485. *Gibberellic Acid. Part XXIII.** *Some Perhydrofluoren-*8a*-ylacetic Acid Lactones.*

By D. C. ALDRIDGE and JOHN FREDERICK GROVE.

Acid-catalysed rearrangement of the perhydrofluoren-8a-ylacetic acid 1 ⟶ 4a-lactone system (VII), obtained by degradation of gibberellic acid, is shown to give the 8a ⟶ 4b-lactone-1-carboxylic acid system (XI) whose absolute configuration is deduced.

CLEMMENSEN reduction of the D-seco-keto-acid $C_{19}H_{24}O_8$ (VII; R = H), obtained by ozonolysis of gibberellin A_1 methyl ester (I), was studied by Sumiki and his collaborators.[1] Oxidation with chromic oxide of the deoxo-product, $C_{19}H_{26}O_7$, gave a neutral ketone, $C_{18}H_{24}O_5$; this was initially [1a] assigned structure (II) in accordance with the views of the Japanese workers on the position of the ring A lactone bridge, since it was considered that the 8a-acetic acid side-chain had undergone decarboxylation. Subsequently,[1b] it was suggested that cleavage of the ring-A lactone bridge occurred under the conditions of the Clemmensen reduction and was followed by relactonisation of the acetic acid residue. The δ-lactone structures (III) and (IV) were proposed for the deoxo-product and the ketone, $C_{18}H_{24}O_5$, respectively, the latter being derived by decarboxylation of the intermediate 2-oxo-1-carboxylic acid. Since the stereochemistry [2] of the keto-acid (VII; R = H), in which the 9-methoxycarbonyl and 8a-acetic acid substituents are *cis*-related, makes structures (III) and (IV) unlikely, we have reinvestigated these reactions. The Clemmensen reduction product and the derived ketone are now shown to have structures (VIII; R = H) and (IX), respectively.

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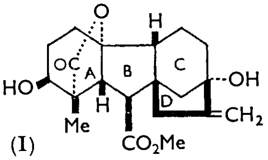
* Part XXII, preceding paper.

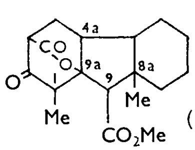
[1] (*a*) Seta, Takahashi, Kitamura, Takai, Tamura, and Sumiki, *Bull. Agric. Chem. Soc. Japan*, **1958**, **22**, 61; (*b*) 1959, **23**, 499.

[2] Bourn, Grove, Mulholland, Tidd, and Klyne, *J.*, **1963**, 154.

The lactone C=O stretching frequency of 1766 cm.$^{-1}$, reported[1] for the ketone, $C_{18}H_{24}O_5$, is more in accord with the presence of a γ-lactone; in confirmation of this assignment we find the deoxo-product and the ketone to absorb at 1774 and 1775 cm.$^{-1}$, respectively, in chloroform. The δ-lactone structures (IV) and (V) can therefore be eliminated, leaving (IX) as the only possible structure for the ketone, $C_{18}H_{24}O_5$. The methyl ester of the deoxo-product was not identical with the ester (XIII; X = OH, H; Y = H_2) obtained[2] by Raney nickel treatment of the thioketal derived from the ketone (VII; R = Me): the deoxo-acid must therefore have structure (VIII; R = H). The optical rotatory dispersion curve of the ketone (IX) showed a negative Cotton effect, unlike the strong positive Cotton effect associated with the 2-oxo-1 ⟶ 4a-lactone system[3] in the ketone (XIII; X = O, Y = H_2), and provided evidence that a major structural change had taken place in ring A. Unlike the 7α-gibbane keto-ester (VI), which undergoes epimerisation at position 4b in boiling 3N-hydrochloric acid (2 hr.),[3] the seco-keto-ester (VII; R = Me) was largely stable under these conditions, apart from hydrolysis of the ester groups. An isomeric keto-ester (XI) was obtained in very low yield by chromatography of the product (after methylation), but larger quantities of the ester (XI) were obtained by using 6N-hydrochloric acid for longer periods. After 18 hours' boiling and methylation, the product consisted of an equilibrium mixture of the ester (VII; R = Me), the isomer (XI), and an unsaturated tricarboxylic ester which was assigned the gibb-4a(4b)-ene structure (X) from the intensity of its ultraviolet end-absorption between 210 and 220 mμ; after 48 hours' boiling the product had the same composition.



(I)



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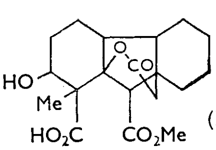

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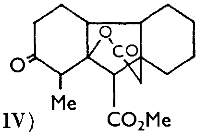

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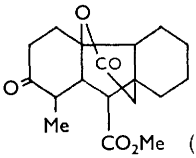

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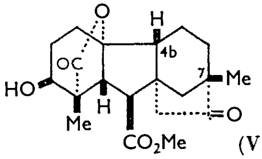
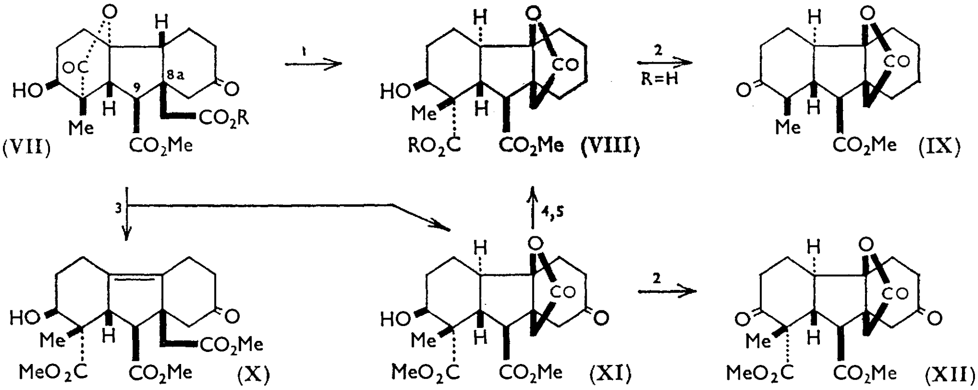


(VI)



Reagents: 1, Zn–Hg–H⁺. 2, CrO₃. 3, H⁺. 4, $(CH_2 \cdot SH)_2$. 5, Raney Ni.

Reduction of the keto-ester (XI), by treatment of the thioketal with Raney nickel,

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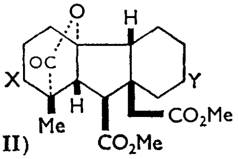
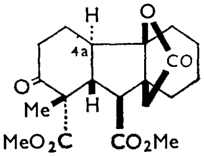
[3] Aldridge, Grove, Speake, Tidd, and Klyne, *J.*, 1963, 143.

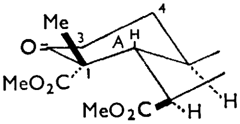
gave an ester, $C_{20}H_{28}O_7$, identical with the methyl ester (VIII; R = Me) of the Clemmensen reduction product. Thus, the formation of the acid (VIII; R = H) from the lactone (VII; R = H) probably proceeds through a 4a(4b)-ene intermediate of type (X), relactonisation occurring at position 4b.



(XIII)

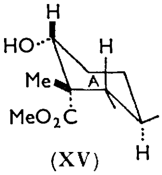


(XIV)

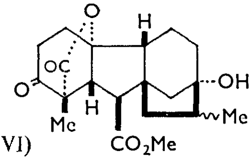


(XIVA)

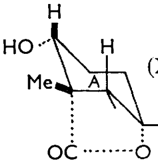
Oxidation of the hydroxy-esters (XI) and (VIII; R = Me) with chromic oxide gave the corresponding 2-ketones (XII) and (XIV). The sum of the optical rotatory dispersion curves for the ketones (XI) and (XIV) closely resembled the curve for (XII), showing the absence of interaction between 2- and 7-ketone groups in this series. Similar additivity of the rotatory dispersion curves occurred in the series derived directly from the lactone (VII; R = Me): summation of the curves for lactones (VII; R = Me) and (XIII; X = O, Y = H_2) gave a resultant almost identical with the curve for the 2,7-diketo-lactone[2] (XIII; X = Y = O).



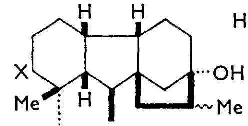
(XV)



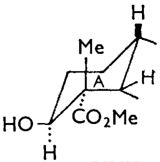
(XVI)



(XVIA)



(XVII)



(XVIIA)

The negative Cotton effect found for the ketone (IX) is consistent only with a 9aβ-configuration. Reduction of the ketone (XIV) with sodium borohydride gave a new $C_{20}H_{28}O_7$ ester considered to be the 2α(*eq*)-hydroxy-epimer (XV) of the ester (VIII; R = Me) since oxidation with chromic oxide regenerated the ketone (XIV). This reduction, therefore, was similar to the reduction of the ketone[4] (XVI) which furnished, predominantly, the 2α-hydroxy-epimer (XVIA) of the starting alcohol, methyl tetrahydrogibberellate. Although it differed from the reduction of the A/B-*cis*-fused ketone[5] (XVII; X = O) which regenerated, predominantly, the 2β-hydroxy-ester (XVII; X = OH, H) ≡ (XVIIA), the major product in every case was the equatorial alcohol. It is concluded that the configuration at position 4a in the ketone (XIV) is α, giving a *trans*-fusion of rings A/B in this series.

Comparison of the curves for the ketones (IX) and (XIV) shows that the introduction of a 1-methoxycarbonyl substituent causes a change in the sign of the Cotton effect from negative to positive, an effect similar to the 4,4-dimethyl effect observed in the steroids.[6] It is reasonable to suggest that 1,3-interaction in the normal chair conformation between the 9-methoxycarbonyl group and the substituents at position 1 forces ring A to adopt the intermediate " distorted chair " conformation[7] (XIVA).

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[4] Cross, Grove, and Morrison, *J.*, 1961, 2498.
[5] Aldridge, Grove, McCloskey, and Klyne, preceding paper.
[6] Djerassi, " Optical Rotatory Dispersion," McGraw-Hill, New York, 1960, p. 90.
[7] Allinger and DaRooge, *Tetrahedron Letters*, 1961, 676.

EXPERIMENTAL

M. p.s are corrected. Light petroleum refers to the fraction of b. p. 60—80°. Woelm's acid alumina of grade II was used in chromatography. Unless otherwise stated, optical rotations were determined for ethanol solutions, and infrared spectral data for Nujol mulls.

Action of Acid on the Ester (VII; R = Me).—(*a*) 3N-*Hydrochloric acid.* The ester (200 mg.) was heated under reflux for 2 hr. with 3N-hydrochloric acid (15 ml.). The cooled solution was continuously extracted with ethyl acetate, and the extract was separated in the usual way into acid and neutral fractions by extraction with sodium hydrogen carbonate and recovery. The acid fraction (181 mg.) was treated with ethereal diazomethane, and the product was crystallised from ethyl acetate–light petroleum, giving the ester (VII; R = Me) (138 mg.), m. p. 164—165°, and a residue (30 mg.) which was chromatographed on alumina (8 × 1 cm.) in benzene. After the ester (VII; R = Me) (20 mg.) had been eluted with benzene–methanol (400 : 1; 125 ml.), benzene–methanol (200 : 1, 75 ml.) furnished the ester (XI), plates, m. p. 170—171° (2 mg.) (see below).

(*b*) 6N-*Hydrochloric acid.* The ester (169 mg.) was heated under reflux for 18 hr. with 6N-hydrochloric acid (6 ml.), and the mixture was worked up as described in (*a*). The methylated product (142 mg.) was chromatographed on alumina (20 × 1 cm.) in benzene and was separated into three fractions: (i) 78 mg. (46%), eluted with benzene–methanol (400 : 1; 200 ml.); (ii) an interband, 19 mg., benzene–methanol (200 : 1; 50 ml.); and (iii) 43 mg. (25%), benzene–methanol (200 : 1; 100 ml.).

Fraction (iii) was twice recrystallised from ethyl acetate–light petroleum, giving 2β,4bβ-*dihydroxy*-1α,9β-*dimethoxycarbonyl*-1β-*methyl*-7-*oxo*-4aα,9aβ-*perhydrofluoren*-8aβ-*ylacetic acid* 4b-*lactone hydrate* (XI) as prisms, m. p. 132—133°, or plates, m. p. 174—175° (31 mg.), $\nu_{max.}$ 3420, 3265 (OH), 1760, 1727, 1694 (C=O), and 1650 cm.$^{-1}$ (H_2O) (Found: C, 58·6; H, 6·9. $C_{20}H_{26}O_8,H_2O$ requires C, 58·2; H, 6·8%). Both crystalline modifications had the same infrared spectrum between 2 and 15 μ. The water of crystallisation was not removed by drying at 66°/10^{-2} cm.

The *monoacetyl derivative* crystallised from ethyl acetate–light petroleum in leaflets, m. p. 172—173° (Found: C, 60·7; H, 6·6. $C_{22}H_{28}O_9$ requires C, 60·5; H, 6·5%), $\nu_{max.}$ OH absent, (C=O), 1763 (lactone), 1748 (ester), 1720 cm.$^{-1}$ (6-ring ketone).

Fraction (i) was separated by fractional crystallisation (hand-picking) from ethyl acetate–light petroleum into needles, m. p. 164° (12 mg.), of the ester (VII; R = Me) and plates (26 mg.), m. p. 154°, $[\alpha]_D^{23}$ +77° (*c* 0·34), of *methyl* 2β-*hydroxy*-1α,9β-*dimethoxycarbonyl*-1β-*methyl*-7-*oxo*-1,2,3,4,5,6,7,8,8a,9aβ-*decahydrofluoren*-8aβ-*ylacetate* (X) (Found: C, 61·5; H, 6·9; OMe, 22·2. $C_{21}H_{28}O_8$ requires C, 61·75; H, 6·9; 3OMe, 22·8%), $\nu_{max.}$ 3505 (OH), 1740, 1719 (sh), and 1700 cm.$^{-1}$ (C=O), ε (mμ) 4300 (210), 3100 (215), and 2450 (220). Similar yields of the products (X) and (XI) were obtained when the reaction time was extended to 48 hr. After 1 hr. the yield of the ester (XI) was 6%, but none of the ester (X) was obtained by fractional crystallisation of the crude product from the band yielding unchanged ester (VII; R = Me) (82%).

2β,4bβ-*Dihydroxy*-1α,9β-*dimethoxycarbonyl*-1β-*methyl*-4aα,9aβ-*perhydrofluoren*-8aβ-*ylacetic acid* 4b-*Lactone* (VIII; R = Me).—(*A*) Clemmensen reduction of the acid (VII; R = H) as described by Seta *et al.*[1b] gave the acid (VIII; R = H), m. p. 258—261° (decomp.), $\nu_{max.}$ (in $CHCl_3$) (C=O), 1774 (γ-lactone), 1736 (ester), 1718 (sh), and 1701 cm.$^{-1}$ (carboxylic acid) (Found: C, 62·2; H, 7·2. Calc. for $C_{19}H_{26}O_7$: C, 62·3; H, 7·15%). The methyl ester (VIII; R = Me), m. p. 155°, was prepared with diazomethane. Seta *et al.*[1b] give m. p. 252—254° (decomp.) and 154—156° for the acid (VIII; R = H) and its methyl ester. The acetyl derivative, prepared in acetic anhydride–pyridine, of the ester (VIII; R = Me) formed prisms, m. p. 185°.

(*B*) *Reduction of the ester* (XI). To the ester (XI) (16 mg.) in chloroform (0·25 ml.) was added boron trifluoride–ether complex (0·014 ml.) and ethane-1,2-dithiol (0·014 ml.). After 24 hr. at room temperature the mixture was diluted with chloroform and washed with water followed by saturated sodium chloride solution. The recovered gummy product, in benzene, was chromatographed on alumina (4 × 0·5 cm.). After residual dithiol had been eluted with 1 : 1 benzene–light petroleum (b. p. 40—60°) (35 ml.), benzene–methanol (200 : 1) eluted a gum (19 mg.). The gum in dioxan (3 ml.) was heated for 9 hr. at 100° with Raney nickel (0·5 g.). The solid was filtered off and washed with acetone. The gummy product (11 mg.) recovered from the combined filtrate and washings was chromatographed on alumina (3 × 0·4 cm.) in benzene. After an intractable gum (5 mg.) had been eluted with benzene–methanol (400 : 1;

20 ml.), further elution (30 ml.) afforded plates (4 mg.), m. p. 155° (from ethyl acetate–light petroleum), of the ester (VIII; R = Me) identical (mixed m. p. and infrared spectra) with the material obtained as in (*A*).

Chromic Oxide Oxidations.—(*A*) *The acid* (VIII; R = H). Oxidation in acetic acid [1b] gave 4bβ-*hydroxy*-9β-*methoxycarbonyl*-1β-*methyl*-2-*oxo*-4aα,9aβ-*perhydrofluoren*-8aβ-*ylacetic acid lactone* (IX), prisms, m. p. 175—176°, $[\alpha]_D^{23}$ +41° (*c* 0·1) (Found: C, 67·2; H, 7·7. Calc. for $C_{18}H_{24}O_5$: C, 67·5; H, 7·55%), $\nu_{max.}$ (in $CHCl_3$) (C=O), 1775 (γ-lactone), 1734 (ester), 1716 cm.$^{-1}$ (6-ring ketone). Seta *et al.*[1b] give m. p. 173—175°, $[\alpha]_D^{25}$ +47° (*c* 0·8), for the ketone (IX).

The following oxidations were carried out in the same way: The ester in acetone was set aside for 1 hr. at 0° with the chromic oxide reagent.[4] The mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water, followed by sodium hydrogen carbonate, and the neutral product was recovered.

(*B*) The ester (XI) (18 mg.) furnished 4bβ-*hydroxy*-1α,9β-*dimethoxycarbonyl*-1β-*methyl*-2,7-*dioxo*-4aα,9aβ-*perhydrofluoren*-8aβ-*ylacetic acid lactone* (XII), needles (15 mg.), m. p. 244—245° (Found: C, 61·4; H, 6·7. $C_{20}H_{24}O_8$ requires C, 61·2; H, 6·2%), $\nu_{max.}$ 1776, 1748, and 1716 cm.$^{-1}$ (C=O).

(*C*) The ester (VIII; R = Me) (125 mg.) gave 4bβ-*hydroxy*-1α,9β-*dimethoxycarbonyl*-1β-*methyl*-2-*oxo*-4aα,9aβ-*perhydrofluoren*-8aβ-*ylacetic acid lactone* (XIV), plates (109 mg.), m. p. 183—184°, $[\alpha]_D^{25}$ +88° (*c* 0·5) (Found: C, 63·7; H, 7·05. $C_{20}H_{26}O_7$ requires C, 63·5; H, 6·9%), $\nu_{max.}$ 1788, 1773 (sh), 1728, and 1715 cm.$^{-1}$ (C=O).

Reduction of the Ketone (XIV).—To the ketone (XIV) (40 mg.) in methanol (2 ml.) at 0° was added sodium borohydride (50 mg.) in methanol (1 ml.). After 1 hr. at room temperature the excess of hydride was decomposed by dropwise addition of acetic acid; water (5 ml.) was added and the solution was extracted with ethyl acetate. The recovered gummy product (40 mg.), in benzene (10 ml.), was chromatographed on alumina (10 × 0·8 cm.). Elution with benzene–ether (1 : 1; 50 ml.) gave a gum (31 mg.) which did not crystallise when seeded with the ester (VIII; R = Me); it was distilled at 140° (bath)/10^{-3} mm., giving 2α,4bβ-*dihydroxy*-1α,9β-*dimethoxycarbonyl*-1β-*methyl*-4aα,9aβ-*perhydrofluoren*-8aβ-*ylacetic acid* 4b-*lactone*, a hygroscopic glass (20 mg.), m. p. 65—70°, $\nu_{max.}$ 3350 (broad), 1770, 1720 (broad), and 1640 cm.$^{-1}$ (H_2O) (Found: C, 62·1; H, 7·7. $C_{20}H_{28}O_7,0{\cdot}5H_2O$ requires C, 61·7; H, 7·5%). The acetyl derivative, prepared in acetic anhydride–pyridine, formed plates, m. p. 144—145° depressed on admixture with the acetyl derivative of the ester (VIII; R = Me).

Oxidation of the alcohol (4 mg.) with the chromic oxide reagent (see above) gave the ketone (XIV) (4 mg.), m. p. and mixed m. p. 182°. Further elution of the column with benzene–methanol (200 : 1; 100 ml.) gave a gum (9 mg.) which crystallised from ethyl acetate–light petroleum in plates (4 mg.), m. p. 178°, of an *alcohol* (Found: C, 64·6; H, 8·3. $C_{19}H_{28}O_6$ requires C, 64·75; H, 8·0%), $\nu_{max.}$ 3300, 1775, and 1735 cm.$^{-1}$.

Rotatory Dispersion Curves.—Values are for [*M*] in methanol for the ketones. (XI): positive Cotton effect curve (500 mμ) +1750°; (315, peak) +4080°; (270, trough) −1790°; (265) −1500°. (XII): positive Cotton effect curve (500 mμ) +290°; (320, peak) +5400°; (278, trough) −3040°; (272) −2500°. (XIV): positive Cotton effect curve (500 mμ) +1000°; (317, peak) +3550°; (280, trough) +1000°; (275) +1500°. (IX): negative Cotton effect curve (500 mμ) +200°; (308, trough) −1750°; (260) +6750°. (XIII; X = Y = O): positive Cotton effect curve (500 mμ) +1000°; (318, peak) +12,000°; (275, trough) −11,500°. (XIII; X = O, Y = H_2): positive Cotton effect curve (500 mμ) +250°; (315, peak) +7500°; (273, trough) −9700°.

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