972. *New Metabolites of* Gibberella fujikuroi. *Part V.*[1] *The Structures of Fujenal and Fujenoic Acid.*

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Fujenal and fujenoic acid have been degraded to 19-methyl dihydrogen 16-oxo-6,7-seco-17-norkaurane-6,17,19-trioate (XV), previously derived from 7-hydroxykaurenolide. On the basis of this and other evidence they are shown to have the structures and absolute configurations represented by (II) and (III), respectively.

The isolation of fujenal and fujenoic acid and the characterisation of the former as a tricarbocyclic compound containing 5-membered ring anhydride, aldehyde, and terminal methylene groups has been described in Part II.[2] The relations of fujenal and fujenoic acid to 7-hydroxykaurenolide [3] (I) and evidence for their structures, which has been briefly reported elsewhere,[4] is set out in full in this paper.

The nuclear magnetic resonance spectrum (see Table) of fujenal (II) showed that the aldehyde group must be tertiary, since it contained a one proton singlet at τ 0·13, and disclosed two tertiary non-equivalent methyl groups (τ 9·14 and 8·62). The presence of the anhydride ring, which is rare in natural products (cf. ref. 5), was confirmed by the infrared spectra of several derivatives of fujenal (see Experimental section). The terminal methylene group in fujenal, which yielded 0·45 mol. of formaldehyde on ozonolysis in acetic acid, was shown to be exocyclic to a 5-membered ring when ozonolysis in ethyl acetate gave the nor-ketone (V), $\nu_{max.}$ (in $CHBr_3$) 1856 and 1779 (5-ring anhydride), 1748 (5-ring ketone), 1720 cm.$^{-1}$ (aldehyde). Infrared estimation [6] of the absorption of the α-methylene ketone at 1404 cm.$^{-1}$ showed the presence of one such group relative to camphor. Attempts to confirm this by oxidation with selenium dioxide and condensation with benzaldehyde failed,* and with *N*-bromosuccinimide fujenal nor-ketone (V) gave only fujenic acid nor-ketone (VI). However, treatment of the nor-ketone (V) with bromine in acetic acid gave a monobromo-compound (VIII). Its nuclear magnetic resonance spectrum (see Table) no longer showed peaks attributable to the grouping CH_2·CO but contained a singlet at τ 5·7 ascribed to C*H*Br·CO. The bromo-compound was inert to dimethyl sulphoxide.

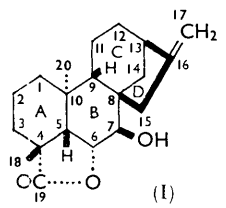
Fujenoic acid, $C_{20}H_{26}O_5$ (III), which titrated as a weak monobasic acid (pK_{H_2O} 5·46), gave a monomethyl ester (IV) and, on hydrogenation,[2] a dihydro-compound. The infrared spectrum of fujenoic acid [$\nu_{max.}$ (in $CHCl_3$) 2609 (OH of carboxyl), 1859 and 1783 (5-ring anhydride), 1699 (carboxyl), and 1662 and 897 cm.$^{-1}$ (terminal methylene)] suggested that it was the acid corresponding to fujenal. This was shown to be the case by oxidation of fujenal with an excess of chromic oxide and sulphuric acid in acetone, which afforded fujenoic acid, the nor-ketone (V) (1% yield) previously obtained by ozonolysis of fujenal, and the nor-ketone acid (VI). The latter acid was also prepared by oxidation of the nor-ketone (V) with chromic oxide. Ozonolysis of methyl fujenoate (IV) gave the nor-ketone (VII).

The anhydride ring of fujenal was stable to boiling ethanol and to cold methanolic ammonia.[2] Alkaline hydrolysis followed by potentiometric back-titration gave an

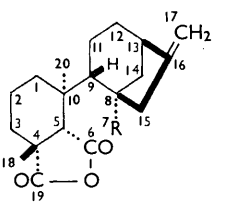
* Attempts to oxidise the structurally similar veatchine 16-ketone with selenium dioxide also failed.[7]

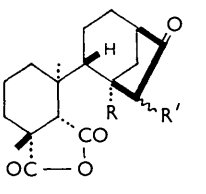
[1] Part IV, Cross, Galt, and Hanson, *J.*, 1963, 3783.
[2] Part II, Cross, Galt, Hanson, Curtis, Grove, and Morrison, *J.*, 1963, 2937.
[3] Part III, Cross, Galt, and Hanson, *J.*, 1963, 2944.
[4] Cross, Galt, Hanson, and Klyne, *Tetrahedron Letters*, 1962, 145.
[5] Baldwin, Barton, Bloomer, Jackman, Rodriguez-Hahn, and Sutherland, *Experientia*, 1962, **18**, 345.
[6] Barnes, Barton, Cole, Fawcett, and Thomas, *J.*, 1953, 571.
[7] Cf. Vorbrueggen and Djerassi, *J. Amer. Chem. Soc.*, 1962, **84**, 2990.

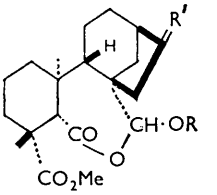
equivalent weight (164) corresponding to a dibasic acid, but when phenolphthalein was used for the back-titration the apparent equivalent weight was 306 (cf. ref. 2). The explanation of this is uncertain but it may be significant that working-up after the back-titrations gave only intractable gums. When fujenal was heated with methanol at 160° in a sealed tube for four days two dimethyl esters, $C_{22}H_{32}O_5$ and $C_{23}H_{36}O_6$, were formed. The former contained one double bond, as revealed by microhydrogenation and titration with perbenzoic acid. As in fujenal, the double bond was shown to constitute an exocyclic methylene grouping by ozonolysis in acetic acid, which gave formaldehyde and a nor-ketone, $C_{21}H_{30}O_6$. The latter was prepared in better yield by ozonolysis in ethyl acetate at −70° followed by working-up with triphenylphosphine. The dimethyl ester, $C_{22}H_{32}O_5$, showed neither hydroxyl nor aldehydic C–H absorption in the infrared spectrum and it did not give an oxime. Its nor-ketone, which gave only a mono-oxime, was resistant to further oxidation and hence the remaining oxygen atom must be present as an ether linkage. For clarity, the degradative sequence described below will be referred to structure (IX) established in the sequel for the ester, $C_{22}H_{32}O_5$.



(I)







(II: R = CHO) (III: R = CO_2H) (IV: R = CO_2Me)

(V: R = CHO, R′ = H) (VI: R = CO_2H, R′ = H) (VII: R = CO_2Me, R′ = H) (VIII: R = CHO, R′ = Br)

(IX: R = Me, R′ = CH_2) (X: R = Me, R′ = O) (XI: R = H, R′ = O) (XII: R = Me, R′ = Me, OMe) (XIII: R = Me, R′ = Me, Cl)

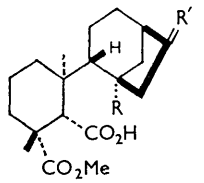
Hydrolysis of the ester (IX) with mineral acid at 60° afforded the monobasic acid, $C_{21}H_{32}O_6$ (XIV), shown by its analysis and infrared spectrum [$\nu_{max.}$ 3455 (OH), 2695 (aldehydic C–H) and 1713 cm.$^{-1}$; no C=C absorption] to be a hydroxy-aldehydic mono-ester. It took up no hydrogen on microhydrogenation. Hence, as in the conversion of 7,18-dihydroxykaurenolide into 7,16,18-trihydroxykaurenolide,[1] hydration of the terminal methylene group had occurred.[8,9] The regeneration of the aldehyde group concomitant with partial hydrolysis of the dimethyl ester, and the disappearance of the ether linkage, suggested that this is a case of pseudo-ester hydrolysis. This interpretation was supported by the nuclear magnetic resonance spectrum of the ester (IX) (see Table) which included resonances due to two tertiary methyl groups (τ 8·76 and 8·63), two distinguishable methoxyl groups (τ 6·49 and 6·31), and a one proton singlet at τ 5·48 attributed to the grouping O·C*H*·O, *i.e.*, to the unique proton attached to C-7. This agrees with the τ value of 5·6 shown by the α-hydroxy-lactone[10] (XVII) derived from actinospectacin but is higher than values given by the 16-proton in dihydroclerodin derivatives[11] which fall in the range τ 4·3—4·7.

Hydrolysis of the pseudo-ester nor-ketone (X) with boiling mineral acid regenerated fujenal nor-ketone (V), showing that no skeletal rearrangement had occurred during the methanolysis. However, if the acid hydrolysis of the pseudo-ester (X) was carried out at 60° the product was a monomethyl ester, $C_{20}H_{28}O_6$, shown by its infrared spectrum [$\nu_{max.}$ 3330 (OH), 1752 (cyclopentanone), 1726 and 1710 cm.$^{-1}$ (ester and 7-ring lactol)] to

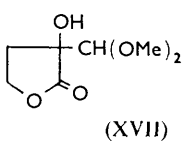
[8] Grove, *J.*, 1961, 3545.
[9] Cross, Galt, and Hanson, *Tetrahedron*, 1962, **18**, 451.
[10] Chapman, Autrey, Gourlay, Johnson, Souts, and Tarbell, *Proc. Nat. Acad. Sci. U.S.A.*, 1962, **48**, 1108.
[11] Barton, Cheung, Cross, Jackman, and Martin-Smith, *J.*, 1961, 5061.

be in the lactol form (XI) [cf. (XIV) above]. Oxidation of the lactol with chromic oxide and sulphuric acid in acetone afforded the dicarboxylic acid (XV), previously obtained [3] from 7-hydroxykaurenolide, thus establishing the carbon skeleton of fujenal as a B-seco-kaurene and determining the stereochemistry at all centres except C-5. It follows that the three oxygenated groups of fujenal correspond to carbon atoms 6, 7, and 19 of 7-hydroxykaurenolide (I). Since the anhydride ring of fujenal is 5-membered it must be derived from 6- and 19-carboxyl groups, and the above relationship established the identity of the methoxycarbonyl group in the methanolysis product (IX) as C-19 of 7-hydroxykaurenolide. The stereochemistry at position 5 has not been rigorously established; however, it is likely that the configuration at this centre is the same as in 7-hydroxykaurenolide (I) for two reasons. First, it has been shown [3] that epimerisation at position 5 does not occur in the two 6-oxokaurenolide derivatives (XVIII) and (XIX). Secondly, if epimerisation did take place at position 5, the anhydride ring could only be formed if ring A either took up a boat conformation or underwent inversion. In the latter event the very bulky rings C and D would have to assume the unfavourable axial conformation at C-10 and this is not compatible with the ease with which the anhydride ring in fujenal is formed. Hence fujenal and fujenoic acid have been assigned the structures and absolute configurations (II) and (III), respectively.

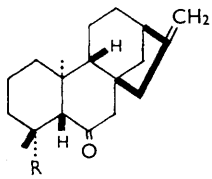
The structure of the other methanolysis product of fujenal, the ester $C_{23}H_{36}O_6$, now follows. In bromoform solution it showed a carbonyl band at 1719 cm.$^{-1}$ but no hydroxyl or olefinic double-bond absorption. It was inert to microhydrogenation and it did not



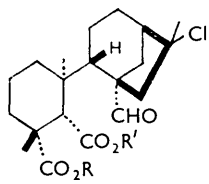
(XIV: R = CHO, R' = OH, Me)
(XV: R = CO_2H, R' = O)
(XVI: R = CO_2H, R' = OH, Me)



(XVII)



(XVIII: R = CHO)
(XIX: R = CO_2H)



(XX: R = Me, R' = H)
(XXI: R = H, R' = Me)

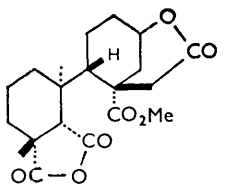
form an oxime. These facts, together with its co-formation with the pseudo-ester (IX), suggested that it had structure (XII), derived by addition of methanol to the double bond. This was borne out by its nuclear magnetic resonance spectrum which showed singlets assigned to three tertiary methyl groups at τ 8·76, 8·72, and 8·64, to three methoxyl groups at τ 6·86, 6·50, and 6·29 and to the 7-proton at τ 5·41. Thus additional tertiary methyl and methoxyl groups have been produced, as compared with the ester (IX). The new methoxyl resonance (at τ 6·86), unlike the other two, is not deshielded by oxygen substituents attached to the same carbon atom.

The pseudo-ester (IX) was also prepared, albeit in lower yield, by treatment of fujenal with methanolic hydrogen chloride. This reaction gave also an isomeric dimethyl ester, a chloro-dimethyl ester, $C_{22}H_{33}ClO_5$, and a chloro-acid, $C_{21}H_{31}ClO_5$. The isomeric dimethyl ester has been formulated as the 15,16-unsaturated compound corresponding to (IX) (cf refs. 1 and 3) on the basis of its infrared spectrum which showed absorption attributed to carbonyl (1736 cm.$^{-1}$) and a trisubstituted double bond (3038, 1682, 833, and 810 cm.$^{-1}$) but no bands due to aldehydic C–H or terminal methylene groups. In carbon tetrachloride solution the chloro-ester showed a broad carbonyl band at 1738 cm.$^{-1}$ but no aldehydic C–H or olefinic double-bond absorption. Consequently it has been assigned the pseudo-ester structure (XIII). Dehydrochlorination of the chloro-ester with sodium iodide in dimethylformamide gave the 15,16-unsaturated ester. The chloro-acid, $C_{21}H_{31}ClO_5$, titrated as a monobasic acid and in bromoform solution it showed bands at 2717 (aldehydic C–H), 1739 (ester), and 1676 cm.$^{-1}$ (carboxyl-carbonyl) but no absorption

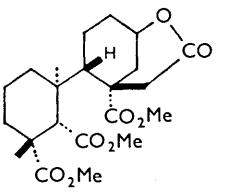
attributable to olefinic double bonds. With diazomethane it gave the chloro-ester (XIII) and it is therefore formulated as (XX) rather than (XXI).

Before the carbon skeleton of fujenal had been established by degradation to the dicarboxylic acid (XV) an attempt was made to prepare a D-seco-derivative suitable for the investigation of the stereochemistry at position 9 by optical rotatory dispersion methods.[12] Baeyer–Villiger oxidation of the nor-ketone ester (VII) gave the δ-lactone (XXII). Although hot hydrolysis of the latter gave a result corresponding to only one carboxyl group, alkaline hydrolysis at room temperature followed by methylation with diazomethane gave the triester δ-lactone (XXIII). The latter again titrated as a monobasic acid after hydrolysis but, on the preparative scale, hydrolysis gave only intractable gums.

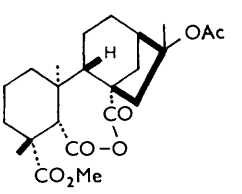
Similarly attempts were made to inter-relate the anhydride and the aldehyde group in fujenal and to substantiate the infrared evidence for a 5-membered anhydride ring. Thus oxidation of the aldehydo-acid (XIV) with chromic oxide and sulphuric acid in acetone gave the dicarboxylic acid (XVI) which in refluxing acetic anhydride formed the acetoxy-anhydride (XXIV). The infrared spectrum of the latter showed, in addition to ester bands, carbonyl bands at 1795 and 1751 cm.$^{-1}$ consistent with the formation of an unstrained 7-membered-ring anhydride. Reduction of fujenal with sodium borohydride



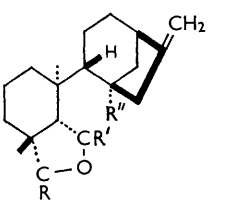
(XXII)



(XXIII)



(XXIV)



(XXV: R = H_2, R′ = O, R″ = CH_2·OH)
(XXVI: R = H_2, R′ = O, R″ = CO_2H)
(XXVII: R = H_2, R′ = O, R″ = CHO)
(XXVIII: R = O, R′ = H_2, R″ = CH_2·OH)

or lithium aluminium hydride led to a monohydroxy-γ-lactone (XXV), $\nu_{max.}$ 1768 cm.$^{-1}$, and with the former reagent, as a minor product, the related lactol, $C_{20}H_{30}O_4$. Similarly reduction of fujenoic acid with lithium aluminium hydride gave a γ-lactonic acid (XXVI), $\nu_{max.}$ 1779 and 1710 cm.$^{-1}$, as the major product.

The lactone (XXV) was resistant to hydrolysis by potassium carbonate and methyl iodide. It was recovered from attempted acetylation, thus showing the hydroxyl group to be hindered, but on mild oxidation in acetone solution with chromic oxide and sulphuric acid it gave an aldehyde (XXVII), $\nu_{max.}$ 2708 (aldehydic C–H) cm.$^{-1}$. The nuclear magnetic resonance spectra of the hydroxy-lactone (XXV) and the aldehydo-lactone (XXVII) distinguished between the two possible orientations of the lactone ring, namely (XXV) and (XXVIII). The former showed a singlet due to the 5-proton (see Table) and both contained sharp doublets at τ 5·95 and 6·24 (J 9 c./sec.), *i.e.*, an AB spectrum ascribed to the 19-protons in each case; in the spectrum of the aldehydo-lactone (XXVII) the resonances due to the protons attached to C-5, C-13, and C-15 were not clearly resolved. If the lactone ring was orientated as in (XXVIII), then the 5-proton resonance would be split by the two protons on C-6 and at least one of the latter (non-equivalent protons) should be further split by the adjacent tertiary proton at position 5, giving rise to a more complex ABX spectrum.

The nuclear magnetic resonance spectroscopy data for fujenal and a number of derivatives are shown in the annexed Table. The methyl resonances ascribed to C-20

[12] Djerassi, "Optical Rotatory Dispersion: Applications to Organic Chemistry," McGraw-Hill, New York, 1960, p. 104.

Nuclear magnetic resonance results (τ values).

Compound	C–Me			Protons at			Methoxyls			$=CH_2$	$C_{(7)}$–H
	20	18	17	15 *	13 *	5	7	19	16		
II	9·14	8·62		7·7	7·15	7·37				5·1	0·13
V	9·05	8·61		7·88—7·1		7·37					
VIII	9·06	8·58		5·7	7·1	7·36					
IX	8·76	8·63		7·75	7·3	6·61	6·49	6·31		5·2	5·48
XII	8·76	8·64 or 8·72	8·72 or 8·64			6·65	6·5	6·29	6·86		5·41
XXV	8·84	8·67		7·6	7·25	7·82				5·2	5·75, 6·75 (J = 12 c./sec.)
XXVII	9·1	8·85		7·7 to 7·2						5·16	0·2
IV	9·08	8·62		7·5—7·2		7·41	6·27			5·1	

* The protons at positions 15 and 13 were differentiated by the relative areas of the peaks which were in the ratio of 2 : 1.

showed a marked shift downfield (from ~9·1 to ~8·8) both on formation of the pseudo-ester and on reduction of the 7-aldehyde or 7-carboxyl group to an alcohol. There is also a marked downfield shift in the position of the 5-proton resonance on formation of the pseudo-ester. That this proton is at position 5 and is not a ring-D proton was established since it is invariant in position when ring D is modified as in (VIII). These changes in chemical shift may be associated with alteration in the shape of the shielding cone of the $C_{(7)}$–O bonds. The alternative suggestion that the changes are associated with inversion of configuration at position 5 seems less likely since the methyl resonance moves back upfield on mild oxidation of the alcohol (XXV) to the aldehyde (XXVII). Examination of molecular models shows not only that is rotation about the 9,10-bond hindered but also that the primary 7-alcohol group in (XXV) must be subject to restricted rotation about the 7,8-bond, thus accounting for the non-equivalent hydroxylmethyl protons.

The optical rotatory dispersion curve of fujenal showed a negative Cotton effect. Like the nor-ketones [3] of the kaurenolides the nor-ketone (VII) showed a positive Cotton effect although of a diminished amplitude ($10^{-2}a$, + 19°).

Experimental

For details of chromatographic materials and conditions used for the determination of physical data, etc., see Part II.[2]

Nuclear magnetic resonance spectra were measured for chloroform or deuterochloroform solutions on a Varian Associates A.60 spectrometer (60 Mc.) and had tetramethylsilane as internal standard with τ 10·00.

Ozonolysis of Fujenal.—(*a*) *In acetic acid.* Ozonised oxygen (6·2 mg. of O_3 per min.) was passed through a solution of fujenal (110 mg.) in acetic acid (10 ml.) for 6 min. at room temperature. The solution was left for 1 hr., diluted with water (25 ml.), and steam-distilled. Treatment of the distillate with saturated aqueous dimedone (30 ml.) gave, after 1 week, formaldehyde dimethone (45 mg., 0·45 mol.) as needles, m. p. 188°, identical with an authentic sample. The non-steam-volatile residue was made alkaline with aqueous sodium hydrogen carbonate, but extraction with ethyl acetate gave an intractable ketonic gum (55 mg.).

(*b*) *In ethyl acetate.* Ozonised oxygen (8·4 mg. of O_3 per min.) was passed through a solution of fujenal (1·04 g.) in ethyl acetate (75 ml.) at −70° for 27 min. Triphenylphosphine (900 mg.) was then added and the solution kept at 0° overnight. The solvent was evaporated and the residual gum chromatographed on silica gel (35 × 3 cm.). Elution with ether gave 7,16-*dioxo*-6,7-*seco*-17-*norkaurane*-6,19-*dioic anhydride* (V) (900 mg.) which crystallised from ethyl acetate–light petroleum as needles, m. p. 176°, $[\alpha]_D^{25}$ −17° (*c* 0·2) (Found: C, 68·5; H, 7·25. $C_{19}H_{24}O_5$ requires C, 68·65; H, 7·3%), $\nu_{max.}$ (in $CHBr_3$) 2744 (aldehyde C–H), 1856 and 1779 (5-ring anhydride), 1748 (cyclopentanone), and 1720 cm.$^{-1}$ (aldehyde C=O). In CCl_4 solution the intensity [6] of the band at 1404 cm.$^{-1}$ corresponded to 0·84 CH_2·CO group relative to the band in camphor at 1420 cm.$^{-1}$. Oxidation of the nor-ketone with selenium dioxide in refluxing acetic anhydride or ethanol for 18 hr. gave, after recovery with ethyl acetate, intractable gums. Treatment with benzaldehyde and piperidine in methanol at room temperature for 42 hr. in

the dark gave gums whose infrared spectra no longer contained bands due to the 5-ring anhydride. The ketone, when shaken with a 1% ethanolic solution of 2,2′-dinitrobiphenyl and one drop of 10% tetraethylammonium hydroxide solution, gave a weak violet colour.

Attempted Brominations of Fujenal Nor-ketone (V).—(1) The nor-ketone (160 mg.), freshly prepared *N*-bromosuccinimide (95 mg.), and benzoyl peroxide (20 mg.) in carbon tetrachloride (25 ml.), were refluxed for 2·5 hr., then cooled and diluted with carbon tetrachloride. The solution was washed with ferrous sulphate solution and water, dried, and evaporated to give a gum which was chromatographed on silica gel. Elution with 1 : 1 ethyl acetate–light petroleum gave fujenoic acid nor-ketone (VI) (80 mg.) as prisms (from chloroform–light petroleum), m. p. 249—250°, identical with the sample prepared as below. Under similar conditions fujenoic acid was recovered.

(2) The nor-ketone (200 mg.) in acetic acid (5 ml.) was treated with a solution [4·2 ml., prepared from bromine (1·25 g.) in acetic acid (25 ml.) and 48% hydrobromic acid (0·2 ml.)] and left at room temperature overnight. The solution was poured into water and made alkaline with sodium hydrogen carbonate solution, and the excess of bromine was discharged with sodium metabisulphite. The product, recovered in ethyl acetate, crystallised from acetone–light petroleum giving 15-*bromo*-7,16-*dioxo*-6,7-*seco*-17-*norkaurane*-6,19-*dioic anhydride* (VIII) as prisms, m. p. 216—217° (decomp.) (Found: C, 56·5, 56·9; H, 5·8, 6·0 $C_{19}H_{23}O_5Br,Me_2CO$ requires C, 56·3; H, 6·2%), $\nu_{max.}$ 1860 and 1783 (5-ring anhydride), 1762 (α-bromocyclopentanone), 1722 cm.$^{-1}$ (aldehyde C=O). The α-bromo-ketone was recovered from refluxing dimethyl sulphoxide.

Preparation of the Fujenal Trimethylene Thioketal.—(1) Fujenal (500 mg.) in chloroform (15 ml.) was treated with propane-1,3-dithiol (1·5 ml.) in ether (15 ml.) and boron trifluoride–ether complex (0·1 ml.) for 2 hr. The solution was diluted with ethyl acetate, washed, and dried. The solvent was evaporated and the residual gum chromatographed on silica gel. Elution with 1 : 4 ether–light petroleum gave the *thioketal* (265 mg.) which crystallised from ethyl acetate as rhombs, m. p. 158—160° (Found: C, 65·2; H, 7·8. $C_{23}H_{32}O_3S_2$ requires C, 65·7; H, 7·6%).

Oxidation of Fujenal.—Fujenal (100 mg.) in pure acetone (5 ml.) was treated with the 8N-chromium trioxide reagent [3,13] (0·2 ml.) at room temperature for 1 hr. Methanol (1 ml.) was then added, followed by water (100 ml.). Isolation of the products in the usual way gave a neutral (67 mg.) and an acidic gum (30 mg.). The former was chromatographed on silica gel (15 × 1 cm.). Elution with 1 : 4 ether–light petroleum gave the starting material (26 mg.); further elution with 1 : 1 ether–light petroleum gave fujenoic acid (III) (30 mg.) which crystallised from ethyl acetate–light petroleum as needles, m. p. 215°, identical (infrared spectrum) with naturally occurring material.[2]

Methyl fujenoate (IV), prepared with diazomethane, crystallised from ethyl acetate–light petroleum as needles, m. p. 175° (Found: C, 70·1; H, 7·8. $C_{21}H_{28}O_5$ requires C, 70·0; H, 7·8%), $\nu_{max.}$ (in $CHBr_3$) 1857 and 1774 (5-ring anhydride), 1723 (ester), and 1655 cm.$^{-1}$ (C=C).

The acidic gum was chromatographed on silica gel–Celite (1 : 2) (15 × 1 cm.). Elution with 1 : 19 ethyl acetate–chloroform gave 16-*oxo*-6,7-*seco*-17-*norkaurane*-6,7,19-*trioic* 6,19-*anhydride* (VI) (17 mg.) which crystallised from chloroform–light petroleum as prisms, m. p. 251—252° (decomp.) [Found: C, 65·2; H, 7·0%; Equiv., 185, 187. $C_{19}H_{24}O_6$ requires C, 65·5; H, 6·9%; Equiv. (dibasic), 174], $\nu_{max.}$ 3150 (br) (OH of CO_2H), 1850 and 1781 (5-ring anhydride), 1735 (cyclopentanone), and 1722 cm.$^{-1}$ (C=O of CO_2H).

The *methyl ester*, prepared with diazomethane, crystallised from ethyl acetate–light petroleum as needles, m. p. 214° (Found: C, 66·0; H, 7·3; OMe, 9·0. $C_{20}H_{26}O_6$ requires C, 66·3; H, 7·2; OMe, 8·6%), $\nu_{max.}$ (in $CHBr_3$) 1855 and 1779 (5-ring anhydride), 1741 (cyclopentanone), and 1729 cm.$^{-1}$ (ester).

Repetition of the oxidation on a larger scale and elution of the column with 3 : 1 ether–light petroleum occasionally gave the nor-ketone (V), m. p. 174—175°, in yields of 1—5%.

Dihydrofujenoic Acid.—On microhydrogenation in acetic acid over palladium black, fujenoic acid (6·537 mg.) took up 1·05 mol. of hydrogen in 32 min. Crystallisation of the product from ethyl acetate–light petroleum gave *dihydrofujenoic acid* as prisms, m. p. 207—210° (decomp.) (Found: C, 68·65; H, 8·25%; Equiv., 362. $C_{20}H_{28}O_5$ requires C, 68·9; H, 8·1%; *M*, 348), $\nu_{max.}$ 2560 (OH of CO_2H), 1857 and 1788 (5-ring anhydride), and 1686 cm.$^{-1}$ (C=O of CO_2H).

Oxidation of the Nor-ketone (V).—The nor-ketone (500 mg.) in acetone (10 ml.) was treated

[13] Curtis, Heilbron, Jones, and Woods, *J.*, 1953, 347.

with the 8N-chromium trioxide reagent (0·5 ml.) for 1 hr. at room temperature. Methanol (2 ml.) was added and the solution diluted with water (200 ml.). Recovery with ethyl acetate gave an acidic gum (470 mg.) which was chromatographed on silica gel (20 × 1·5 cm.). Elution with 1 : 1 ethyl acetate–light petroleum gave the keto-acid (VI) (400 mg.) which crystallised from chloroform–light petroleum as prisms, m. p. 250—252°, identical with the material prepared as above.

Ozonolysis of Methyl Fujenoate (IV).—Ozonised oxygen (4·2 mg. of O_3 per min) was passed through a solution of methyl fujenoate (50 mg.) in ethyl acetate (10 ml.) at −70° for 2 min. Triphenylphosphine (47 mg.) in ethyl acetate (5 ml.) was then added and the solution left at 0° overnight. Evaporation of the solvent and chromatography of the residual gum on silica gel (15 × 1 cm.) gave, in the fractions eluted with 1 : 3 ethyl acetate–light petroleum, the methyl ester (VII) (35 mg.) which crystallised from ethyl acetate–light petroleum as needles, m. p. 210°, identical with the material prepared above.

Hydrolysis of Fujenal with Methanol.—Fujenal (1·8 g.) was heated in a sealed tube with methanol (25 ml.) at 160° for 4 days. The excess of methanol was evaporated and the residue chromatographed on silica gel (35 × 4 cm.). Elution with 7·5% of ethyl acetate in light petroleum gave 7-*hydroxy*-7-*methoxy*-6,7-*secokaur*-16-*ene*-6,19-*dioic acid* 19-*methyl ester* 6→7-*lactone* (IX) (800 mg.) which crystallised from acetone–light petroleum as needles, m. p. 190°, $[\alpha]_D^{20}$ −46° (*c* 0·2) (Found: C, 70·1; H, 8·7; OMe, 15·6. $C_{22}H_{32}O_5$ requires C, 70·2; H, 8·5; 2OMe, 16·5%), $\nu_{max.}$ (in $CHBr_3$) 1726 (C=O), 1655 and 877 cm.$^{-1}$ (C=CH_2). It absorbed 0·75 mol. of hydrogen on microhydrogenation and consumed 1 mol. of perbenzoic acid in chloroform. Elution with 1 : 9 ethyl acetate–light petroleum gave 7-*hydroxy*-7,16-*dimethoxy*-6,7-*secokaurane*-6,19-*dioic acid* 19-*methyl ester* 6→7-*lactone* (XII) (400 mg.) which crystallised from acetone–light petroleum as needles, m. p. 190° (Found: C, 68·0; H, 9·0; OMe, 20·8. $C_{23}H_{36}O_6$ requires C, 67·6; H, 9·0; 3OMe, 22·8%), $\nu_{max.}$ (in $CHBr_3$) 1719 cm.$^{-1}$. There was no uptake of hydrogen on microhydrogenation and it failed to give an oxime by the pyridine method.

Ozonolysis of the Dimethyl Ester (IX).—(*a*) *In acetic acid.* Ozonised oxygen (6·8 mg. of O_3 per min.) was passed through a solution of the ester (80 mg.) in acetic acid (15 ml.) at room temperature for 2 min. The solution was left for 3 hr., diluted with water, and steam-distilled. Treatment of the distillate (150 ml.) with saturated aqueous dimedone (25 ml.) gave, after 1 week, formaldehyde dimethone (26 mg.) as needles, m. p. 188°, identical with an authentic sample. The residue, non-volatile in steam, was made alkaline with sodium hydrogen carbonate and extracted with ethyl acetate, giving a neutral fraction which was chromatographed on silica gel (15 × 1 cm.). Elution with 1 : 3 ethyl acetate–light petroleum gave the keto-ester (X) (50 mg.) as needles, m. p. 210° (from ethyl acetate–light petroleum), identical with the sample prepared as below.

(*b*) *In ethyl acetate.* Ozonised oxygen (5·3 mg. of O_3 per min.) was passed through a solution of the ester (260 mg.) in ethyl acetate (30 ml.) at −70° for 6 min. Triphenylphosphine (300 mg.) was added and the solution allowed to attain room temperature overnight. The solvent was evaporated and the residual gum chromatographed on silica gel (25 × 2 cm.). Elution with 1 : 1 ether–light petroleum gave 7-*hydroxy*-7-*methoxy*-16-*oxo*-6,7-*seco*-17-*norkaurane*-6,19-*dioic acid* 19-*methyl ester* 6→7-*lactone* (X) (240 mg.) which crystallised from ethyl acetate–light petroleum as needles, m. p. 210—211°, $[\alpha]_D^{18}$ −24° (*c* 0·2) (Found: C, 66·5; H, 7·9; OMe, 15·6. $C_{21}H_{30}O_6$ requires C, 66·6; H, 8·0; 2OMe, 14·2%), $\nu_{max.}$ (in CCl_4) 1749 (cyclopentanone) and 1737 cm.$^{-1}$ (esters).

The *oxime*, prepared by the pyridine method, crystallised from ethanol as needles, m. p. 270—272° (decomp.) (Found: C, 64·2; H, 8·2; N, 3·8. $C_{21}H_{31}O_6N$ requires C, 64·1; H, 7·9; N, 3·6%).

The nor-ketone was recovered after treatment with (i) the 8N-chromium trioxide reagent in acetone, (ii) alkaline potassium permanganate at 50°, and (iii) methanolic sodium methoxide (1 mol.) and benzaldehyde at 0° for 18 hr.

Acid Hydrolysis of the Ester (IX).—The ester (250 mg.) in acetone (10 ml.) and dilute hydrochloric acid (15 ml.) was heated at 60° for 5 hr. Evaporation of the acetone, dilution with water (150 ml.), and recovery with ethyl acetate gave gummy crystals which crystallised from acetone–light petroleum as plates of 19-*methyl hydrogen* 16-*hydroxy*-7-*oxo*-6,7-*secokaurane*-6,19-*dioate* (XIV) (200 mg.), m. p. 176—178° (Found: C, 66·1; H, 8·5; OMe, 7·5%; Equiv., 381. $C_{21}H_{32}O_6$ requires C, 66·3; H, 8·5; OMe, 8·1%; *M*, 380), $\nu_{max.}$ 3455 (OH), 2695 (aldehyde C–H), 1713 cm.$^{-1}$ (C=O). There was no uptake of hydrogen on microhydrogenation.

Acid Hydrolysis of the Ester (X).—(*a*) *At* 60°. The ester (50 mg.) in acetone (5 ml.) and dilute sulphuric acid (15 ml.) was heated at 60° for 2 hr. The solution was diluted with water and extracted with ethyl acetate, and the product was separated in the usual manner into a neutral gum (20 mg.), which deposited the starting material on trituration with ether, and an acidic gum (23 mg.). Crystallisation of the latter from ethyl acetate–light petroleum gave 7,7-*dihydroxy*-16-*oxo*-6,7-*seco*-17-*norkaurane*-6,19-*dioic acid* 19-*methyl ester* 6→7-*lactone* (XI) (15 mg.) as prisms, m. p. 167° (Found: C, 66·3; H, 7·8; OMe, 8·5. $C_{20}H_{28}O_6$ requires C, 65·9; H, 7·7; OMe, 8·5%), $\nu_{max.}$ 3330 (OH), 1752 (cyclopentanone), 1726 and 1710 cm.$^{-1}$ (C=O of ester and lactol).

(*b*) *At* 100°. The ester (X) (35 mg.) in acetone (5 ml.) and dilute sulphuric acid (15 ml.) was heated at 95—100° for 2 hr., diluted with water (100 ml.), and made alkaline with aqueous sodium hydrogen carbonate. Extraction with ethyl acetate gave a neutral gum (17 mg.) which crystallised from ethanol in needles, m. p. 176°, of fujenal nor-ketone (V), identified by mixed m. p. and infrared spectra. The acidic product was an intractable gum (18 mg.).

Oxidation of the Compound (XI).—The compound (25 mg.) in purified acetone (2 ml.), was treated at room temperature with the 8N-chromium trioxide reagent (0·02 ml.). After 1 hr. methanol (10 drops) was added, and the solution was diluted with water (100 ml.), and extracted with ethyl acetate. Evaporation of the solvent gave a gum (20 mg.) which was chromatographed on silica gel (12 × 1 cm.). Elution with 3 : 2 ethyl acetate–light petroleum and crystallisation from acetone–light petroleum gave needles (9 mg.), m. p. 172—173° (decomp.), then reset, m. p. 205° (decomp.), $[\alpha]_D^{20}$ −45° (*c* 0·7) (Found: C, 63·3; H, 7·7; OMe, 8·3. Calc. for $C_{20}H_{28}O_7$: C, 63·1; H, 7·4; OMe, 8·2%), identified as 19-methyl dihydrogen 16-oxo-6,7-seco-17-norkaurane-6,7,19-trioate [3] (XV) by mixed m. p. and infrared spectrum.

Hydrolysis of Fujenal with Methanolic Hydrogen Chloride.—Fujenal (200 mg.) in methanol (25 ml.) was added to methanol (10 ml.) previously saturated with dry hydrogen chloride. A gentle stream of dry hydrogen chloride gas was passed through the solution for 4 hr., then the product was concentrated at room temperature *in vacuo*, diluted with ethyl acetate (200 ml.), washed with water, dried, and evaporated. The residual gum was chromatographed on silica gel (20 × 1·5 cm.). Elution with 1 : 4 ether–light petroleum gave the pseudo-ester (IX) (44 mg.) which crystallised from ether–light petroleum as needles, m. p. 186°, identical (infrared spectrum) with the sample prepared as above. The next fraction gave 7-*hydroxy*-7-*methoxy*-6,7-*seco*-*kaur*-15-*ene*-6,19-*dioic acid* 19-*methyl ester* 6→7-*lactone* (28 mg.) which crystallised as needles (from light petroleum), m. p. 185—187° (Found: C, 70·2; H, 8·55. $C_{22}H_{32}O_5$ requires C, 70·2; H, 8·5%), $\nu_{max.}$ 1736 and 1730 (ester and lactone), 3038, 1682, 833, and 810 cm.$^{-1}$ (RR′C=CHR″). The following fraction gave 16-*chloro*-7-*hydroxy*-7-*methoxy*-6,7-*secokaurane*-6,19-*dioic acid* 19-*methyl ester* 6→7-*lactone* (XIII) (34 mg.) which crystallised as needles (from light petroleum), m. p. 176° (Found: C, 64·2; H, 8·0; Cl, 9·0. $C_{22}H_{33}ClO_5$ requires C, 64·1; H, 8·1; Cl, 8·6%), $\nu_{max.}$ (in CCl_4) 1738 cm.$^{-1}$. Elution with ether gave 19-*methyl hydrogen* 16-*chloro*-7-*oxo*-6,7-*secokaurane*-6,19-*dioate* (XX) (65 mg.) which crystallised from ethyl acetate–light petroleum as prisms, m. p. 215° (decomp.) (Found: C, 63·3; H, 8·0; Cl, 8·9%; Equiv., 417. $C_{21}H_{31}ClO_5$ requires C, 63·2; H, 7·8; Cl, 8·9%; *M*, 399), $\nu_{max.}$ (in $CHBr_3$) 2717 (aldehyde C–H), 1739 and 1676 cm.$^{-1}$ (C=O). The methyl ester, prepared with diazomethane, had m. p. 175° and was identical (infrared spectrum) with the chloro-ester described above. Treatment of the chloro-ester (XIII) with sodium iodide in refluxing dimethylformamide gave the 15-unsaturated ester described above.

Baeyer–Villiger Oxidation of the Nor-ketone (VII).—The nor-ketone (80 mg.) in dry chloroform (10 ml.) was treated at 0° for 18 hr. with a solution of perbenzoic acid in chloroform (1·5 mol.) and toluene-*p*-sulphonic acid (90 mg.). The solution was diluted with chloroform, washed with aqueous ferrous sulphate, aqueous sodium hydrogen carbonate, and water, dried, and evaporated to give a gum. Chromatography on silica gel and elution with 3 : 1 ethyl acetate–light petroleum gave (i) starting material (20 mg.), (ii) 13-*hydroxy*-6,7;13,16-*diseco*-17-*norkaurane*-6,7,16,19-*tetraoic acid* 6,19-*anhydride* 7-*methyl ester* 16→13-*lactone* (XXII) (50 mg.) which crystallised from ethyl acetate–light petroleum as needles, m. p. 246—248° (Found: C, 63·6; H, 6·95%; Equiv., 378. $C_{20}H_{26}O_7$ requires C, 63·5; H, 6·9%; *M*, 378), $\nu_{max.}$ (in $CHBr_3$) 1854 and 1778 (5-ring anhydride), 1728 (br) cm.$^{-1}$ (ester and δ-lactone).

Hydrolysis of the δ-*Lactone* (XXII).—The lactone (100 mg.) in methanol (5 ml.) was treated at 0° with 0·096N-potassium hydroxide (3 ml.) and sufficient dioxan to maintain a clear solution. It was left at 0° for 18 hr., then cautiously acidified with 0·1N-hydrochloric acid and extracted

with ethyl acetate. Recovery gave a gum which was methylated and chromatographed on silica gel. Elution with 1 : 1 ethyl acetate–light petroleum gave 13-*hydroxy*-6,7;13,16-*diseco*-17-*norkaurane*-6,7,16,19-*tetraoic acid* 6,7,19-*trimethyl ester* 16→13-*lactone* (XXIII) (80 mg.) which crystallised from ether as prisms, m. p. 155—156° (Found: C, 62·4; H, 7·8; OMe, 22·2%; Equiv., 469. $C_{22}H_{32}O_8$ requires C, 62·25; H, 7·6; 3OMe, 21·9%; *M*, 424), $\nu_{max.}$ 1728 (br) cm.$^{-1}$.

Oxidation of the Aldehydic Acid (XIV).—The acid (25 mg.) in purified acetone (3 ml.) was treated with the 8N-chromium trioxide reagent (0·01 ml.) at room temperature for 2 hr. Methanol (10 drops) was added and the solution diluted with water to 100 ml. Recovery with ethyl acetate gave a gum (23 mg.) which slowly deposited needles of 19-*methyl dihydrogen* 16-*hydroxy*-6,7-*secokaurane*-6,7,19-*trioate* (XVI) (15 mg.). It crystallised from ethyl acetate–light petroleum as needles, m. p. 176—178° (decomp.) (Found: C, 63·6; H, 8·1. $C_{21}H_{32}O_7$ requires C, 63·6; H, 8·1%).

Preparation of the Anhydride (XXIV).—The above acid (XVI) (40 mg.) was refluxed with acetic anhydride (5 ml.) for 5 hr. and the excess of reagent then removed *in vacuo*. The residual gum was taken up in ethyl acetate and washed with sodium hydrogen carbonate solution and water. Recovery gave a gum (30 mg.) which was chromatographed on silica gel (12·5 × 1 cm.). Elution with 1 : 4 ethyl acetate–light petroleum gave 16-*acetoxy*-6,7-*secokaurane*-6,7,19-*trioic acid* 6,7-*anhydride* 19-*methyl ester* (XXIV) (20 mg.) which crystallised from ethyl acetate–light petroleum as prisms, m. p. 200—202° (Found: C, 65·8; H, 7·8. $C_{23}H_{32}O_7$ requires C, 65·7; H, 7·7%), $\nu_{max.}$ (in $CHBr_3$) 1795 and 1751 (unstrained anhydride), 1723 cm.$^{-1}$ (esters).

Reduction of Fujenal with Sodium Borohydride.—Fujenal (530 mg.) in dry tetrahydrofuran (20 ml.) was treated at room temperature for 1·5 hr. with sodium borohydride (400 mg.) suspended in methanol (20 ml.). The solvents were evaporated, dilute hydrochloric acid was added, and the product was extracted with ethyl acetate. The extract was washed with dilute hydrochloric acid and water, dried, and evaporated. The residue crystallised from light petroleum in needles (390 mg.) of 7,19-*dihydroxy*-6,7-*secokauran*-6-*oic acid* 6→19-*lactone* (XXV), m. p. 149—151° (Found: C, 75·6; H, 9·5. $C_{20}H_{30}O_3$ requires C, 75·4; H, 9·5%), $\nu_{max.}$ 3520, 3410, 1730, 1654, and 875 cm.$^{-1}$, $\nu_{max.}$ (in CCl_4) 3580 (OH), 1768 (γ-lactone), 3075, 1653, and 876 cm.$^{-1}$ (C=CH_2). Repetition of this experiment with methanol alone as solvent and allowing the reduction to proceed for 30 min. led to the isolation in low yield (4%) of a *lactol*, m. p. 192° (Found: C, 71·55; H, 9·0. $C_{20}H_{30}O_4$ requires C, 71·8; H, 9·8%), $\nu_{max.}$ (Infracord) 3400, 1750, 1655, and 875 cm.$^{-1}$.

The lactone was recovered after treatment (*a*) with acetic anhydride and pyridine at room temperature and (*b*) with methyl iodide and potassium carbonate in refluxing acetone.

Reduction of Fujenal with Lithium Aluminium Hydride.—A slurry of lithium aluminium hydride (600 mg.) in dry ether (30 ml.) was added to a solution of fujenal (500 mg.) in dry ether (50 ml.) and dry dioxan (5 ml.), and the whole was heated under reflux for 2 hr. Ethyl acetate (50 ml.) followed by dilute sulphuric acid (100 ml.) were then added to the solution. Recovery with ethyl acetate gave a gum (500 mg.) which was chromatographed on silica gel (20 × 1·5 cm.). Elution with 1 : 1 ether–light petroleum gave the lactone (XXV) (250 mg.) as needles, m. p. 132—135°, raised to 145—147° by crystallisation from light petroleum and identical (infrared spectrum) with the specimen prepared as above.

Reduction of Fujenoic Acid with Lithium Aluminium Hydride.—Fujenoic acid (310 mg.), suspended in dry ether (15 ml.), was heated under reflux with lithium aluminium hydride (200 mg.) for 2 hr. The solution was cooled, and ethyl acetate, water, and dilute hydrochloric acid were added. Recovery of the product in ether and crystallisation from acetone–light petroleum gave 19-*hydroxy*-6,7-*secokaurane*-6,7-*dioic acid* 6→19-*lactone* (XXVI) (204 mg.) which crystallised from acetone–light petroleum as prisms, m. p. 185—187° (Found: C, 72·5; H, 8·7. $C_{20}H_{28}O_4$ requires C, 72·3; H, 8·5%), $\nu_{max.}$ 1779 (γ-lactone), 1710 (C=O of CO_2H), 3057, 1658, and 877 cm.$^{-1}$ (C=CH_2). The methyl ester was a gum.

On one occasion a small amount of a second compound, m. p. 246—252° (decomp.), $\nu_{max.}$ 3175, 1745, 1731, 1661, and 874 cm.$^{-1}$, was also isolated.

Oxidation of the Lactone (XXV).—The lactone (500 mg.) in acetone (5 ml.) was treated with the 8N-chromium trioxide reagent (0·5 ml.) for 1 hr. Methanol was added, and the solution was concentrated and diluted with water. Recovery of the product in ethyl acetate and crystallisation of the residue from light petroleum gave 19-*hydroxy*-7-*oxo*-6,7-*secokaur*-16-*en*-6-*oic acid* 6→19-*lactone* (XXVIII) (412 mg.) as needles, m. p. 156—157° (Found: C, 75·3; H, 8·9.

$C_{20}H_{28}O_3$ requires C, 75·9; H, 8·9%), $\nu_{max.}$ 2708 (aldehyde C–H), 1752 (γ-lactone), 1720 (aldehyde), 3074, 1655, and 881 cm.$^{-1}$ (C=CH_2).

Rotatory Dispersion Curves.—Values are for [*M*], in methanol, for fujenal (II); negative Cotton effect curve (500 mμ) — 425°; (308, trough) — 2500°; (271, peak) — 475°; (269) — 550°. The ketone (VII); positive Cotton effect curve (500 mμ) — 475°; (323, peak) + 475°; (294, trough) — 1450°; (291) — 1375°.

We are indebted to Mr. B. K. Tidd for the nuclear magnetic resonance spectra, to Professor W. Klyne and Miss J. Jackson for the optical rotatory dispersion data, and to Mr. P. L. Hazell for technical assistance.

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