric acid the double bond was isomerised to the trisubstituted (*i.e.*, 15,16) position [4] as shown by its infrared spectrum ($\nu_{max.}$ 828 cm.$^{-1}$).

7-Hydroxykaurenolide readily formed a monoacetate, $C_{22}H_{30}O_4$, and a monotoluene-*p*-sulphonate, $C_{27}H_{34}O_5S$, neither of which showed hydroxyl absorption in the infrared spectrum. Oxidation of 7-hydroxykaurenolide, its dihydro-derivatives (Ia) and (Ib), and the nor-ketone (III) in acetone with 8N-chromic oxide in sulphuric acid gave the ketones (V), (IVa), (IVb), and (VI), respectively, which all showed new infrared absorption in chloroform solution in the range 1700—1720 cm.$^{-1}$ corresponding to a cyclohexanone carbonyl group. Thus the hydroxyl group is secondary and attached to a 6-membered ring. The γ-lactone ring was stable to alkali at room temperature but was opened by boiling dilute alkali without rearrangement. Thus the dihydroxy-acid $C_{19}H_{28}O_5$ (IX; R = H), obtained from the nor-ketone (III), gave a methyl ester (IX; R = Me) which on pyrolysis at 240° quantitatively regenerated the parent nor-ketone.

[1] Part II, Cross, Galt, Hanson, Curtis, Grove, and Morrison, preceding paper.
[2] Cross, Galt, Hanson, and Klyne, *Tetrahedron Letters*, 1962, 145.
[3] Cross, Galt, and Hanson, unpublished work.
[4] Cf. Briggs, Cawley, Loe, and Taylor, *J.*, 1950, 955.



1, H_2—Pd. 2, O_3. 3, CrO_3—H_2SO_4. 4, OH^-. 5, CH_2N_2. 6, At 240°. 7, Zn—HOAc. 8, $LiAlH_4$. 9, CrO_3,$2C_5H_5N$. 10, Toluene-*p*-sulphonyl chloride. 11, Wolff–Kishner. 12, $POCl_3$–C_5H_5N.

Attempts to dehydrogenate the dihydroxy-acid (IX; R = H) with selenium gave mainly the lactone (III) and only traces of aromatic compounds although the presence of a phenanthrene derivative in the latter was indicated by the ultraviolet spectrum. In view of the failure of other similar experiments this approach to the carbon skeleton was abandoned. The co-occurrence of 7-hydroxykaurenolide with (—)-kaurene (XIX; R = CH_2) suggested that they might have a common ring system and it was decided to carry out a stepwise removal of the oxygen from the former. Several attempts to achieve this were unsuccessful. Thus, although reduction of 7-hydroxykaurenolide toluene-*p*-sulphonate by lithium aluminium hydride gave the diol (XII), treatment of the latter with toluene-*p*-sulphonyl chloride gave a compound $C_{20}H_{30}O$ assumed to be the ether (XV). Further difficulties were encountered in attempts to deoxygenate the keto-acids (Xa) and (Xb) which were derived from the α- and β-dihydro-keto-lactones (IVa) and (IVb), respectively, by use of zinc dust in acetic acid. Methylation of the keto-acids followed by reduction with lithium aluminium hydride gave the diols (XIa) and (XIb) in which the 7-hydroxyl group is assumed to be α-oriented by analogy with the products obtained from 7-keto-lactones by reduction with sodium borohydride (see below). However, oxidation of the β-dihydro-diol (XIb) with the chromic oxide–pyridine reagent gave a mixture from which the keto-acid (Xb) but none of the desired keto-aldehyde was isolated; with shorter reaction times much of the diol was recovered. Although the acid (XIIIb) was obtained by Wolff–Kishner reduction of the β-dihydro-keto-acid (Xb) attempts to reduce its acid chloride by the Rosenmund reaction failed to give the desired aldehyde, but yielded a small amount of a compound believed to be the intermolecular anhydride. Methylation of the acid (XIIIb) followed by reduction with lithium aluminium hydride gave the mono-alcohol (XIVb) identical in physical constants with the alcohol obtained from steviol by Mosettig *et al.*[5a] Owing to shortage of material the deoxygenation of the dihydro-kaurenolides was completed only in the α-dihydro-series. The α-dihydro-diol (XIa) gave a di-toluene-*p*-sulphonate which on reduction with lithium aluminium hydride gave the monoalcohol (XIVa) together with some of the starting diol. The monoalcohol, obtained in better yield from (XIIIa) by the route used to prepare its epimer (XIVb), was oxidised by chromic oxide in acetone–sulphuric acid to the aldehyde (XVI). Wolff–Kishner reduction then gave (—)-kaurane [α-dihydro-(—)-kaurene][6] (XVII), identical with a specimen prepared from (—)-kauranol.[1]

The elegant work of Mosettig, Djerassi, and their collaborators[5] on the inter-relations of garryfoline, steviol, and (—)-kaurene has shown that the 16-methyl group in (—)-kaurane is β-oriented and hence the absolute configurations at C-16 shown in the chart can be assigned to the dihydro-derivatives of 7-hydroxykaurenolide and their degradation products.

Since the above degradative sequence precluded epimerisation at ring junctions it not only completely established the carbon skeleton of 7-hydroxykaurenolide but also related its stereochemistry at positions 5, 8, 9, 10, and 13 to that of (—)-kaurene. The stereochemistry of the latter was, however, uncertain at the time this work was in progress.[7,8]

The position of the oxygen atoms in 7-hydroxykaurenolide must now be considered. The hydrogenolysis of the keto-lactones (IVa and b) referred to above and the preparation of the ester (XX; R = Me, R′ = CO_2Me, R″ = O) from the lactone (VI) under the same conditions implied the presence of an acylated α-glycol system in 7-hydroxykaurenolide and this was confirmed by some revealing oxidation experiments. The β-dihydro-diol

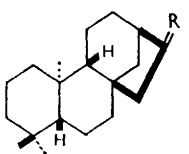
[5] (*a*) Mosettig, Quitt, Beglinger, Waters, Vorbrueggen, and Djerassi, *J. Amer. Chem. Soc.*, **1961**, **83**, 3163; (*b*) Vorbrueggen and Djerassi, *ibid.*, 1962, **84**, 2990.

[6] Briggs and Cawley, *J.*, 1948, 1888; Briggs, Cain, Cambie, Davis, Rutledge, and Wilmshurst, *J.*, 1963, 1345.

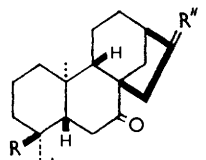
[7] Briggs, Cain, Davis, and Wilmshurst, *Tetrahedron Letters*, 1959, No. 8, 8.

[8] Briggs, Cain, Cambie, and Davis, *Tetrahedron Letters*, 1960, No. 24, 18.

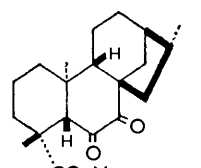
ester (VIIb; R = Me) with chromic oxide–sulphuric acid in acetone gave a yellow α-diketone, $C_{21}H_{30}O_4$ (XXI), ($\lambda_{max.}$ 280 mμ, ε 790), a gummy diosphenol [$\lambda_{max.}$ 281 mμ, ε 8100; $\lambda_{max.}$ (in EtOH–NaOH) 333—337 mμ], and a dibasic acid, $C_{21}H_{32}O_6$ (XXII; R = R′ = CO_2H, R″ = β-H, α-Me). When kept in alkaline solution the α-diketone gave the ultraviolet absorption of the diosphenol. A similar oxidation of the nor-ketone diol ester (IX; R = Me) afforded a gummy diosphenol and a dibasic acid, $C_{20}H_{28}O_7$, (XXII; R = R′ = CO_2H, R″ = O). The formation of a hydroxyl-free (infrared spectrum) α-diketone and of the dibasic acids established the presence of a disecondary α-glycol. The above diosphenols could not be obtained crystalline, but alkaline hydrolysis of the keto-lactone (IVa) gave the crystalline diosphenol-acid (XXIII; R = H) which showed $\lambda_{max.}$ 280 mμ (ε 10,200). Methylation of this acid gave a gummy ester (XXIII; R = Me) identical in the infrared spectrum with gummy diosphenols obtained (*a*) as the major product of oxidation of the α-dihydro-diol ester (VIIa; R = Me) and (*b*) by methylation of the lactol (XXIV) which resulted from chromic oxide oxidation of the α-dihydro-diol acid (VIIa; R = H). The ultraviolet absorption spectra of the diosphenols showed [9] that the



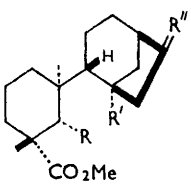
(XIX)



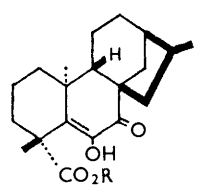
(XX)



(XXI)



(XXII)



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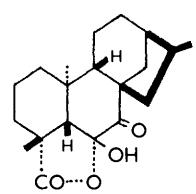


(XXIV)

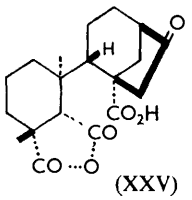
olefinic double bond was exocyclic and tetrasubstituted. The chromophore must therefore be situated in ring B or C. The latter was excluded because the keto-dicarboxylic acid (XXII; R = R′ = CO_2H, R″ = O) is not a β-keto-acid. On treatment with boiling water it was not decarboxylated but gave fujenoic acid nor-ketone (XXV).[3] Supporting evidence for the conclusion that the oxygen substituents are at positions 6 and 7 would be provided by converting the nor-ketone (III) or the related keto-ester (IX; R = Me) into the 7,15,16-triketo-compounds, *i.e.*, into β-diketones. However, a number of attempts to introduce a substituent at position 15 in these compounds as the first stage in such a transformation were unsuccessful (they are reported in the Experimental part).

The lactone-carbonyl group can only be attached to either C-4 or C-10. The production of the enol-lactones (XXVI; R = :CH_2), $\nu_{max.}$ 1793, 1692, 1655, 871, and 826 cm.$^{-1}$ and (XXVI; R = β-H, α-Me) on treatment of the toluene-*p*-sulphonates of 7-hydroxykaurenolide and its β-dihydro-derivative, respectively, with boiling collidine show that the lactone-carbonyl group is situated at position 4 because enol-lactones derived from 20→6-lactones are sterically impossible. This conclusion is confirmed by the chemistry of 7,18-dihydroxykaurenolide.[3] Hence 7-hydroxykaurenolide has structure (II).

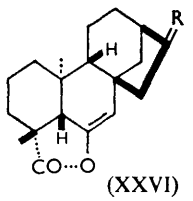
The stereochemistry of 7-hydroxykaurenolide and (—)-kaurene and, in particular, the relative stereochemistry of the vicinal oxygen substituents in ring B of the former can now be considered. Hydrogenolysis of the keto-lactones to 7-keto-acids (*e.g.*, IVa ⟶ Xa)

[9] Cf. Dorfman, *Chem. Rev.*, 1953, **53**, 83.

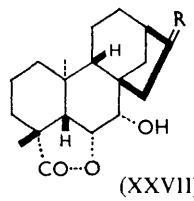
(see above) suggested that the 6-oxygen substituent was axial.[10] Reduction of the 7-keto-lactone (V) and its dihydro-derivatives (IVa) and (IVb) with sodium borohydride gave in 75—90% yield the corresponding 7-epi-alcohols (XXVII; R = :CH_2), (XXVIIIa), and



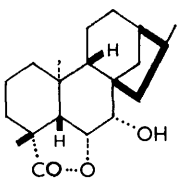
(XXV)



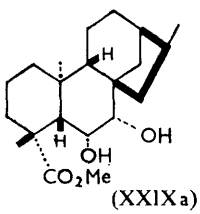
(XXVI)



(XXVII)

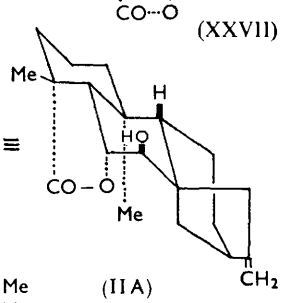


(XXVIIIa) 16β-Me
(XXVIIIb) 16α-Me



(XXIXa) 16β-Me
(XXIXb) 16α-Me

(II) ≡



(II A)

(XXVIIIb). Oxidation of the dihydro-7-epi-alcohols (XXVIIIa) and (XXVIIIb) regenerated the parent ketones. Thus attack of hydride ion took place almost exclusively from the less hindered face of the molecule (cf. IIa) to form, as will be shown in the sequel, the equatorial alcohols. The evidence set out below completely establishes the stereochemistry at positions 6 and 7. Alkaline hydrolysis of 7-hydroxykaurenolide, its α- and β-dihydro-derivatives (Ia and b), and the nor-ketone (III), followed by methylation of the products, gave the diol methyl esters (VIII; R = Me), (VIIa and b; R = Me) and (IX; R = Me) in high yield. However similar treatment of the corresponding 7-epihydroxy-lactones afforded diol-esters in only 60% yield. For example, the β-dihydro-7-epihydroxy-compound (XXVIIIb) gave the diol (XXIXb) together with a 30% yield of a keto-ester shown to be identical with the methyl ester of the 7-keto-compound (Xb). Similarly the 7-epihydroxy-lactone (XXVII; R = :CH_2), its α-dihydro-derivative (XXVIIIa), and the 7-epihydroxynor-ketone (XXVII; R = O) afforded the mixtures of diol- and 7-keto-esters (XXX; R = :CH_2) and (XX; R = Me, R′ = CO_2Me, R″ = :CH_2), (XXIXa) (XX; R = Me, R′ = CO_2Me, R″ = α-H, β-Me), and (XXX; R = O) and (XX; R = Me, R′ = CO_2Me, R″ = O), respectively. The formation of the 7-keto-compounds by dehydration under these conditions strongly suggested a *trans*-diaxial arrangement of the 7-hydrogen atom and the 6-hydroxyl group in the 7-epi-alcohols. This conclusion was supported when a study of the rate of formation of the enol-lactone (XXVI; R = β-H, α-Me) by elimination

TABLE 1.

Yield (%) of enol-lactone from 7-toluene-*p*-sulphonates.

Time of reflux (min.)	(Ib)	(XXVIIIb)
15	7	7
30	17	20
90	33	46
240	55, 60	70, 75

of toluene-*p*-sulphonic acid from the 7- and 7-epi-toluene-*p*-sulphonates derived from β-dihydro-7-hydroxykaurenolide showed little difference between the epimers (Table 1), *i.e.*, the relation between the 6-hydrogen atom and the ester grouping is not *trans* and

[10] Cf. Baird, Halsall, Jones, and Lowe, *Proc. Chem. Soc.*, **1961**, 257.

diaxial in either case. Confirmation was provided by the observations that the nor-ketone diol-ester (IX; R = Me) was stable to sodium periodate in methanol, whereas its 7-epimer (XXX; R = O) was cleaved to a compound $C_{20}H_{28}O_5$ shown to be the dialdehyde (XXII; R = R′ = CHO, R″ = O) by its nuclear magnetic resonance spectrum (two aldehydic protons, at τ +0·05 and −0·01) and by oxidation to the dicarboxylic acid (XXII; R = R′ = CO_2H, R″ = O). The nor-ketone diol (IX; R = Me) was also stable to lead tetra-acetate in benzene but addition of pyridine [11] reduced the steric requirement of the system so that oxidation occurred, giving the dialdehyde (XXII; R = R′ = CHO, R″ = O). Similarly the β-dihydro-diol (VIIb; R = Me) was stable to periodate but its 7-epimer (XXIXb) gave the dialdehyde (XXII; R = R′ = CHO, R″ = β-H, α-Me).

Finally, measurements of the hydroxyl absorption of the diol-esters (VIII; R = Me) and (IX; R = Me) and the corresponding 7-epimers (XXX; R = :CH_2) and (XXX; R = O) in dilute carbon tetrachloride solution (see Table 2) show that hydrogen bonding between the hydroxyl groups only occurs in the 7-epi-compounds.[12]

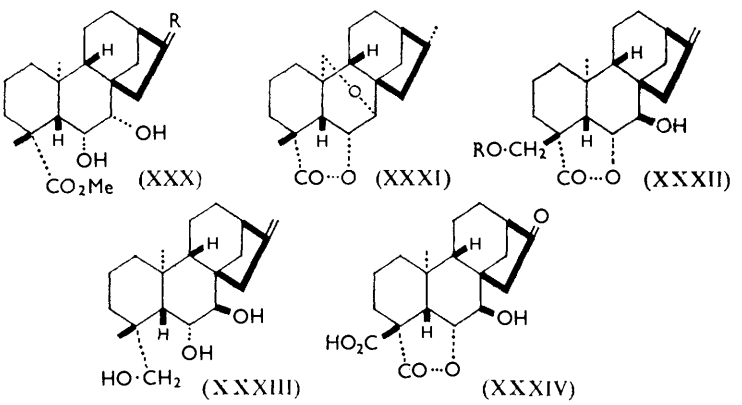
TABLE 2.

Compound	OH frequencies (cm.$^{-1}$)		$\Delta\nu$	Assignments at C-6 and C-7
VIII; R = Me	3623s	3455 *	—	Diaxial
IX; R = Me	3624s	3428 *	—	Diaxial
XXX; R = :CH_2	3609w, 3563s	3436 *	46	Axial-equatorial
XXX; R = O	3609w, 3565s	3422 *	44	Axial-equatorial

* 6-Hydroxyl hydrogen-bonded to ester-carbonyl.

The evidence presented above clearly establishes that the 6,7-oxygen substituents in 7-hydroxykaurenolide are diaxial and *trans* so that ring B must exist in the chair conformation.

The orientation of the angular 10-methyl group relative to the 7-hydroxyl group was established by prolonged oxidation of the β-dihydro-7-epihydroxy-lactone (XXVIIIb) with lead tetra-acetate in boiling benzene. The product consisted of unchanged material and a mixture of the β-dihydro-keto-lactone (IVb) and an ether, $C_{20}H_{28}O_3$. The nuclear magnetic resonance spectrum of the ether compared with that of the alcohol from which it was derived showed that the 10-methyl group had reacted and hence this ether was



assigned structure (XXXI) in which ring B had been forced into a boat form.[13] It follows that the angular methyl group must lie on the same side of the molecule as the 7-epi-hydroxyl group.

[11] Goldschmid and Perlin, *Canad. J. Chem.*, 1960, **38**, 2280.
[12] Kuhn, *J. Amer. Chem. Soc.*, 1952, **74**, 2492; 1954, **76**, 4323; Angyal and Young, *ibid.*, 1959, **81**, 5251.
[13] Cf. Immer, Mihailovic, Schaffner, Arigoni, and Jeger, *Experientia*, 1960, **16**, 530; Dvornik and Edwards, *Tetrahedron*, 1961, **14**, 54.

The evidence presented so far would allow either a diaxial 19→6-lactone or a skew 18→6-lactone although the ready relactonisation and ether formation (XII ⟶ XV) between the axial 6-hydroxyl group and substituents attached to C-4 favour the former. The 19→6-lactone formulation has been established in two ways. First, in the diol (XIa) the 19-hydroxymethyl group is derived from the lactone-carbonyl group of 7-hydroxykaurenolide, but in 7,18-dihydroxykaurenolide which has been shown [2,3] to have structure (XXXII; R = H) the hydroxymethyl group represents C-18. In one of these compounds the hydroxymethyl group must be axial. On reduction by lithium aluminium hydride of the ditoluene-*p*-sulphonate of the diol (XIa) and of the monotoluene-*p*-sulphonate (XXXII; R = *p*-$C_6H_4Me{\cdot}SO_2$) of 7,18-dihydroxykaurenolide, the former gave the monoalcohol (XIVa) by hydrolysis at position 19, whilst the latter has been shown to be hydrogenolysed at position 18 to give the triol (XXXIII).[2,3] By analogy with, for example, vouacapenic and vinhaticoic acid derivatives [14] it is concluded that the lactone-carbonyl group in 7-hydroxykaurenolide is axial. Secondly, the pK^*_{MCS} of the acid (XIIIa) like those of steviol derivatives,[5] lies in the range 8·4—8·9 and hence the correlation by Sommer, Arya, and Simon [15] indicates three 1,3-interactions. This requires the 19-carboxyl group to be axial. It should be noted that in the 6-keto-acid (XXXV; R = CO_2H, R′ = :CH_2) (see below) hydrogen-bonding with the keto-group weakens the acid so that its pK^*_{MCS} value is 9·25. Furthermore, two acids, namely, (XX; R = CO_2Me, R′ = CO_2H, R″ = O) and (XXXIV), have been prepared [2,3] from 7,18-dihydroxykaurenolide, the carboxyl group of the former being derived from the lactone-carbonyl group and that of the latter from the hydroxymethyl group in 7,18-dihydroxykaurenolide. The pK_{H_2O} values of these acids were 4·36 and 2·86, respectively, showing that the acid (XX; R = CO_2Me, R′ = CO_2H, R″ = O) has the more hindered, *i.e.*, axial, carboxyl group. It follows that in 7-hydroxykaurenolide the lactone is diaxial.

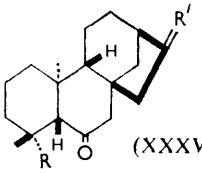
The absolute stereochemistry of 7-hydroxykaurenolide and of (—)-kaurene has been determined in the following way. The nor-ketones (III) and (IX; R = Me), derived from 7-hydroxykaurenolide, like (—)-kaurene nor-ketone [8] (XIX; R = O) show positive Cotton effects similar to that of phyllocladene nor-ketone,[16] so that the absolute configuration of the 15,16-bridge is β. Of the eight possible configurations involving the asymmetric centres 5, 9, and 10, one is that of phyllocladene.[17] Of the remainder, three possess a *trans*-A/B fusion and four a *cis*-A/B fusion. The latter preclude a diaxial lactone in the kaurenolides whilst only one, namely, (XIX; R = :CH_2) of the three A/B-*trans*-structures permits ring B to exist as a chair. Hence we conclude that 7-hydroxykaurenolide and (—)-kaurene have the absolute configurations (II) and (XIX; R = :CH_2), respectively. This conclusion is in agreement with that of Djerassi, Mosettig, Briggs, and their co-workers [5b,18] for (—)-kaurene. Optical rotatory dispersion measurements of 7-keto-compounds support this assignment. The 7-keto-acid (Xa) and its methyl ester showed positive Cotton effects in agreement with the octant rule,[19] whilst the corresponding keto-lactone (IVa) showed a small negative effect (superimposed on a positive background) indicating that the lactone ring comes axially into a negative octant on closing and is therefore α-oriented. The large amplitudes of the Cotton effects of the 7-keto-acid and its ester, *e.g.*, $10^{-2}a = +125°$ for (Xa), cannot be due to a completely twist conformation [20] of ring B in these compounds since this is prevented by the rigidity of the backbone of the molecule. However, they may be due to a partially twisted conformation which relieves the interaction between the 20-methyl group and C-14.

The octant rule [19] cannot readily be applied to 7-deoxy-6-keto-compounds derived from

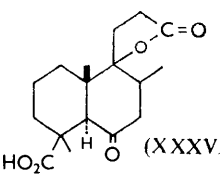
[14] King, Godson, and King, *J.*, 1955, 1117.
[15] Sommer, Arya, and Simon, *Tetrahedron Letters*, 1960, No. 20, 18.
[16] Djerassi, Cais, and Mitscher, *J. Amer. Chem. Soc.*, 1959, **81**, 2386.
[17] Turner and Ganshirt, *Tetrahedron Letters*, 1961, No. 7, 231 and refs. therein.
[18] Djerassi, Quitt, Mosettig, Cambie, Rutledge, and Briggs, *J. Amer. Chem. Soc.*, 1961, **83**, 3720.
[19] Moffitt, Woodward, Moscowitz, Klyne, and Djerassi, *J. Amer. Chem. Soc.*, 1961, **83**, 4013.
[20] Djerassi and Klyne, *Proc. Nat. Acad. Sci. U.S.A.*, 1962, **48**, 1093.

the kaurenolides because of the near-octant contributions of the groups attached to C-4, but the lack of information on the Cotton effects produced by such structures justified their preparation and measurement of their optical rotatory dispersion curves. Attempts to prepare the 6-keto-acid from the 6,19-diol (XII) were unsuccessful. In contrast to the oxidation of the 7,19-diol (XIb) (see above), oxidation of the 6,19-diol (XII) with chromic oxide in either pyridine or sulphuric acid gave the keto-aldehyde (XXXV; R = CHO, R′ = :CH_2) as the only isolable product. The aldehyde could not be further oxidised with alkaline potassium permanganate, chromic oxide in sulphuric acid, or silver oxide. On one occasion a monoalcohol, $C_{20}H_{30}O_2$, $\nu_{max.}$ 3340, 1708, 1661, and 886 cm.$^{-1}$, was obtained with the chromic oxide–pyridine reagent. Since its nuclear magnetic resonance spectrum did not show a resonance due to an aldehydic proton it has been assigned the 6-keto-19-alcohol structure (XXXV; R = CH_2·OH, R′ = :CH_2).

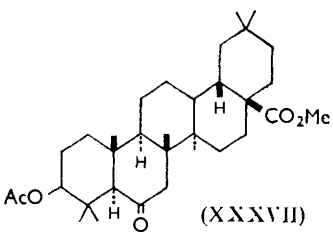
Hydrolysis of the enol-lactone (XXVI; R = :CH_2) with boiling mineral acid afforded the hydroxy-6-keto-acid, $C_{20}H_{30}O_4$ (XXXV; R = CO_2H, R′ = OH,Me), in which hydration of the terminal methylene group had occurred (cf. ref. 3). The methyl ester, $C_{21}H_{32}O_4$, showed $\nu_{max.}$ 3480 (OH), 1728 (ester) and 1717 (6-ring ketone) cm.$^{-1}$. The 6-keto-acid (XXXV; R = CO_2H, R′ = :CH_2) was finally prepared by treatment of the toluene-*p*-sulphonate of 7-hydroxykaurenolide with dry lithium iodide in boiling collidine. On methylation it gave a gum. The two acids (XXXV; R = CO_2H, R′ = OH,Me) and (XXXV; R = CO_2H, R′ = :CH_2) and the ester (XXXV; R = CO_2Me, R′ = OH,Me) retain the 5β-configuration since both (i) reduction by lithium aluminium hydride of the 6-keto-aldehyde (XXXV; R = CHO, R′ = :CH_2) and (ii) reduction by sodium borohydride of the 6-keto-acid (XXXV; R = CO_2H, R′ = :CH_2) followed by methylation and reduction by lithium aluminium hydride gave the 6,19-diol (XII). This conclusion was supported by the stability of the 6-keto-aldehyde (XXXV; R = CHO, R′ = :CH_2) to boiling alkali. The three 6-keto-compounds showed negative Cotton effects, presumably due to the near-octant contribution of the 18-methyl group. 6-Oxolabdan-15-oic acid and



(XXXV)



(XXXVI)



(XXXVII)

the marrubiin ketone (XXXVI), which are antipodal to the kaurenolide derivatives about the A/B-fusion, show [21] positive Cotton effects. They are not, however, good models because they have only one 8-substituent and it should be noted that methyl sumaresinoate 3-acetate (XXXVII) shows [22] a weak negative Cotton effect.

The aldehyde (XVI) showed a positive Cotton effect on a negative plain curve; the acid (XIIIa) and the monoalcohol (XIVa) showed negative plain curves.

We have shown that (−)-[17-^{14}C]kaurene is utilised by *G. fujikuroi* as a precursor of gibberellic acid.* This work and the role of 7-hydroxykaurenolide in the biosynthesis of the gibberellins will form the subject of another paper.

Experimental

Chromatographic materials and general experimental methods were as described in Part II.[1] In addition expressions of the type " chromatography on silica gel or alumina (ethyl

* A preliminary account of this work was given in a paper read at the International Symposium on Organic Chemistry of Natural Products held in Brussels in June 1962.

[21] Halsall and Moyle, *J.*, 1960, 1324.

[22] Djerassi, Osiecki, and Closson, *J. Amer. Chem. Soc.*, 1959, **81**, 4587.

acetate–light petroleum)" denote chromatography on silica gel or alumina and elution with light petroleum containing increasing (usually in 5% steps) concentrations of ethyl acetate.

Nuclear magnetic resonance spectra were measured for chloroform solutions at either 40 or 60 Mc. and, unless otherwise stated, had tetramethylsilane as internal reference.

7-Hydroxykaurenolide.—7-Hydroxykaurenolide [1] crystallised from acetone- or ethyl acetate–light petroleum in thin rods or clusters of thick rods, m. p. 187—188°, $[\alpha]_D^{22}$ −25° (*c* 0·5), $\nu_{max.}$ (thin rods) 3500, 1744, 1660, and 889 cm.$^{-1}$, $\nu_{max.}$ (thick rods) 3485, 1776 (sh), 1750, 1656, and 899 cm.$^{-1}$, $\nu_{max.}$ (in $CHCl_3$) 3595, 3495, 1767, 1656, and 888 cm.$^{-1}$, τ 9·13 and 8·72.

The *acetate*, prepared by reaction with acetic anhydride in pyridine solution at room temperature for 24 hr., had m. p. 182—184° (Found: C, 73·7; H, 8·35. $C_{22}H_{30}O_4$ requires C, 73·7; H, 8·4%), $\nu_{max.}$ 1767, 1748, and 1655 cm.$^{-1}$. The *toluene-*p*-sulphonate*, prepared similarly with toluene-*p*-sulphonyl chloride, had m. p. 167—169° (Found: C, 68·9; H, 7·3. $C_{27}H_{34}O_5S$ requires C, 69·2; H, 7·3%), $\nu_{max.}$ 1772 and 1650 cm.$^{-1}$.

Hydrogenation of 7-Hydroxykaurenolide.—25% Palladised charcoal (50 mg.), suspended in ethyl acetate (20 ml.), was saturated with hydrogen, then 7-hydroxykaurenolide (370 mg.) in ethyl acetate (30 ml.) was added and the mixture shaken. One mol. of hydrogen was absorbed rapidly. Recovery gave a solid which crystallised from acetone–light petroleum, giving *β-dihydro-7-hydroxykaurenolide* (Ib) as needles (160 mg.), m. p. 226—228° (Found: C, 75·2; H, 9·5. $C_{20}H_{30}O_3$ requires C, 75·4; H, 9·5%), $\nu_{max.}$ 3543, 3492 (sh), and 1748 cm.$^{-1}$.

On gradient chromatography of the mother-liquor the fractions eluted with 25% and 30% of ethyl acetate were combined and crystallised from acetone–light petroleum. The first crop (45 mg.) was β-dihydro-7-hydroxykaurenolide, and the second crop (113 mg.) after 3 crystallisations from acetone–light petroleum gave *α-dihydro-7-hydroxykaurenolide* (Ia), m. p. 142—144° (Found: C, 75·4; H, 9·0%), $\nu_{max.}$ 3540, 3470 (sh), and 1752 cm.$^{-1}$, ε 1010 at 200 mμ. By this method of separation, followed by repeated crystallisation, the β-dihydro-epimer can be obtained as a pure compound but the α-dihydro-epimer, m. p. 142—144°, contains 5—10% of the β-dihydro-compound as shown by reduction of the derived ketone with sodium borohydride (see below). The *toluene-*p*-sulphonate* of β-dihydro-7-hydroxykaurenolide crystallised from acetone–light petroleum in needles, m. p. 174—175° (Found: C, 68·4; H, 7·6. $C_{27}H_{36}O_5S$ requires C, 68·6; H, 7·7%).

Ozonolysis of 7-Hydroxykaurenolide.—Ozonised oxygen (5·5 mg. of O_3 per min.) was passed through a solution of 7-hydroxykaurenolide (42 mg.) in acetic acid (10 ml.) for 2 min. at room temperature. The solution was diluted with water (10 ml.), shaken, and steam-distilled, and the distillate (50 ml.) was added to an equal volume of saturated aqueous dimedone solution. After 48 hr. formaldehyde dimethone (23 mg., 0·6 mol.) was collected (m. p. 186—188°). Neutralisation of the aqueous non-volatile residue with sodium carbonate solution followed by extraction with ethyl acetate afforded *6α,7β-dihydroxy-16-oxo-17-nor-(−)-kauran-19-oic acid 19→6α-lactone* (III) which crystallised from ethyl acetate–light petroleum in needles (35 mg.), m. p. 308—311° (Found: C, 72·0; H, 8·45. $C_{19}H_{26}O_4$ requires C, 71·7; H, 8·2%), $\nu_{max.}$ (in $CHCl_3$) 1772 and 1740 cm.$^{-1}$.

Epoxidation of 7-Hydroxykaurenolide.—7-Hydroxykaurenolide (400 mg.) was dissolved in a 1·3N-solution (5 ml.) of perbenzoic acid in chloroform and left at 0° for 18 hr. The solution was diluted with ethyl acetate (100 ml.) and washed successively with aqueous ferrous sulphate, water, and sodium hydrogen carbonate solution, and dried. Evaporation of the solvent and crystallisation of the residue from acetone–light petroleum gave *16,17-epoxy-6α,7β-dihydroxy-(−)-kauran-19-oic acid 19→6α-lactone* as needles (228 mg.), m. p. 250—252° (Found: C, 72·0; H, 8·6. $C_{20}H_{28}O_4$ requires C, 72·3; H, 8·5%), $\nu_{max.}$ 3452, 3393, and 1759 cm.$^{-1}$.

Isomerisation of 7-Hydroxykaurenolide.—7-Hydroxykaurenolide (200 mg.) was refluxed for 1·5 hr. in a 5% v/v solution (10 ml.) of sulphuric acid in ethanol. The solution was concentrated *in vacuo*, diluted with water to 100 ml., and extracted with ether. The extract was washed with sodium hydrogen carbonate solution and water and dried. Evaporation of the solvent and chromatography of the residue on alumina gave, on elution with 20% ethyl acetate in light petroleum, *6α,7β-dihydroxy-(−)-kaur-15-en-19-oic acid 19→6α-lactone* as needles (128 mg.), m. p. 196—197° (from acetone–light petroleum) (Found: C, 75·9; H, 9·0. $C_{20}H_{28}O_3$ requires C, 75·9; H, 8·9%), $\nu_{max.}$ 3550, 1758, 1650, and 828 cm.$^{-1}$.

Oxidation with Chromium Trioxide–Sulphuric Acid.— The compound for oxidation was dissolved in pure acetone and treated with 8N-chromium trioxide in sulphuric acid [23] (hereafter

[23] Curtis, Heilbron, Jones, and Woods, *J.*, 1953, 457.

called the chromium trioxide reagent). Methanol was added to decompose the excess of reagent, followed by a little water; the methanol and acetone were removed *in vacuo*, the solution was extracted with ethyl acetate, and the extract was separated into acidic and neutral fractions where necessary.

(1) 6α-*Hydroxy*-7-*oxo*-(−)-*kaur*-16-*en*-19-*oic acid lactone* (V). 7-Hydroxykaurenolide (125 mg.) in acetone (5 ml.) was treated with the chromium trioxide reagent (0·15 ml.) for 1 hr. The neutral fraction (100 mg.) recrystallised from acetone–light petroleum, giving needles of the *keto-lactone* (V), m. p. 264—265° (Found: C, 76·2; H, 8·3. $C_{20}H_{26}O_3$ requires C, 76·4; H, 8·3%), $\nu_{max.}$ 1780, 1702, 1656, and 885 cm.$^{-1}$.

(2) 6α-*Hydroxy*-7-*oxo*-(−)-*kauran*-19-*oic acid lactone* (IVa) *and* 6α-*hydroxy*-7-*oxo*-16-*epi*-(−)-*kauran*-19-*oic acid lactone* (IVb). α-Dihydro-7-hydroxykaurenolide (50 mg.) in acetone (5 ml.) was treated with the chromium trioxide reagent (0·13 ml.) for 2 hr. The neutral fraction (48 mg.) crystallised from acetone–light petroleum, giving the *keto-lactone* (IVa) as needles, m. p. 264° (Found: C, 76·0; H, 9·3. $C_{20}H_{28}O_3$ requires C, 75·9; H, 8·9%), $\nu_{max.}$ 1773 and 1702 cm.$^{-1}$. Similarly the β-dihydro-epimer (Ib) yielded the *keto-lactone* (IVb), m. p. 298—301° (sealed tube) (Found: C, 75·6; H, 9·0%), $\nu_{max.}$ 1776 and 1704 cm.$^{-1}$.

(3) 6α-*Hydroxy*-7,16-*dioxo*-17-*nor*-(−)-*kauran*-19-*oic acid lactone* (VI). The nor-ketone (III) (25 mg.) in acetone (5 ml.) was treated with the chromium trioxide reagent (0·06 ml.) for 2 hr. The neutral fraction (23 mg.) crystallised from methanol in feathery needles of the *diketo-lactone* (VI), m. p. 290—295° (Found: C, 71·5; H, 7·5. $C_{19}H_{24}O_4$ requires C, 72·1; H, 7·65%), $\nu_{max.}$ (in $CHCl_3$) 1778, 1741, and 1720 cm.$^{-1}$.

Alkaline Hydrolyses.—(1) 7-*Hydroxykaurenolide*. 7-Hydroxykaurenolide (1·1 g.) in methanol (30 ml.) was refluxed with N-sodium hydroxide solution (30 ml.) for 4 hr. The methanol was evaporated *in vacuo*, and the solution diluted with water, cautiously acidified with dilute hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate was evaporated *in vacuo* below 40° and the residual gum taken up in methanol (15 ml.) and treated with ethereal diazomethane. The solvents were evaporated; the product crystallised from acetone–light petroleum to give *methyl* 6α,7β-*dihydroxy*-(−)-*kaur*-16-*en*-19-*oate* (VIII; R = Me) as needles (805 mg.), m. p. 228—231° (Found: C, 71·9; H, 9·1. $C_{21}H_{32}O_4$ requires C, 72·4; H, 9·3%), $\nu_{max.}$ 3360, 3265, 3060, 1690, 1659, and 872 cm.$^{-1}$.

(2) β-*Dihydro*-7-*hydroxykaurenolide*. 0·5N-Sodium hydroxide (4 ml.) was added to β-dihydro-7-hydroxykaurenolide (140 mg.) in ethanol (8 ml.), and the mixture was refluxed for 5 hr. A little water was added, the ethanol removed *in vacuo*, then the solution was acidified at 0° with 0·5N-hydrochloric acid, and the product recovered in ethyl acetate. 6α,7β-*Dihydroxy*-16-*epi*-(−)-*kauran*-19-*oic acid* (VIIb; R = H) crystallised from ethyl acetate–light petroleum with m. p. 210—212° (Found: C, 71·3; H, 9·7. $C_{20}H_{32}O_4$ requires C, 71·4; H, 9·6%), $\nu_{max.}$ 3530, 3320, and 1675 cm.$^{-1}$. The *methyl ester* crystallised from acetone–light petroleum in needles, m. p. 188—191° (Found: C, 72·1; H, 9·8. $C_{21}H_{34}O_4$ requires C, 72·0; H, 9·8%), $\nu_{max.}$ 3380, 3315, and 1687 cm.$^{-1}$.

(3) α-*Dihydro*-7-*hydroxykaurenolide*. By the same procedure the α-dihydro-compound (Ia) was converted into 6α,7β-*dihydroxy*-(−)-*kauran*-19-*oic acid* (VIIa; R = H) which crystallised from acetone–light petroleum with m. p. 215—218° (Found: C, 71·3; H, 9·7%), $\nu_{max.}$ 3535, 3390, and 1712 cm.$^{-1}$. The *methyl ester* crystallised from acetone–light petroleum in needles, m. p. 203—205° (Found: C, 71·8; H, 9·9%).

(4) 6α,7β-*Dihydroxy*-16-*oxo*-17-*nor*-(−)-*kauran*-19-*oic acid* 19→6α-*lactone* (III). Similarly the nor-ketone gave 6α,7β-*dihydroxy*-16-*oxo*-17-*nor*-(−)-*kauran*-19-*oic acid* (IX; R = H) which crystallised from aqueous methanol with m. p. 310—315° (Found: C, 67·9; H, 8·5. $C_{19}H_{28}O_5$ requires C, 67·8; H, 8·4%), $\nu_{max.}$ 3315, 3185, 1719, and 1688 cm.$^{-1}$. The *methyl ester* (IX; R = Me) crystallised from acetone–light petroleum with m. p. 204—209° (resets and remelts at 305—309°) (Found: C, 68·35; H, 8·8. $C_{20}H_{30}O_5$ requires C, 68·5; H, 8·6%), $\nu_{max.}$ 3368, 3280, 1744, and 1685 cm.$^{-1}$. The ester was converted quantitatively into the lactone (III) by heating it at 240° for 2 hr.

Selenium Dehydrogenation of 6α,7β-*Dihydroxy*-16-*oxo*-17-*nor*-(−)-*kauran*-19-*oic Acid* (IX; R = H).—The diol-acid (80 mg.) was prepared as above and without purification was heated with selenium powder (200 mg.) at 340—350° for 22 hr. The cooled mixture was extracted with ether and acetone. Recovery gave a yellow gum (21 mg.) which was chromatographed on alumina (ethyl acetate–light petroleum). Elution with light petroleum afforded a colourless gum (1 mg.) with very weak carbonyl absorption in the infrared region and with ultraviolet

absorption maxima at 257, 279, 288, 301, 319 (sh), 326, 334, 342 (sh), and 351 mμ ($E^{1\%}_{1\,cm.}$ 611·0, 178·1, 150·7, 157·5, 11·5, 10·0, 8·2, 5·8, and 5·1, respectively). Subsequent fractions were also small and possessed strong infrared carbonyl absorption. Elution with 100% ethyl acetate gave 6α,7β-dihydroxy-16-oxo-17-nor-(−)-kauran-19-oic acid 19→6α-lactone (10 mg.), m. p. 306—310°, identified by its infrared spectrum.

Preparation of (−)-*Kaur*-16-*ene*-6α,19-*diol* (XII).—Lithium aluminium hydride (110 mg.) and 7-toluene-*p*-sulphonyloxykaurenolide (120 mg.) in dry ether (50 ml.) were refluxed for 11 hr. The excess of reagent was decomposed with ethyl acetate, water was added, and the ethyl acetate–ether layer washed with sodium hydrogen carbonate solution and water and dried. The gummy crystals (85 mg.) obtained were chromatographed on Celite–silica gel (2 : 1). The fractions eluted with 5%, 10%, and 15% of ethyl acetate in light petroleum were combined (52 mg.) and crystallised from acetone–light petroleum, giving the *diol* (XII) as needles, m. p. 174—175·5° (Found: C, 78·4; H, 10·8. $C_{20}H_{32}O_2$ requires C, 78·9; H, 10·6%), $\nu_{max.}$ 3200 (broad), 1657, and 876 cm.$^{-1}$.

Treatment of (−)-*Kaur*-16-*ene*-6α,19-*diol with Toluene*-p-*sulphonyl Chloride in Pyridine.*—The diol (XII) (35 mg.) and toluene-*p*-sulphonyl chloride (144 mg.) in pyridine (2·5 ml.) were left at room temperature for 48 hr. The mixture was poured into dilute hydrochloric acid, then extracted with ethyl acetate and the organic layer was washed with dilute hydrochloric acid and water and dried. Recovery afforded gummy crystals which were chromatographed on alumina. Elution with 5% and 10% of ethyl acetate in light petroleum followed by crystallisation from aqueous methanol gave 6α,19-*epoxy*-(−)-*kaurene* (XV) as needles (21 mg.), m. p. 130—135° (Found: C, 83·5; H, 10·9. $C_{20}H_{30}O$ requires C, 83·9; H, 10·6%), $\nu_{max.}$ OH absent, 1650 and 880 cm.$^{-1}$.

7-*Oxo*-(−)-*kauran*-19-*oic Acid* (Xa).—6α-Hydroxy-7-oxo-(−)-kauran-19-oic acid lactone (IVa) (1·05 g.) and zinc dust (10 g.) in acetic acid (200 ml.) were refluxed for 18 hr. The cooled mixture was filtered, the filtrate evaporated to dryness *in vacuo*, and the residue crystallised from acetone–light petroleum, giving the *keto-acid* (Xa) as plates (0·95 g.), m. p. 213—215° (Found: C, 75·5; H, 9·6. $C_{20}H_{30}O_3$ requires C, 75·4; H, 9·5%), $\nu_{max.}$ 1724 and 1674 cm.$^{-1}$ (C=O). The *methyl ester*, prepared with diazomethane, crystallised from aqueous methanol in plates, m. p. 99·5—100·5° (Found: C, 76·0; H, 9·9. $C_{21}H_{32}O_3$ requires C, 75·9; H, 9·7%), $\nu_{max.}$ 1716 and 1702 cm.$^{-1}$.

7-*Oxo*-16-*epi*-(−)-*kauran*-19-*oic Acid* (Xb).—Prepared from the keto-lactone (IVb) by the method used in the preceding experiment this *keto-acid* had m. p. 264—266° (Found: C, 75·35; H, 9·5%), $\nu_{max.}$ 1725 and 1673 cm.$^{-1}$ (C=O). The *methyl ester* crystallised from aqueous methanol in needles, m. p. 126—128° (Found: C, 76·0; H, 9·8%), $\nu_{max.}$ 1719 and 1700 cm.$^{-1}$.

7,16-*Dioxo*-17-*nor*-(−)-*kauran*-19-*oic Acid* (XX; R = Me, R′ = CO_2H, R″ = O).—6α-Hydroxy-7,16-dioxo-17-nor-(−)-kauran-19-oic acid lactone (VI) (100 mg.) in acetic anhydride (15 ml.) was refluxed with zinc dust (2 g.) overnight. The cooled mixture was filtered and evaporated *in vacuo*. The residue was taken up in ethyl acetate and extracted with aqueous sodium hydrogen carbonate. Acidification of the extract with dilute hydrochloric acid and recovery in ethyl acetate afforded the *acid* which crystallised from acetone–light petroleum in needles, m. p. 254—257° (Found: C, 70·35; H, 8·15. $C_{19}H_{26}O_5,0{\cdot}5H_2O$ requires C, 69·9; H, 8·0%). The *methyl ester*, prepared with diazomethane, crystallised from acetone–light petroleum as needles, m. p. 130—131° (Found: C, 72·1; H, 8·4. $C_{20}H_{28}O_4$ requires C, 72·3; H, 8·5%), $\nu_{max.}$ 1745, 1717, and 1701 cm.$^{-1}$.

(−)-*Kaurane*-7α,19-*diol* (XIa).—Methyl 7-oxo-(−)-kauran-19-oate (46 mg.) and lithium aluminium hydride (100 mg.) in ether (20 ml.) were heated under reflux for 5 hr. Isolation of the product as for the 6α,19-diol (see above) followed by crystallisation from acetone–light petroleum gave the *diol* (XIa) as rhombs, m. p. 208—209° (Found: C, 78·3; H, 11·3. $C_{20}H_{34}O_2$ requires C, 78·4; H, 11·2%), $\nu_{max.}$ 3285 (broad) cm.$^{-1}$. The *ditoluene*-p-*sulphonate*, prepared by treatment with toluene-*p*-sulphonyl chloride in pyridine at room temperature for 48 hr., crystallised from acetone–light petroleum in needles, m. p. 120° (Found: C, 66·7; H, 7·7. $C_{34}H_{46}O_6S_2$ requires C, 66·4; H, 7·5%).

16-*Epi*-(−)-*kaurane*-7α,19-*diol* (XIb).—This *diol*, prepared by reduction of methyl 7-oxo-16-epi-(−)-kauran-19-oate as in the preceding experiment, crystallised from acetone–light petroleum as needles, m. p. 198—200° (Found: C, 78·8; H, 11·2. $C_{20}H_{34}O_2$ requires C, 78·4; H, 11·2%). The *ditoluene*-p-*sulphonate*, crystallised from acetone–light petroleum, had m. p. 124—127° (Found: C, 66·3; H, 7·6. $C_{34}H_{46}O_6S_2$ requires C, 66·4; H, 7·5%).

Oxidation of 16-*Epi*-(−)-*kaurane*-7α,19-*diol* (XIb).—(i) The diol (130 mg.) in pyridine (7 ml.) was treated with chromium trioxide (0·5 g.) at 5° for 65 hr. The mixture was poured into dilute hydrochloric acid and extracted with ethyl acetate and the organic layer was washed with water, then separated into acidic and neutral fractions with sodium hydrogen carbonate solution. The neutral fraction (115 mg.) was chromatographed on Celite–silica gel (2 : 1) in ethyl acetate–light petroleum; the only crystalline product was 7-oxo-16-epi-(−)-kauran-19-oic acid (81 mg.), identified by its infrared spectrum.

(ii) The diol (80 mg.) in pyridine (8 ml.) was treated with chromium trioxide (200 mg.) at 0° for 18 hr. The neutral fraction (75 mg.) was chromatographed on alumina ethyl acetate–light petroleum). Elution with 10% of ethyl acetate gave a semi-solid keto-aldehyde (5 mg.), $\nu_{max.}$ 2705, 1715, 1685 cm.$^{-1}$; use of 40 and 50% of ethyl acetate gave a gum (14 mg.) which was probably the keto-alcohol since it possessed no aldehydic infrared bands but showed both hydroxyl and carbonyl absorption; use of 70%, 80%, and 90% ethyl acetate gave starting material (25 mg.).

(−)-*Kauran*-19-*oic Acid* (XIIIa).—7-Oxo-(−)-kauran-19-oic acid (0·525 g.), diethylene glycol (25 ml.), and 64% hydrazine (5 ml.) were heated at 140—150° for 2 hr. Potassium hydroxide pellets (6 g.) were added and the temperature was raised to 195—205° and maintained there for 2·5 hr. The cooled mixture was added to dilute hydrochloric acid and extracted with ethyl acetate. Recovery gave a gum which was chromatographed on silica gel (ethyl acetate–light petroleum). The pale yellow gum (0·48 g.), eluted with 10% of ethyl acetate, slowly solidified and crystallised from methanol in needles (350 mg.) of (−)-*kauran*-19-*oic acid* (XIIIa), m. p. 198—209°, pK^*_{MCS} 8·4 (Found: C, 79·2; H, 10·3. $C_{20}H_{32}O_2$ requires C, 78·9; H, 10·6%), $\nu_{max.}$ 1694 cm.$^{-1}$.

16-*Epi*-(−)-*kauran*-19-*oic Acid* (XIIIb).—Reduction of the keto-acid (Xb) as in the preceding experiment gave 16-*epi*-(−)-*kauran*-19-*oic acid*, m. p. 212—216° (from aqueous methanol) (Found: C, 79·2; H, 10·6%), $\nu_{max.}$ 1687 cm.$^{-1}$. The *methyl ester*, prepared with diazomethane and crystallised from methanol, had m. p. 118—120° (Found: C, 79·0; H, 11·0. $C_{21}H_{34}O_2$ requires C, 79·2; H, 10·8%). The *acid chloride*, prepared by refluxing the acid with thionyl chloride for 2 hr. and purified by sublimation, had m. p. 118—121° (Found: C, 74·8; H, 9·7. $C_{20}H_{31}OCl$ requires C, 74·4; H, 9·6%).

Attempted Rosenmund Reduction of 16-*Epi*-(−)-*kauran*-19-*oyl Chloride*.—A suspension of 5% palladium on barium sulphate (10 mg.) in xylene (0·5 ml.) was heated until boiling in a stream of hydrogen, then the acid chloride (55 mg.) in xylene (0·5 ml.) was added. During 1·5 hr. 1 mol. of hydrogen chloride was evolved. The filtrate from the catalyst was evaporated *in vacuo* and the residual gum was chromatographed on silica gel. The only crystalline compound isolated (3 mg.) had m. p. 189—194° (prisms from ether), $\nu_{max.}$ 1790 and 1725 cm.$^{-1}$, and was probably an intermolecular anhydride.

(−)-*Kauran*-19-*ol* (XIVa).—(i) (−)-Kauran-19-oic acid (250 mg.) was methylated with diazomethane, and the ester, without purification, was heated under reflux for 2 hr. with a solution of lithium aluminium hydride (200 mg.) in ether (150 ml.). The product, isolated in the usual way, crystallised from aqueous methanol in needles (220 mg.) of the *alcohol* (XIVa), m. p. 148—150° (Found: C, 83·1; H, 11·5. $C_{20}H_{34}O$ requires C, 82·7; H, 11·8%), $\nu_{max.}$ 3345 cm.$^{-1}$.

(ii) Lithium aluminium hydride (200 mg.) was added to the 7α,19-ditoluene-*p*-sulphonyloxy-(−)-kaurane (60 mg.) in ether (30 ml.), and the mixture was refluxed for 10 hr. The product (36 mg.) was chromatographed on alumina (ethyl acetate–light petroleum) and (−)-kauran-19-ol (11 mg.), m. p. 146—149°, was eluted with 15% and 20% of ethyl acetate. (−)-Kaurane-7α,19-diol (6 mg.), identified by its infrared spectrum, was eluted with 60% of ethyl acetate; the other fractions were intractable.

16-*Epi*-(−)-*kauran*-19-*ol* (XIVb).—Methyl 16-epi-(−)-kauran-19-oate (430 mg.) was reduced with lithium aluminium hydride as in the previous experiment. The crude monoalcohol (390 mg.), m. p. 120—132°, was chromatographed on alumina (ethyl acetate–light petroleum). The fractions eluted with 15% and 20% ethyl acetate were crystallised from aqueous methanol, giving the monoalcohol, m. p. 142—144°, $[\alpha]_D^{17}$ −62° (*c* 0·25). Mosettig *et al.*[5] record m. p. 142—144°, $[\alpha]_D$ −62°.

(−)-*Kauran*-19-*al* (XVI).—(−)-Kauran-19-ol (58 mg.) in acetone (8 ml.) was treated with the chromium trioxide reagent (0·05 ml.; 1 mol.) at room temperature for 15 min. The mixture was worked up as in oxidations described above. Chromatography of the crude product on

alumina (ethyl acetate–light petroleum) followed by crystallisation from aqueous methanol gave the *aldehyde* (18 mg.), m. p. 90—98° (Found: C, 83·6; H, 11·4. $C_{20}H_{32}O$ requires C, 83·3; H, 11·2%), $\nu_{max.}$ 2715 and 1715 cm.$^{-1}$.

(−)-*Kaurane* (XVII).—(−)-Kauran-19-al (16 mg.), diethylene glycol (2 ml.), and 64% hydrazine (0·5 ml.) were heated together at 145—155° for 2 hr. Potassium hydroxide pellets (0·5 g.) were added, the temperature raised to 195—205° and maintained there for 1 hr. The mixture was poured into water, neutralised with dilute hydrochloric acid, and extracted with ethyl acetate. The product was chromatographed on alumina and the first fraction (7 mg.) eluted with light petroleum was crystallised twice from methanol, giving needles, m. p. 85—87°, $[\alpha]_D^{26}$ −33° (*c* 0·5 in $CHCl_3$), identical with (−)-kaurane prepared by hydrogenation of (−)-kaurene.

Oxidation of Methyl 6α,7β-*Dihydroxy*-16-*epi*-(−)-*kauran*-19-*oate* (VIIb; R = Me).—The diol (110 mg.) in acetone (10 ml.) was treated with the chromium trioxide reagent (0·25 ml.) for 2 hr. Working-up as above gave a yellow gum (100 mg.) as the neutral fraction and a colourless acidic gum (9 mg.). The neutral fraction was chromatographed on Celite–silica gel (2 : 1) (ethyl acetate–light petroleum); the main fraction (75 mg. of a yellow gum) was eluted with 10% of ethyl acetate. It crystallised from acetone–light petroleum in yellow rods (15 mg.) of *methyl* 6,7-*dioxo*-16-*epi*-(−)-*kauran*-19-*oate* (XXI), m. p. 130—133° (Found: C, 72·8; H, 8·8. $C_{21}H_{30}O_4$ requires C, 72·8; H, 8·7%), $\nu_{max.}$ 1736 and 1706 cm.$^{-1}$, $\lambda_{max.}$ 280 mμ (ε 790), $\lambda_{max.}$ (in EtOH–NaOH) 336 mμ (ε 6350). The mother-liquors contained the corresponding diosphenol which remained a gum even after repeated chromatography, $\lambda_{max.}$ 281 mμ (ε 8100), $\lambda_{max.}$ (in NaOH) 333—337 mμ, $\nu_{max.}$ (Infracord spectrophotometer) 3350, 1730, 1660, and 1625 cm.$^{-1}$. The acidic fraction crystallised from acetone–light petroleum, giving 6,7-*seco*-16-*epi*-(−)-*kaurane*-6,7-*dioic acid* (XXII; R = R′ = CO_2H, R″ = β-H, α-Me), m. p. 177—179° (decomp.) (Found: C, 66·3; H, 8·6. $C_{21}H_{32}O_6$ requires C, 66·3; H, 8·5%), $\nu_{max.}$ 1727 and 1693 cm.$^{-1}$.

Oxidation of Methyl 6α,7β-*Dihydroxy*-16-*oxo*-17-*nor*-(−)-*kauran*-19-*oate* (IX; R = Me).—The ester (160 mg.) in acetone (20 ml.) was treated with the chromium trioxide reagent (0·37 ml.) for 2·5 hr. The product was separated into acidic (42 mg.) and neutral (102 mg.) fractions. The former were chromatographed on Celite–silica gel (2 : 1) (ethyl acetate–light petroleum), and the fractions eluted with 60% and 70% of ethyl acetate were combined (25 mg.) and crystallised from acetone–light petroleum, giving 19-*methyl dihydrogen* 16-*oxo*-6,7-*seco*-17-*nor*-(−)-*kaurane*-6,7,19-*trioate* (XXII; R = R′ = CO_2H, R″ = O) as needles, m. p. 172—173° (decomp.) then 215°, $[\alpha]_D^{24}$ −45° (*c* 0·7) [Found: C, 63·3; H, 7·7%; equiv., 188. $C_{20}H_{28}O_7$ requires C, 63·1; H, 7·4%; equiv. (dibasic acid), 190], $\nu_{max.}$ 3235, 2660, 1735, and 1697 cm.$^{-1}$. The neutral fraction was a pale yellow gum which was chromatographed similarly and the main product (64 mg.), eluted with 20% ethyl acetate, was the diosphenol [$\lambda_{max.}$ 281 mμ (ε 8100)] which remained a gum after repeated chromatography although the intensity of the maximum at 281 mμ increased to ε = 9400.

Alkaline Hydrolysis of 6α-*Hydroxy*-7-*oxo*-(−)-*kauran*-19-*oic Acid Lactone* (IVa).—The keto-lactone (100 mg.) was refluxed in 0·2N-aqueous-ethanolic sodium hydroxide solution for 5 hr. Neutralisation with 0·2N-hydrochloric acid and extraction with ethyl acetate gave a mixture of gum and crystals (100 mg.) which was chromatographed on silica gel (ethyl acetate–light petroleum). The fractions eluted with 25 and 30% ethyl acetate (67 mg.) were combined and crystallised from acetone–light petroleum giving the *diosphenol-acid* (XXIII) as plates, m. p. 152° (decomp.) (Found: C, 72·1; H, 8·8. $C_{20}H_{28}O_4$ requires C, 72·3; H, 8·5%), $\nu_{max.}$ 3395, 3240, 1712, 1642, and 1613 cm.$^{-1}$, $\lambda_{max.}$ 280 mμ (ε 10,200), $\lambda_{max.}$ (in EtOH–NaOH) 290 mμ (ε 6720) shifting to 337 mμ (ε 6460) on storage. With diazomethane it gave a gum, $\lambda_{max.}$ 280 mμ (ε 8750), the infrared spectrum of which, $\nu_{max.}$ (Infracord spectrophotometer) 3375, 1730, 1655, and 1620 cm.$^{-1}$, was identical with those of the diosphenol methyl esters obtained below (*a*) by oxidation of the α-dihydro-diol ester (VIIa; R = Me) and (*b*) by methylation of the lactol (XXIV).

Oxidation of Methyl 6α,7β-*Dihydroxy*-(−)-*kauran*-19-*oate* (VIIa; R = Me).—The diol (30 mg.) in pyridine (1 ml.) was added to chromium trioxide (100 mg.) in pyridine (3 ml.) and left at room temperature for 23 hr. The mixture was poured into dilute hydrochloric acid. Recovery with ethyl acetate gave only a trace of acids and a neutral fraction (27 mg.) which was chromatographed on Celite–silica gel (ethyl acetate–light petroleum). The major product, eluted with 5% and 10% of ethyl acetate, was a gummy diosphenol methyl ester, $\lambda_{max.}$ 279 mμ (ε 4000).

Oxidation of 6α,7β-*Dihydroxy*-(−)-*kauran*-19-*oic Acid* (VIIa; R = H).—When oxidised as in the preceding experiment the dihydroxy-acid (VIIa; R = H) (103 mg.) gave mainly neutral

products (100 mg.) which were chromatographed on silica gel (ethyl acetate–light petroleum). The fractions eluted with 25% and 30% ethyl acetate were combined (57 mg.) and crystallised from acetone–light petroleum, giving 6α,6β-*dihydroxy*-7-*oxo*-(−)-*kauran*-19-*oic acid* 19→6α-*lactone* (XXIV) as plates, m. p. 133° (decomp.) (Found: C, 72·2; H, 8·6. $C_{20}H_{28}O_4$ requires C, 72·3; H, 8·5%), $\nu_{max.}$ 3290, 1759, and 1722 cm.$^{-1}$. Methylation of this keto-lactol with diazomethane gave a gummy yellow diosphenol methyl ester.

Attempted Decarboxylation of the Dicarboxylic Acid (XXII; R = R′ = CO_2H, R″ = O).—The dicarboxylic acid (46 mg.) was refluxed with water (5 ml.) for 1 hr. The solution was cooled, diluted, and extracted with ethyl acetate. Evaporation of the solvent and crystallisation of the residue from acetone–light petroleum gave 16-oxo-6,7-seco-17-nor-(−)-kaurane-6,7,19-trioic acid 6,19-anhydride (XXV) (25 mg.), m. p. 252—254°, identical (infrared spectrum) with a sample prepared from fujenal.[3]

Attempted Substitution at C-15 *in the Nor-ketone* (III).—(i) *Hydroxymethylation.* The nor-ketone (250 mg.), dissolved in dry methanol (15 ml.), was treated with sodium methoxide (from sodium, 50 mg.) and ethyl formate (2 ml.) under nitrogen at room temperature for 5 hr. The starting material was recovered (infrared spectrum and m. p.).

(ii) *Bromination.* The nor-ketone (175 mg.) in acetic acid (4 ml.) was treated for 5·5 hr. with a solution (4 ml.) of bromine in acetic acid (1·26 g. of bromine in 25 ml. of acetic acid) and 48% aqueous hydrogen bromide (0·2 ml.). Recovery gave the starting material (149 mg.), m. p. 295—304°, identified by its infrared spectrum.

(iii) *Nitrosation.* The nor-ketone (200 mg.) in dry methanol (20 ml.) and sodium methoxide (from 103 mg. of sodium) was treated with pentyl nitrite (2 ml.) at room temperature for 70 hr. Recovery gave the starting material (155 mg.) as needles, m. p. 298—302°, identified by its infrared spectrum.

(iv) *Enol-acetylation.* The nor-ketone (100 mg.) in isopropenyl acetate (10 ml.) was refluxed for 16 hr. with toluene-*p*-sulphonic acid (15 mg.). Recovery gave 7β-*acetoxy*-6α-*hydroxy*-16-*oxo*-17-*nor*-(−)-*kauran*-19-*oic acid lactone* (58 mg.) as needles (from acetone–light petroleum), m. p. 240—242° (Found: C, 70·1; H, 8·0. $C_{21}H_{28}O_5$ requires C, 70·0; H, 7·8%), $\nu_{max.}$ 1769 and 1742 (br) cm.$^{-1}$, identical with a specimen prepared by acetylation of the nor-ketone with acetic anhydride in pyridine.

Attempted Hydroxymethylation of Methyl 6α,7β-*Dihydroxy*-16-*oxo*-17-*nor*-(−)-*kauran*-19-*oate* (IX; R = Me).—The keto-ester (200 mg.) in dry methanol (8 ml.), sodium methoxide (from sodium 75 mg.), and ethyl formate (2 ml.) was refluxed under nitrogen for 4·5 hr. Recovery gave the nor-ketone (III) (133 mg.), m. p. 307—308°, identified by its infrared spectrum.

6-*Hydroxy*-(−)-*kaura*-6,16-*dien*-19-*oic Acid Lactone* (XXVI; R = :CH_2).—The 7-toluene-*p*-sulphonyloxykaurenolide (250 mg.) was refluxed in pure collidine (15 ml.) for 4 hr. The solution was poured into dilute hydrochloric acid and extracted with ethyl acetate. The extract was washed with dilute hydrochloric acid and water and dried. Evaporation of the solvent gave a gum which was chromatographed on alumina (ethyl acetate–light petroleum). Elution with 5% of ethyl acetate gave the *enol-lactone* (XXVI; R = :CH_2) (150 mg.) which crystallised from light petroleum as needles, m. p. 205° (Found: C, 79·9; H, 8·8. $C_{20}H_{26}O_2$ requires C, 80·5; H, 8·8%), $\nu_{max.}$ 1793, 1693, 1655, 871, and 826 cm.$^{-1}$.

6-*Hydroxy*-16-*epi*-(−)-*kaur*-6-*en*-19-*oic Acid Lactone* (XXVI; R = β-H, α-Me).—Treatment of β-dihydro-7-toluene-*p*-sulphonyloxykaurenolide (22 mg.) as in the preceding experiment afforded the *enol-lactone* (14 mg.) which crystallised as plates (from methanol), m. p. 176—180° (Found: C, 79·4; H, 9·4. $C_{20}H_{28}O_2$ requires C, 79·95; H, 9·5%), $\nu_{max.}$ (in $CHCl_3$) 1792 and 1698 cm.$^{-1}$.

Reduction of 6α-*Hydroxy*-7-*oxo*-(−)-*kaur*-16-*en*-19-*oic Acid Lactone* (V).—The keto-lactone (600 mg.) in dry methanol (100 ml.) was treated with sodium borohydride (800 mg.) at room temperature overnight. Dilute hydrochloric acid (5 ml.) was added and the methanol removed *in vacuo*. The solution was diluted to 150 ml. with water and extracted with ethyl acetate. The extract was washed with aqueous sodium hydrogen carbonate and water and dried. Recovery afforded 6α,7α-*dihydroxy*-(−)-*kaur*-16-*en*-19-*oic acid* 19→6α-*lactone* (XXVII; R = :CH_2) (450 mg.) which crystallised from acetone–light petroleum as needles, m. p. 178—179° (Found: C, 75·7; H, 9·05. $C_{20}H_{28}O_3$ requires C, 75·9; H, 8·9%), $\nu_{max.}$ 3520, 1764, 1653, and 892 cm.$^{-1}$.

Reduction of 6α-*Hydroxy*-7-*oxo*-16-*epi*-(−)-*kauran*-19-*oic Acid Lactone* (IVb).—The 16-epi-keto-lactone (200 mg.) in methanol was reduced with sodium borohydride (300 mg.) as in the

preceding experiment. The product (191 mg.) was chromatographed on alumina (ethyl acetate–light petroleum). 6α,7α-*Dihydroxy*-16-*epi*-(−)-*kauran*-19-*oic acid* 19→6α-*lactone* (XXVIIIb) (175 mg.) was eluted with 30% of ethyl acetate and crystallised from acetone–light petroleum in needles, m. p. 128—129° (Found: C, 75·5; H, 9·6. $C_{20}H_{30}O_3$ requires C, 75·4; H, 9·5%), $\nu_{max.}$ 3540 and 1775 cm.$^{-1}$, τ 9·06 and 8·91 (doublet, >CH·CH_3), 8·91 (>C·CH_3), and 8·70 (−CO·C·CH_3). It was oxidised quantitatively to the keto-lactone (IVb) with the chromium trioxide reagent.

The *toluene*-p-*sulphonate* crystallised from acetone–light petroleum in needles, m. p. 121—122° (Found: C, 69·1; H, 7·7. $C_{27}H_{36}O_5S$ requires C, 68·6; H, 7·7%).

Reduction of 6α-*Hydroxy*-7-*oxo*-(−)-*kauran*-19-*oic Acid Lactone* (IVa).—The keto-lactone (150 mg.) was reduced and the product chromatographed as in the preceding experiment. Crystallisation of the first fraction (20 mg.) eluted with 30% of ethyl acetate afforded 6α,7α-dihydroxy-16-epi-(−)-kauran-19-oic acid 19→6α-lactone (10 mg.), m. p. 119—124°, identical (infrared spectrum) with the specimen obtained in the preceding experiment. This compound was derived from a small amount of the 16-epi-compound present in the starting keto-lactone. The next two fractions eluted with 30% of ethyl acetate gave 6α,7α-*dihydroxy*-(−)-*kauran*-19-*oic acid* 19→6α-*lactone* (XXVIIIa) which crystallised from acetone–light petroleum in needles, m. p. 200—201·5° (Found: C, 75·7; H, 9·6%). It was oxidised quantitatively to the keto-lactone (IVa) by the chromium trioxide reagent.

The *toluene*-p-*sulphonate*, prepared with toluene-*p*-sulphonyl chloride in pyridine, had m. p. 147—148° (Found: C, 68·9; H, 7·8%).

Alkaline Hydrolyses—(i) 6α,7α-*Dihydroxy*-16-*epi*-(−)-*kauran*-19-*oic acid* 19→6α-*lactone* (XXVIIIa). The hydroxy-lactone (85 mg.) in ethanol (15 ml.) was refluxed with 0·5N-sodium hydroxide (8 ml.) for 5 hr. A little water was added, the methanol removed *in vacuo*, and the solution acidified with 0·5N-hydrochloric acid. The product was recovered in ethyl acetate, methylated with diazomethane, and chromatographed on alumina (ethyl acetate–light petroleum). The fraction eluted with 10% of ethyl acetate crystallised from acetone–light petroleum in needles (17 mg.) of methyl 7-oxo-16-epi-(−)-kauran-19-oate, m. p. 126—128°, identical (infrared spectrum) with the sample prepared as above. Elution with 20% of ethyl acetate yielded *methyl* 6α,7α-*dihydroxy*-16-*epi*-(−)-*kauran*-19-*oate* (XXIXb) (44 mg.) which crystallised from acetone–light petroleum in felted needles, m. p. 179—181° (Found: C, 72·0; H, 9·75. $C_{21}H_{34}O_4$ requires C, 72·0; H, 9·8%), $\nu_{max.}$ 3415 and 1696 cm.$^{-1}$.

(ii) 6α,7α-*Dihydroxy*-(−)-*kauran*-19-*oic acid* 19→6α-*lactone* (XXVIIIb). The hydroxy-lactone (28 mg.) was hydrolysed and the product isolated, methylated, and chromatographed as in (i), giving methyl 7-oxo-(−)-kauran-19-oate (10 mg.), m. p. 98—100°, identified by its infrared spectrum, and *methyl* 6α,7α-*dihydroxy*-(−)-*kauran*-19-*oate* (XXIXa) (15 mg.) which crystallised from light petroleum (b. p. 40—60°) in needles, m. p. 170—172° (Found: C, 72·0; H, 9·7. $C_{21}H_{34}O_4$ requires C, 72·0; H, 9·8%), $\nu_{max.}$ 3500, 3460, and 1695 cm.$^{-1}$.

(iii) 6α,7α-*Dihydroxy*-(−)-*kaur*-16-*en*-19-*oic acid* 19→6α-*lactone* (XXVII; R = :CH_2). The hydroxy-lactone (100 mg.) in ethanol (20 ml.) was refluxed with N-sodium hydroxide (20 ml.) for 4 hr. The product was isolated, methylated, and chromatographed as in (i). Elution with 2·5% of ethyl acetate afforded *methyl* 7-*oxo*-(−)-*kaur*-16-*en*-19-*oate* (XX; R = Me, R′ = CO_2Me, R″ = :CH_2) (30 mg.) which crystallised from light petroleum as needles, m. p. 110—112° (Found: C, 76·3; H, 9·3. $C_{21}H_{30}O_3$ requires C, 76·3; H, 9·15%), $\nu_{max.}$ 1706, 1656, and 871 cm.$^{-1}$. The fraction eluted with 10% of ethyl acetate crystallised from acetone–light petroleum in needles (60 mg.) of *methyl* 6α,7α-*dihydroxy*-(−)-*kaur*-16-*en*-19-*oate* (XXX; R = :CH_2), m. p. 165—167° (Found: C, 72·3; H, 9·4. $C_{21}H_{32}O_4$ requires C, 72·4; H, 9·3%), $\nu_{max.}$ (in $CHCl_3$) 1698 and 1653 cm.$^{-1}$.

(iv) 6α,7α-*Dihydroxy*-16-*oxo*-17-*nor*-(−)-*kauran*-19-*oic acid* 19→6α-*lactone* (XXVII; R = O). The hydroxy-lactone (100 mg.) was hydrolysed and the product isolated, methylated, and chromatographed as in (i). Elution with 20% ethyl acetate–light petroleum gave methyl 7,16-dioxo-17-nor-(−)-kauran-19-oate (XX; R = Me, R′ = CO_2CH_3, R″ = O) (25 mg.) which crystallised from acetone–light petroleum as needles, m. p. 130—131°. Further elution with 40—60% of ethyl acetate–light petroleum gave *methyl* 6α,7α-*dihydroxy*-16-*oxo*-17-*nor*-(−)-*kauran*-19-*oate* (XXX; R = O) (50 mg.) which crystallised from acetone–light petroleum as needles, m. p. 186—188° (Found: C, 68·8; H, 8·8. $C_{20}H_{30}O_5$ requires C, 68·5; H, 8·6%), $\nu_{max.}$ (in $CHCl_3$), 3609, 3565, 3422, 1737, and 1704 cm.$^{-1}$.

Ozonolysis of 6α,7α-*Dihydroxy*-(−)-*kaur*-16-*en*-19-*oic Acid* 19→6α-*Lactone* (XXVII; R = $:CH_2$).—The hydroxy-lactone (300 mg.) in acetic acid (15 ml.) was ozonised for 5 min. (12 mg. of O_3 per min.). The solution was made alkaline with aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The extract was washed with water, dried, and evaporated, to give 6α,7α-*dihydroxy*-16-*oxo*-17-*nor*-(−)-*kauran*-19-*oic acid* 19→6α-*lactone* (XXVII; R = O) (250 mg.) which crystallised from acetone–light petroleum as needles, m. p. 234—235° (Found: C, 71·7; H, 8·4. $C_{19}H_{26}O_4$ requires C, 71·7; H, 8·2%), $\nu_{max.}$ 3550, 1766, and 1733 cm.$^{-1}$.

Elimination of Toluene-p-*sulphonic Acid from the Toluene*-p-*sulphonates of* β-*Dihydro*-7-*hydroxykaurenolide* (Ib) *and its* 7-*Epimer* (XXVIIIb).—β-Dihydro-7-toluene-*p*-sulphonyloxykaurenolide (22 mg.) was refluxed in collidine for 15 min. The cooled solution was added to iced dilute hydrochloric acid and extracted with ethyl acetate. The extract was washed with dilute hydrochloric acid and water, and the product was chromatographed on alumina (ethyl acetate–light petroleum). Elution with 5% of ethyl acetate gave the enol-lactone (XXVI; R = β-H, α-Me) (1 mg.); the 10% ethyl acetate fraction furnished starting material (18 mg.).

Treatment of the toluene-*p*-sulphonate of the 7-epi-alcohol (XXVIIIb) (22 mg.) under identical conditions gave the enol-lactone (XXVI; R = β-H, α-Me) (1 mg.) and starting material (17 mg.). The comparative percentage yields (±5%) of enol-lactone obtained from the two toluene-*p*-sulphonates at various reflux times are given in Table 1.

Treatment of Methyl 6α,7α-*Dihydroxy*-16-*oxo*-17-*nor*-(−)-*kauran*-19-*oate* (XXX; R = O) *and its* 7β-*Epimer* (IX; R = Me) *with Periodate.*—The 6α,7α-diol (85 mg.) was dissolved in methanol (2 ml.) and treated overnight with a solution of sodium metaperiodate (100 mg.) in dilute hydrochloric acid (2 ml.). The solution was diluted with water and extracted with ethyl acetate. The extract was washed with sodium hydrogen carbonate solution and water and dried. Evaporation of the solvent gave a gum which was chromatographed on alumina. Elution with 15% ethyl acetate–light petroleum gave *methyl* 6,7,16-*trioxo*-6,7-*seco*-17-*nor*-(−)-*kauran*-19-*oate* (XXII; R = R′ = CHO, R″ = O) (23 mg.) which crystallised from acetone–light petroleum as needles, m. p. 127—128° (Found: C, 68·9; H, 8·1. $C_{20}H_{28}O_5$ requires C, 68·9; H, 8·1%), $\nu_{max.}$ 1753, 1732, and 1713 cm.$^{-1}$, τ 9·0, 8·75, 7·8, 7·4, 6·15, 0·05, and −0·01.

The 6α,7β-diol was recovered after treatment with sodium periodate in water.

Oxidation of the Dialdehyde (XXII; R = R′ = CHO, R″ = O).—The above dialdehyde (35 mg.) in pure acetone (2 ml.) was treated with the chromium trioxide reagent (0·02 ml.) at room temperature for 1·5 hr. A few drops of methanol were added, the solution diluted with water and extracted with ethyl acetate, and the extract washed with sodium hydrogen carbonate solution. Acidification of the washings and recovery in ethyl acetate followed by crystallisation of the residue from acetone–light petroleum gave the dicarboxylic acid (XXII; R = R′ = CO_2H, R″ = O) as needles (21 mg.), m. p. 172—173° and 210—212°, identical (infrared spectrum) with the sample prepared as above.

Oxidation of Methyl 6α,7β-*Dihydroxy*-16-*oxo*-17-*nor*-(−)-*kauran*-19-*oate* (IX; R = Me) *with Lead Tetra-acetate.*—(i) *In benzene.* The diol was recovered after treatment with lead tetra-acetate in benzene at room temperature overnight.

(ii) *In benzene–pyridine.* The diol (250 mg.) and lead tetra-acetate (1 g.) in benzene (40 ml.) and dry pyridine (10 ml.) were refluxed for 3 hr. The solution was cooled, then poured into dilute hydrochloric acid (150 ml.) and extracted with ethyl acetate. The extract was washed with dilute hydrochloric acid, sodium hydrogen carbonate solution, and water and dried. Evaporation of the solvent gave a neutral gum (220 mg.). Chromatography of this on silica gel and elution with 15% of ethyl acetate in light petroleum gave the dialdehyde (XXII; R = R′ = CHO, R″ = O) which crystallised from acetone–light petroleum as needles (120 mg.), m. p. 127—129°, identical (infrared spectrum) with the specimen prepared as above.

Treatment of Methyl 6α,7α-*Dihydroxy*-16-*epi*-(−)-*kauran*-19-*oate* (XXIXb) *and Methyl* 6α,7β-*Dihydroxy*-16-*epi*-(−)-*kauran*-19-*oate* (VIIb; R = Me) *with Periodate.*—The 6α,7α-diol (50 mg.) in methanol (10 ml.) was treated with sodium metaperiodate (300 mg.) in water (1 ml.). Dilute sulphuric acid (1 ml.) was added and the mixture left at room temperature for 16 hr. Water (30 ml.) was added, the solution extracted with ethyl acetate, and the gummy product (48 mg.) recovered and chromatographed on alumina (ethyl acetate–light petroleum). The fraction eluted with 15% of ethyl acetate (30 mg.) crystallised from light petroleum (b. p. 40—60°) in feathery needles of *methyl* 6,7-*dioxo*-6,7-*seco*-16-*epi*-(−)-*kauran*-19-*oate* (XXII; R = R′ = CHO, R″ = β-H, α-Me), m. p. 124—128° (decomp.) (Found: C, 72·1; H, 9·4. $C_{21}H_{32}O_4$ requires C, 72·4; H, 9·3%), $\nu_{max.}$ 2715, 1723 (sh), and 1709 cm.$^{-1}$.

In these conditions, methyl 6α,7β-dihydroxy-16-epi-(−)-kauran-19-oate was recovered.

Oxidation of 6α,7α-*Dihydroxy*-16-*epi*-(−)-*kauran*-19-*oic Acid* 19→6α-*Lactone* (XXVIIIb) *with Lead Tetra-acetate.*—The hydroxy-lactone (200 mg.) and lead tetra-acetate (500 mg.) in benzene (50 ml.) were refluxed for 40 hr. The benzene solution was washed with water and dried, the solvent removed, and the product chromatographed on alumina (ethyl acetate–light petroleum). Elution with 20% of ethyl acetate gave (i) 6α-hydroxy-7-oxo-16-epi-(−)-kauran-19-oic acid lactone (IVb) (8 mg.), identified by its infrared spectrum, (ii) a mixture (34 mg.) of the keto-lactone (IVb) and the ether (XXXI), (iii) a mixture (44 mg.) of the keto-lactone (IVb) and starting material, and (iv) starting material (35 mg.). The mixture in fraction (ii) could not be separated by fractional crystallisation or by the Girard technique. Subsequently in a similar oxidation the crude product was treated with an excess of sodium borohydride in methanol to reduce the keto-lactone to the more polar 7-epi-alcohol (XXVIIIb). Chromatography then gave pure 7α,20-*epoxy*-6α-*hydroxy*-16-*epi*-(−)-*kauran*-19-*oic acid lactone* (XXXI) which crystallised from acetone–light petroleum in needles, m. p. 143°, $[\alpha]_D^{24}$ +16° (*c* 0·2) (Found: C, 75·4; H, 8·8. $C_{20}H_{28}O_3$ requires C, 75·9; H, 8·9%), $\nu_{max.}$ no OH absorption, 1780 cm.$^{-1}$ (γ-lactone). The nuclear magnetic resonance spectrum showed peaks at τ 9·1, 8·9 (doublet, $>$CH·CH_3), 8·7 ($CO-\overset{|}{\underset{|}{C}}-CH_3$), and a 2-proton multiplet centred at 6·50 (O·CH_2). Further elution with 20% of ethyl acetate gave the starting diol.

Oxidation of (−)-*Kaur*-16-*ene*-6,19-*diol* (XII).—(i) *With chromic oxide–sulphuric acid.* The chromium trioxide reagent (0·15 ml.) was added dropwise to the diol (50 mg.) in pure acetone (8 ml.), and the mixture left at 0° for 2 hr. Isolation of the products in the usual way gave an acidic (7 mg.) and a neutral (42 mg.) fraction. The latter was chromatographed on alumina. Elution with benzene and 5% of ether in benzene followed by crystallisation from aqueous methanol gave 6-*oxo*-(−)-*kaur*-16-*en*-19-*al* (XXXV; R = CHO, R′ = :CH_2) as long needles, m. p. 165—167° (Found: C, 80·05; H, 9·4. $C_{20}H_{28}O_2$ requires C, 79·95; H, 9·4%), $\nu_{max.}$ (in $CHCl_3$) 1716 (sh), 1705, 1657, and 885 cm.$^{-1}$.

The aldehyde was recovered after treatment with alkaline silver oxide for 1 hr. or alkaline potassium permanganate at room temperature for 2·5 hr. The crude product from prolonged oxidation of the aldehyde with the chromium trioxide reagent showed diminution in the intensity of the terminal methylene band in the infrared.

(ii) *With chromic oxide–pyridine.* (*a*) The diol (180 mg.) in pyridine (1 ml.) was mixed with the complex from chromic oxide (360 mg.) and pyridine (15 ml.) and left for 18 hr. at 0°. The solution was poured into dilute hydrochloric acid (100 ml.) and extracted with ethyl acetate. The extract was washed with dilute hydrochloric acid, ferrous sulphate solution, sodium hydrogen carbonate solution, and water. Recovery gave a gummy residue which was chromatographed on silica gel. Elution with 20% of ethyl acetate in light petroleum followed by crystallisation from ethyl acetate–light petroleum gave 19-*hydroxy*-(−)-*kaur*-16-*en*-6-*one* (XXXV; R = CH_2·OH, R′ = :CH_2) (80 mg.) as needles, m. p. 158—159° (Found: C, 79·8; H, 9·5. $C_{20}H_{30}O_2$ requires C, 79·5; H, 9·9%), $\nu_{max.}$ 3340, 1708, 1661, and 886 cm.$^{-1}$. The nuclear magnetic resonance spectrum showed peaks at τ 9·17 and 9·1 (doublet; 10-methyl; splitting possibly being due to hindered rotation of the hydroxymethyl group [24]), 9·0 (singlet) for C-18, 7·85 (CH_2·C=C), 7·45 (doublet; CH_2·CO), 7·1 ($>$CH·CO), and 5·25 (CH_2·OH). The product did not give a silver mirror with Tollens reagent.

(*b*) Treatment of the diol in pyridine with the chromic oxide–pyridine complex at room temperature for 18 hr. gave the keto-aldehyde (XXXV; R = CHO, R′ = :CH_2) identical with a specimen prepared by method (i).

Hydrolysis of the Enol-lactone (XXVI; R = CH_2) *with Mineral Acid.*—The enol-lactone (75 mg.) in acetone (10 ml.) was refluxed with dilute hydrochloric acid (10 ml.) for 2 hr., the acetone was evaporated, the solution diluted to 250 ml. with water, and the product recovered in ethyl acetate. Crystallisation from acetone–light petroleum gave 16-ξ-*hydroxy*-6-*oxo*-(−)-*kauran*-19-*oic acid* (XXXV; R = CO_2H, R′ = OH,Me) as needles (35 mg.), m. p. 274—275°, pK^*_{MCS} 9·6 (Found: C, 71·6; H, 9·0. $C_{20}H_{30}O_4$ requires C, 71·8; H, 9·0%), $\nu_{max.}$ 3500 (OH), 2745 (OH of CO_2H), 1745 and 1661 cm.$^{-1}$ (C=O). The *methyl ester*, prepared with diazomethane, crystallised from light petroleum as needles, m. p. 112—113° (Found: C, 72·5; H, 9·3. $C_{21}H_{32}O_4$ requires C, 72·4; H, 9·3%), $\nu_{max.}$ 3430, 1741, and 1706 cm.$^{-1}$; (in $CHCl_3$) 3480, 1728, and 1717 cm.$^{-1}$.

[24] Enzell, *Acta Chem. Scand.*, 1961, **15**, 1303.

Preparation of 6-*Oxo*-(−)-*kaur*-16-*en*-19-*oic Acid* (XXXV; R = CO_2H, R′ = :CH_2).—A solution of 7-toluene-*p*-sulphonyloxykaurenolide (400 mg.) and dry lithium iodide (500 mg.) in dry collidine (15 ml.) was refluxed for 5 hr., then poured into dilute hydrochloric acid (100 ml.) and extracted with ether. The extract was washed with dilute hydrochloric acid, sodium thiosulphate solution, and water and dried. Evaporation gave a crystalline residue which recrystallised from acetone–light petroleum to give 6-*oxo*-(−)-*kaur*-16-*en*-19-*oic acid* as needles (320 mg.), m. p. 205—206°, pK^*_{MCS} 9·25 (Found: C, 75·8; H, 8·9. $C_{20}H_{28}O_3$ requires C, 75·9; H, 8·9%), $\nu_{max.}$ 2720 (br.), 1740, 1659s (C=O and C=C), and 893 cm.$^{-1}$. The methyl ester, prepared with diazomethane, was a gum.

Reduction of 6-*Oxo*-(−)-*kaur*-16-*en*-19-*al* (XXXV; R = CHO, R′ = :CH_2).—The aldehyde (20 mg.) was reduced with lithium aluminium hydride (30 mg.) in ether (10 ml.) at room temperature for 12 hr. Isolation of the product in the usual way afforded (−)-kaur-16-ene-6α,19-diol (XII) (13 mg.), m. p. 174—175°, identical with the sample prepared by reduction of 7-toluene-*p*-sulphonyloxykaurenolide (above). The mother-liquors gave the crude diol (6 mg.), m. p. 168—175°.

Reduction of 6-*Oxo*-(−)-*kaur*-16-*en*-19-*oic Acid to the Diol* (XII).—The keto-acid (50 mg.), in tetrahydrofuran (2 ml.) and methanol (2 ml.), was treated with sodium borohydride (52 mg.) with cooling. After 2 hr. the solution was acidified, diluted with water to 100 ml., and extracted with ether. The recovered gum was methylated with diazomethane, taken up in dry ether (5 ml.), and treated with lithium aluminium hydride (49 mg.) at room temperature for 2 hr. The excess of lithium aluminium hydride was destroyed with 20% of ethyl acetate in ether, followed by water and dilute hydrochloric acid. The solution was extracted with ether, and the extract washed with water, dried, and evaporated. The residue crystallised from acetone–light petroleum as needles (15 mg.) of (−)-kaur-16-ene-6α,19-diol (XII), m. p. 173—175°, identified by its infrared spectrum.

Stability of 6-*Oxo*-(−)-*kaur*-16-*en*-19-*al* (XXXV; R = CHO, R′ = :CH_2) *to Alkali*.—6-Oxo-(−)-kaur-16-en-19-al (24 mg.) in methanol (0·5 ml.) was refluxed with 0·1N-sodium hydroxide solution (5 ml.) for 1 hr. The solution was acidified, diluted with water, and extracted with ether. Evaporation of the solvent and crystallisation of the residue from acetone–light petroleum gave the starting keto-aldehyde (15 mg.) as needles, m. p. 165—167°, identified by its infrared spectrum.

Rotatory Dispersion Curves.—Values are for [*M*], in methanol, for the ketones. (XIX; R = O): positive Cotton effect curve (500 mμ) +40°; (317·5, peak) +3650°; (276, trough) −6600°; (273) −6500°. (III): positive Cotton effect curve (500 mμ) +500°; (316, peak) +6200°; (274, trough) −7150°; (270) −6850°. (IX; R = Me): positive Cotton effect curve (500 mμ) −200°; (317·5, peak) +3575°; (277·5, trough) −6200°; (272·5) −5800°. (Xa): positive Cotton effect curve (500 mμ) −175°; (311, peak) +3400°; (269, trough) −9175°; (266) −9075°. Methyl ester of (Xa): positive Cotton effect curve (500 mμ) −250°; (309, peak) +3125°; (264) −9300°. (IVa): negative Cotton effect curve (500 mμ) +200°; (340, peak) +800°; (317·5, trough) +325°; (281, peak) +825°; (278) +625°. (XXXV; R = CO_2H, R′ = OH, Me): negative Cotton effect curve (500 mμ) −1950°; (319, trough) −2825°; (312 peak) −2400°; (304, trough) −3250°; (299, peak) −3125°; (292·5, trough) −3525°; (285 peak) −2125°; (281) −2225°. (XXXV; R = CO_2Me, R′ = OH, Me): negative Cotton effect curve (500 mμ) −500°; (310, trough) −3300°; (270, peak) +1725°; (266) +1350°. (XXXV; R = CO_2H, R′ = :CH_2): negative Cotton effect curve (500 mμ) −1000°; (305, trough) −4650°; (272, peak) −2725°; (267) −3175°. The aldehyde (XVI): positive Cotton effect curve (500 mμ) −475°; (314, peak) +350°; (269, trough) −2800°; (267) −2600°. The acid (XIIIa): negative plain curve (500 mμ) −200°; (400) −450°; (285) −1100°. The alcohol (XIVa): negative plain curve (500 mμ) −100°; (400) −175°; (285) −550°.

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