304. *Gibberellic Acid. Part XXVII.* Some Functional Derivatives and Transformation Products of Gibberellic Acid*

By P. J. KEAY, J. S. MOFFATT, and T. P. C. MULHOLLAND

Some new derivatives and transformation products of gibberellic acid are described.

THE preparation of some functional derivatives and transformation products of gibberellic acid (I; R = H, β-OH), which were required for studies of structure–activity relationships, is described below. Plant-growth-promoting activity of the derivatives has been reported briefly [1] and will be fully described elsewhere.

Esters of gibberellic acid have been obtained previously by interaction of (*a*) the acid and a diazohydrocarbon,[2] (*b*) an alkali salt of the acid and an alkyl halide,[3] and (*c*) gibberellic anhydride and an alcohol [4] at 100°. Application of the last method gave the t-butyl and benzyl esters in addition to the propyl [3] and butyl [2,3] esters. Interaction of silver gibberellate and 2,3,4,5-tetra-*O*-acetylbromoglucose gave the tetra-acetylglucosyl ester. Interaction of the acid and *p*-nitrophenol in the presence of *NN'*-dicyclohexylcarbodi-imide gave the *p*-nitrophenyl ester, and, with the appropriate thiol, gibberellic anhydride in pyridine at 100° gave the corresponding thiobenzyl and thiophenyl esters.

Of a number of methods tried, only treatment of the anhydride in hot pyridine with gaseous ammonia yielded gibberellamide. With octylamine in place of ammonia this method afforded *N*-octylgibberellamide, but it failed with propylamine. Gibberellic acid, with the appropriate amine and *NN'*-dicyclohexylcarbodi-imide gave the *N*-propylamide, *p*-toluidide, and *p*-diethylaminoanilide; this method failed with ethylamine, butylamine, and benzylamine.

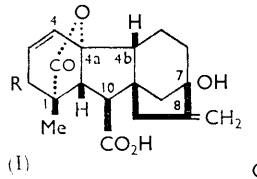
2-Acetylgibberellic acid, with trifluoroacetic anhydride, gave the 7-trifluoroacetate which was readily hydrolysed to starting material by aqueous potassium hydrogen carbonate.

With an excess of perbenzoic acid, gibberellic acid gave only a monoepoxide, $C_{19}H_{22}O_7$, shown to be the 8-epoxide by oxidation of its methyl ester with manganese dioxide; the gummy product showed increased absorption at about 230 mμ (C=C–C=O). Gibberellin A_1 (II; R = H, R' = OH, R'' = H, β-OH) similarly gave an epoxide, but the 2,3-ethylenic bond in the dehydro-ester (VI; R = Me) (see below) resisted epoxidation.

* Part XXVI, Jones, Grove, and MacMillan, *J.*, 1964, 1835.

[1] Mulholland, Vth. International Pesticides Congress, London, 1963.
[2] Moffatt and Radley, *J. Sci. Food Agric.*, 1960, 386.
[3] Sell, Rafos, Bukovac, and Wittwer, *J. Org. Chem.*, 1959, **24**, 1822.
[4] MacMillan and Moffatt, *J.*, 1962, 4727.

Oxidation of gibberellic acid with manganese dioxide in dioxan gave the 2-oxo-derivative (I; R = O). Selective hydrogenation of this oxo-acid with a partially poisoned catalyst resulted, as with gibberellic acid [5] and gibberellin A_7,[6] in reduction of the 3,4-ethylenic bond giving the dihydro-derivative (II; R = H, R′ = OH, R″ = O), the 2-oxo-derivative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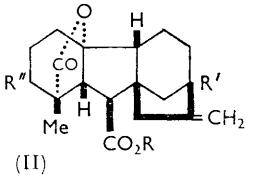
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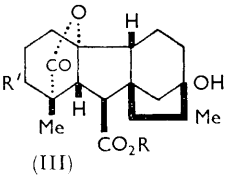
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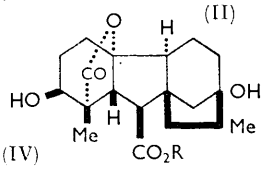
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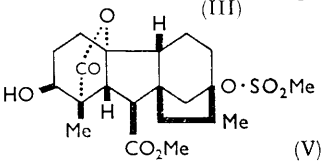
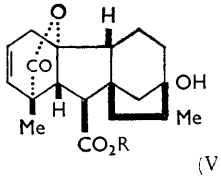

(V)

of gibberellin A_1, together with hydrogenolysis products. The derivative could not be obtained directly from gibberellin A_1 by oxidation with a chromium trioxide reagent.[7] In the preparation of the 2α-epimer (II; R = H, R′ = OH, R″ = H, α-OH) of gibberellin A_1 by alkaline hydrolysis of the corresponding 2α-methyl ester, as described previously,[8] the 2α-acid was accompanied by gibberellin A_1, from which it was separable only by chromatography.

Tetrahydrogibberellic acid (III; R = H, R′ = H, β-OH) with chromium trioxide gave the 2-oxo-derivative (III; R = H, R′ = O) whose methyl ester, m. p. 161—163°, has been described,[9] and with 2N-hydrochloric acid tetrahydrogibberellic acid yielded the 4b-epimer (IV; R = H), m. p. 241—247° of tetrahydrogibberellic acid. The epimer yielded the known [10] methyl ester with diazomethane.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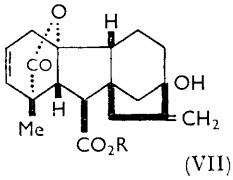
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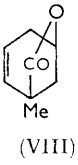
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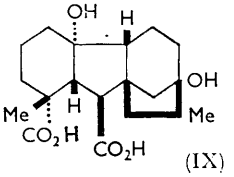
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MacMillan, Seaton, and Suter [11] showed that an 8-epimeric mixture of methyl tetrahydrogibberellates (III; R = Me, R′ = H, β-OH) reacted with methanesulphonyl chloride giving a mixture of monomethanesulphonyloxy-derivatives and gummy bis-derivatives. The former fraction was converted by boiling collidine into a mixture of 8-epimeric 2,3-dehydro-esters (VI; R = Me), the 8-dihydro-derivatives of gibberellin A_5 methyl ester (VII; R = Me).

Dehydration of the mixture of methyl tetrahydrogibberellates was further examined. With methanesulphonyl chloride in pyridine it gave a complex mixture of starting material and methanesulphonyloxy-derivatives which were separated by crystallisation and chromatography into (*a*) the 2,7-bis-derivatives described by MacMillan *et al.* (*loc. cit.*); these, with collidine followed by alkaline hydrolysis of the product, gave a mixture of the 8-epimeric 2,3-dehydro-acids (VI; R = H), and (*b*) a mixture of monomethanesulphonyloxy-derivatives. In some experiments this fraction yielded the 2-methanesulphonyloxy-8-epi-derivative (III; R = Me, R′ = H, β-OSO_2Me) m. p. 171—173°, and its 8-epimer,

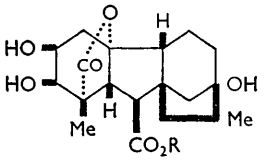
[5] Jones and McCloskey, *J. Appl. Chem.*, 1963, **13**, 324.
[6] Cross, Galt, and Hanson, *Tetrahedron*, 1962, **18**, 451.
[7] Curtis, Heilbron, Jones, and Woods, *J.*, 1953, 457.
[8] Cross, Grove, and Morrison, *J.*, 1961, 2498.
[9] Cross, *J.*, 1960, 3022.
[10] Bourn, Grove, Mulholland, Tidd, and Klyne, *J.*, 1963, 154.
[11] MacMillan, Seaton, and Suter, *Tetrahedron*, 1960, **11**, 60.

m. p. 206—208° (decomp.). The former, with collidine, gave the 8-epi-2,3-dehydro-ester (VI; R = Me), identical with material prepared from pure methyl 8-epi-tetrahydrogibberellate. Similarly, the 8-epimer, m. p. 206—208° (decomp.) afforded the corresponding 2,3-dehydro-ester. In other experiments, fraction (*b*) could not be resolved by chromatography. However, treatment with collidine gave a mixture from which the above 2,3-dehydro-esters (VI; R = Me) were isolated, together with a methanesulphonyloxy-derivative, m. p. 169—171°. This, from its resistance to collidine, must be the 7-derivative (V) and it is assigned the 8-epi-configuration because with hot aqueous alkali it yielded the 2α-epimer (III; R = H, R′ = H, α-OH) [12] of 8-epi-tetrahydrogibberellic acid.

Alkaline hydrolysis of the epimeric 2,3-dehydro-esters (VI; R = Me) yielded the corresponding acids (VI; R = H). The 8-epi-acid was also obtained, but in poor yield, by dehydrating 8-epi-tetrahydrogibberellic acid (III; R = H, R′ = H, β-OH) as for its methyl ester. Like gibberellin A_5 (VII; R = H) [11] and the monocyclic lactone (VIII),[13] the 2,3-dehydro-acids and their methyl esters (VI; R = H or Me) showed maxima or inflections at about 220 mμ.

Catalytic hydrogenation of the esters (VI; R = Me) gave the corresponding 8-epimeric dihydro-derivatives (III; R = Me, R′ = H, H), which were hydrolysed by alkali to the corresponding acids (III; R = H, R′ = H, H), (tetrahydrogibberellins A_5). Hydrolysis of the 8-epi-ester, m. p. 205—207°, gave also a small amount of the hydroxy-acid (IX). Esterification of this acid was accompanied by lactonisation giving the above 8-epi-methyl ester, m. p. 205—207°.

The saturated methyl esters (III; R = Me, R′ = H, H) were more conveniently prepared by reduction, through the thioketals, of the corresponding 8-epimeric 2-oxo-esters (III; R = Me, R′ = O) which are separable by crystallisation.[9] Thus prepared, each ester contained a little of the 8-epimer; however, the epimeric acids (III; R = H, R′ = H, H) obtained on saponification, could be purified by crystallisation.



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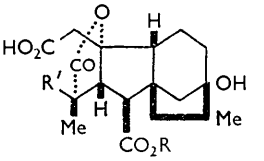

(XI)

MacMillan *et al.*[14] obtained a mixture of 8-epimeric 2,3-diols (X; R = Me) by treating the corresponding mixture of 2,3-dehydro-esters (VI; R = Me) with osmium tetroxide.

On similar treatment, the 8-epi-ester (VI; R = Me) yielded the pure 8-epi-diol (X; R = Me), and each of the 2,3-dehydro-acids (VI; R = H) gave, in lower yield, the corresponding 8-epimeric 2,3-diols (X; R = H) (8- and 8-epi-dihydrogibberellin A_8).

Oxidation of the 8-epi-diol (X; R = H) with periodate gave a gummy uncharacterised aldehyde which was further oxidised with chromium trioxide to the expected tricarboxylic seco-acid (XI; R = H, R′ = CO_2H). The corresponding mixture of 8-epimeric acids was prepared similarly. But when the gummy aldehyde, obtained by the action of periodate on the 8-epi ester (X; R = Me) was oxidised with chromium trioxide, simultaneous decarboxylation at position 1 took place, giving the monobasic seco-acid (XI; R = Me, R′ = H). Methylation gave the dimethyl ester.

Experimental

Melting points are corrected. Unless otherwise stated infrared spectra were obtained for Nujol mulls, and ultraviolet spectra and optical rotations for ethanol solutions. " Hyflo Super

[12] Mulholland, *J.*, 1963, 2606.
[13] Moffatt, *J.*, 1963, 2595.
[14] MacMillan, Seaton, and Suter, *Tetrahedron*, 1962, **18**, 349.

Cel " Celite and Woelm grade II acid alumina were used for chromatography. Light petroleum had b. p. 40—60°, unless stated otherwise, and solutions were dried with sodium sulphate.

Derivatives of Gibberellic Acid.—Butyrylgibberellic acid [2] had m. p. 168—172° raised to 172—175° (prisms) by chromatography on Celite buffered at pH 6·2, and crystallisation from ethyl acetate–light petroleum (Found: C, 66·65; H, 6·9; Active H, 0·57. Calc. for $C_{23}H_{28}O_7$: C, 66·3; H, 6·8; 2 Active H, 0·48%). The infrared spectrum (in $CHCl_3$) was identical with that of the dimorphic form,[2] m. p. 192°.

Propionylgibberellic acid crystallised from ethyl acetate–light petroleum as prisms, m. p. 185—188° [Found (for sample dried at 100° *in vacuo* for 8 hr.): C, 63·2; H, 6·7. $C_{22}H_{26}O_7,H_2O$ requires C, 62·8; H, 6·7%].

2-Acetyl-7-trifluoroacetylgibberellic Acid.—2-Acetylgibberellic acid (164 mg.), suspended in purified dioxan (0·2 ml.), was treated with trifluoroacetic anhydride (1·2 ml.) and stored for 22 hr. The resulting solution was evaporated at 22° *in vacuo*. The residue, in benzene (2 ml.), was again evaporated, at 35°, *in vacuo*. The residue, in acetone (1·7 ml.) and water (0·2 ml.) was stored for 2 hr. The solution was evaporated at 20° *in vacuo*. The residue was extracted with ether. The extract was washed with water, dried, and evaporated *in vacuo*. Crystallisation of the residue from ether–light petroleum (b. p. 40—60°) gave the *acid* as nodules of prisms (134 mg.), m. p. 175—176° (Found: C, 57·4; H, 5·0; F, 11·8. $C_{23}H_{23}F_3O_8$ requires C, 57·0; H, 4·8; F, 11·8%), $\nu_{max.}$ 3200 br, 1778, 1748, 1703 cm.$^{-1}$. Shaking the acid, in ether, with 2N-potassium hydrogen carbonate for 3 min. and recovery from the aqueous layer by acidification and extraction with ethyl acetate regenerated 2-acetylgibberellic acid, identified by m. p. and infrared spectrum. With ethereal diazomethane, 2-acetyl-7-trifluoroacetylgibberellic acid gave the *methyl ester*, needles [from light petroleum (b. p. 60—80°)], m. p. 131—132° (Found: C, 58·1; H, 5·3. $C_{24}H_{25}F_3O_8$ requires C, 57·9; H, 5·1%).

Neutral Derivatives of Gibberellic Acid.—The following esters of gibberellic acid were prepared as described [4] for the butylcellosolve ester, by the action of the appropriate alcohol on gibberellic acid anhydride monohydrate at 100°: *benzyl gibberellate*, needles, m. p. 164—168° [from acetone–light petroleum (b. p. 60—80°)] (Found: C, 71·6; H, 6·5. $C_{26}H_{28}O_6$ requires C, 71·5; H, 6·4%), $\nu_{max.}$ 3350, 1770, 1735, 1655 cm.$^{-1}$; *t-butyl gibberellate*, prisms (from benzene), m. p. 149—152° (Found: C, 68·4; H, 7·65. $C_{23}H_{30}O_6$ requires C, 68·6; H, 7·5%); propyl gibberellate, prisms, m. p. 141—143° (from ethyl acetate–light petroleum) (lit.,[3] 138°) (Found: C, 67·5; H, 7·2. Calc. for $C_{22}H_{28}O_6$: C, 68·0; H, 7·3%); butyl gibberellate, prisms, m. p. 157—158·5° [from ethyl acetate–light petroleum (b. p. 60—80°)] (lit.,[3] 145°) (Found: C, 69·0; H, 7·4. Calc. for $C_{23}H_{30}O_6$ C, 68·6; H, 7·5%).

Gibberellamide.—A stream of ammonia was passed into gibberellic anhydride [4] (500 mg.) in pyridine (4 ml.) at 100° during 2 hr. The mixture was evaporated *in vacuo*. The residue, in ethyl acetate, was washed with dilute sodium hydrogen carbonate and water. The recovered neutral gum (105 mg.), on crystallisation from ethyl acetate followed by acetone–light petroleum (b. p. 60—80°) gave the *amide*, prisms (48 mg.), m. p. 211—213° (Found: C, 65·8; H, 6·9; N, 4·0 $C_{19}H_{23}NO_5$ requires C, 66·1; H, 6·7; N, 4·0%), $\nu_{max.}$ 3395, 3310, 3205, 1756, 1678, 1610 cm.$^{-1}$. Impure gibberellic acid (271 mg.) was recovered from the alkaline washings.

2,7-Diacetylgibberellamide.—Gibberellic anhydride (5 g.) was boiled for 3·25 hr. with acetic anhydride (30 ml.) giving, on recovery, crude diacetylgibberellic anhydride (4·38 g.), m. p. 206—220°. This (3·78 g.) was treated with ammonia, as described for gibberellamide, giving diacetylgibberellic acid (650 mg.) and the *amide*, which, after chromatography on silica [elution with ethyl acetate–light petroleum (2 : 3)] and crystallisation from ethyl acetate–light petroleum (b. p. 60—80°), formed prisms (973 mg.), m. p. 238—241° (Found: C, 64·5; H, 6·45. $C_{23}H_{27}NO_7$ requires C, 64·3; H, 6·3%).

The following derivatives were prepared by the method described for gibberellamide, using 1 mol. of the appropriate amine or thiol instead of ammonia; *N-octylgibberellamide* formed prisms, m. p. 170—173° [from ethyl acetate–light petroleum (b. p. 60—80°)] (Found: C, 70·7; H, 8·6; N, 3·1. $C_{27}H_{39}NO_5$ requires C, 70·9; H, 8·6; N, 3·1%), $\nu_{max.}$ 3479, 3383, 3300, 1755, 1650, 1643 cm.$^{-1}$. *Thiophenylgibberellate* formed needles, m. p. 153—155° [from ethyl acetate–light petroleum (b. p. 60—80°)] (Found: C, 67·9; H, 6·3; S, 6·0. $C_{25}H_{26}O_5S$ requires C, 68·5; H, 6·0; S, 7·3%), $\nu_{max.}$ 1767, 1686 cm.$^{-1}$; $\nu_{max.}$ ($CHCl_3$) 1766, 1725, 1697 cm.$^{-1}$. Crude thiobenzylgibberellate did not crystallise and was chromatographed on silica gel. Elution with light petroleum (b. p. 60—80°)–ethyl acetate (9 : 1) gave benzenethiol; further elution with a 2 : 3 mixture gave the *derivative*, needles, m. p. 166—170° [from ethyl acetate–light petroleum

(b. p. 60—80°)] (Found: C, 69·0; H, 6·2; S, 6·7. $C_{26}H_{28}O_5S$ requires C, 69·0; H, 6·2; S, 7·1%), $\nu_{max.}$ 3265, 1768, 1683 cm.$^{-1}$.

An attempt to prepare *N*-propylgibberellamide by this method failed.

N-*Propylgibberellamide*.—Propylamine (0·05 ml.) and *NN'*-dicyclohexylcarbodi-imide (32 mg.) were added to gibberellic acid (100 mg.) in dioxan (1·2 ml.). The solution was refluxed for 30 min., then evaporated. The residue, in ethyl acetate, was washed with dilute sodium hydrogen carbonate and water. Recovery gave a gum (59 mg.) which, with acetone, afforded *NN'*-dicyclohexylurea (20 mg.) and a gum (39 mg.). The latter, combined with material from an identical experiment, in light petroleum (b. p. 60—80°), was chromatographed on a column (17 × 1·5 cm.) of silica. Elution with light petroleum–ethyl acetate (3 : 2) gave the urea derivative (8 mg.); elution with light petroleum–ethyl acetate (2 : 3) gave the *amide*, a gum (79 mg.) (Found: C, 65·8; H, 8·3, N, 4·4. $C_{22}H_{29}NO_5,H_2O$ requires C, 65·2; H, 7·7; N, 3·5%), $\nu_{max.}$ 3350, 1760, 1688, 1638, 1508 cm.$^{-1}$. $\nu_{max.}$ ($CHCl_3$) 3600, 3445, 3400—3300, 1769, 1704, 1655, 1495 cm.$^{-1}$.

N-Butylgibberellamide could not be prepared by this method but thiophenylgibberellate was obtained in good yield.

N-p-*Tolylgibberellamide*.—Gibberellic acid (250 mg.), in dioxan (4 ml.) at 15°, was treated with *p*-toluidine (77 mg.) followed by *NN'*-dicyclohexylcarbodi-imide (149 mg.). After being kept at room temperature for 22 hr. the mixture was filtered and the filtrate was evaporated *in vacuo*. The residue, in ethyl acetate, was washed with sodium hydrogen carbonate solution. Recovery from the organic fraction gave a foam (320 mg.) which was extracted with warm benzene (30 ml.). The insoluble material (146 mg.; m. p. 177—182°) purified by precipitation with light petroleum (b. p. 60—80°) from ethyl acetate, afforded the p-*toluidide* as an amorphous powder (110 mg.); m. p. 186—189° (Found: C, 71·2; H, 6·8; N, 3·2. $C_{26}H_{29}NO_5$ requires C, 71·7; H, 6·7; N, 3·2%), $\nu_{max.}$ 3453, 3358, 1750, 1666, 1599, 1529 cm.$^{-1}$.

Prepared similarly, with *p*-aminodiethylaniline, the p-*diethylaminoanilide* formed prismatic needles (34%), m. p. 217—219° (from ethyl acetate) (Found: C, 70·2; H, 7·3; N, 5·95. $C_{29}H_{36}N_2O_5$ requires C, 70·7; H, 7·4; N, 5·7%), $\nu_{max.}$ 3300, 1750, 1660, 1620, 1600 cm.$^{-1}$.

Interaction of gibberellic acid and *p*-nitrophenol in the presence of *NN'*-dicyclohexylcarbodi-imide, in a similar manner, at room temperature, gave p-*nitrophenyl gibberellate* (49%), purified by chromatography in chloroform on grade II neutral alumina followed by precipitation from acetone with light petroleum (b. p. 60—80°) as an amorphous powder, m. p. 181—184° (Found: C, 64·1; H, 5·7; N, 3·4. $C_{25}H_{25}NO_8$ requires C, 64·2; H, 5·4; N, 3·0%), $\nu_{max.}$ 3300, 3240, 3120, 3080, 1776, 1766, 1760, 1612, 1590 cm.$^{-1}$.

2',3',4',6'-*Tetra*-O-*acetyl*-D-*glucopyranosyl Gibberellate*.—A suspension of silver gibberellate dihydrate [2] (1·2 g.), in anhydrous benzene (60 ml.), was distilled to dryness from a water-bath. The residue was shaken with tetra-acetylbromo-α-D-glucose [15] (1·08 g.), in purified dioxan (13·5 ml.), for 23 hr. with protection from light. The mixture was filtered and the filtrate evaporated at 40° *in vacuo*. The residue, in ethyl acetate, was extracted with 2N-potassium hydrogen carbonate. Recovery of the acidic component by acidification and extraction with ethyl acetate afforded gibberellic acid (126 mg.). Recovery of the neutral product gave a foam (970 mg.) which, on crystallisation from benzene, gave prisms (320 mg.; 20%), m. p. 212—214° after recrystallisation, of the *derivative* (Found: C, 58·6; H, 6·0. $C_{33}H_{40}O_{15}$ requires C, 58·6; H, 5·95%).

2-*Epi-gibberellin* A_1 (II; R = H, R' = OH, R'' = H, α-OH).—Hydrolysis of 2-epi-gibberellin A_1 methyl ester (274 mg.) m. p. 190—192°) with boiling N-sodium hydroxide during 1 hr. as described by Cross *et al.*[8] gave an intractable product (186 mg.). Crude product (240 mg.) was chromatographed on a column of Celite (50 g.) buffered with a phosphate buffer [16] of pH 6·2 (50 ml.) and made up in chloroform. The column was eluted with 250 ml. portions of solvents giving fractions (solvent and ratio in parentheses): (1—3) (chloroform) yielding starting material (54 mg.); (4—7) (chloroform–ethyl acetate, 20 : 1, 10 : 1), no product; (8—11) (5 : 1, 3 : 1) giving gibberellin A_1 (3 mg.), m. p. 246—250° (decomp.); (12—18) (3 : 1), mixtures (81 mg.); (19—30), giving 2-epi-gibberellin A_1 (74 mg.) which crystallised from ethyl acetate–light petroleum as prisms (63 mg.), m. p. (after drying *in vacuo* at 100° for 3 days) 228—231° (decomp.), $[\alpha]_D^{22}$ +41° (*c* 0·64) (Found: C, 65·1; H, 7·1. Calc. for $C_{19}H_{24}O_6$ C, 65·5; H, 6·9%). Methylation gave starting material, m. p. 192°.

[15] Scheurer and Smith, *J. Amer. Chem. Soc.*, 1954, **76**, 3224.
[16] Stodola, Nelson, and Spence, *Arch. Biochem. Biophys.*, 1957, **66**, 438.

Gibberellic Acid 8-Epoxide.—A mixture of gibberellic acid (500 mg.) in acetone (25 ml.) and perbenzoic acid (1·4 g.) in chloroform (18 ml.) was stored at 0° for 165 hr. After dilution with an equal volume of chloroform the mixture was shaken with aqueous ferrous sulphate solution (giving a brown precipitate) and with water. Benzoic acid was recovered from the organic layer.

The precipitate and aqueous fractions were treated with 3N-sulphuric acid until the precipitate dissolved. 3N-Sodium hydroxide was then added until the solution had pH 3 and the mixture was extracted with ethyl acetate immediately. Recovery from the extract have the *8-epoxide* (319 mg.) which crytallised from ethyl acetate–light petroleum (b. p. 60—80°) as prisms, m. p. 234—238° (decomp.) (Found: C, 63·0; H, 6·2. $C_{19}H_{22}O_7$ requires C, 63·0; H, 6·1%), $\nu_{max.}$ 1755, 1717, 1252, 1165, 1100 cm.$^{-1}$.

The epoxide (11 mg.) was esterified with ethereal diazomethane and the crude methyl ester was shaken with manganese dioxide (100 mg.) [17] in dioxan (1·5 ml.) for 72 hr. A control experiment was carried out with methyl gibberellate. Recovery gave gums whose absorption at 230 mμ was measured: oxidised 8-epoxide (ε 445), oxidised methyl gibberellate (ε 1198). The 8-epoxide and methyl gibberellate had ε (230 mμ) 119 and 316, respectively.

Gibberellin A_1 Epoxide.—Gibberellin A_1 (45 mg.) was epoxidised as described for gibberellic acid giving a gummy product (38 mg.) which yielded the *epoxide* as prisms (11 mg.), m. p. 210—215° [from acetone–light petroleum (b. p. 60—80°)] (Found: C, 62·8; H, 6·7. $C_{19}H_{24}O_7$ requires C, 62·6; H, 6·6%), $\nu_{max.}$ 1757, 1723, 1250, 1170, 1100 cm.$^{-1}$.

Oxidation of Gibberellic Acid with Manganese Dioxide.—Gibberellic acid (500 mg.), manganese dioxide (5·0 g.), and dioxan (50 ml.) were shaken together at room temperature for 72 hr. and the mixture was filtered. The filtrate and washings of the cake were evaporated giving a gum (362 mg.). The combined products [748 mg., $\nu_{max.}$ (shoulder) 226 mμ ($E^{1\%}_{1\,cm.}$ 42)] from two identical experiments were reoxidised with fresh manganese dioxide for 140 hr., giving a gum (619 mg., $E^{1\%}_{1\,cm.}$ 60 at 226 mμ). The gum was chromatographed on Celite (80 g.) previously treated with the phosphate buffer (80 ml.) and made up in chloroform. Elution of the column with portions of solvents gave fractions (i), (chloroform, 500 ml.) yielding gums (50 mg.) on recovery; (ii), (1 l.) yielding a solid (143 mg.); (iii) chloroform, 200 ml.; chloroform–ethyl acetate (1 : 3, 700 ml.), yielding gums (17 mg.); (iv) (ethyl acetate, 750 ml.) yielding starting material (285 mg.). Fraction (ii) crystallised from ethyl acetate–light petroleum in prisms (136 mg.), m. p. 214—216° (decomp.), $[\alpha]_D^{24}$ +71° (*c* 1·22) of *4aα,7-dihydroxy-1β-methyl-8-methylene-2-oxogibb-3-ene-1α,10β-dicarboxylic acid 1→4a-lactone* (I; R = O) (Found: C, 66·2; H, 5·95. $C_{19}H_{20}O_6$ requires C, 66·3; H, 5·85%), $\nu_{max.}$ 3480, ~2620, 1784, 1723, 1694 cm.$^{-1}$; $\nu_{max.}$ (dioxan) 1791, 1733, and 1701 cm.$^{-1}$, $\lambda_{max.}$ 228 mμ (log ε 3·82).

The methyl ester, m. p. 184—187°, was identical with an authentic specimen.[9]

Hydrogenation of the Oxo-acid (I; R = O) (with Mr. R. I. W. Honeywood).—The acid (300 mg.), in ethyl acetate (15 ml.) containing pyridine (2 ml.), was shaken in hydrogen at room temperature in the presence of a 2% palladium–barium carbonate catalyst (103 mg.). Uptake of hydrogen (1·0 mol.) ceased after 3 hr. The recovered product was chromatographed on Celite (60 g.) buffered with the phosphate buffer (60 ml.) and made up in chloroform–light petroleum (5 : 1). Elution of the column with portions of the solvent removed intractable non-lactonic (infrared spectra) gums (142 mg.). Further elution with a 6 : 1 mixture yielded a solid (80 mg.) which crystallised from ethyl acetate–light petroleum giving *4aα,7-dihydroxy-1β-methyl-8-methylene-2-oxogibbane-1α,10β-dicarboxylic acid 1→4a-lactone* (II; R = H, R′ = OH, R″ = O) as prisms (62 mg.), m. p. 207—209° (decomp.), $[\alpha]_D^{18}$ +138° (*c* 1·04) (Found: C, 66·1; H, 6·5. $C_{19}H_{22}O_6$ requires C, 65·9; H, 6·4%), $\nu_{max.}$ 3630, 3516, 1778, 1728, 1711, 891, 877 cm.$^{-1}$.

Attempted preparation of the above oxo-acid by oxidation of gibberellin A_1 with a chromium trioxide–sulphuric acid reagent [7] failed.

Tetrahydrogibberellic Acid.—(i) *Oxidation.* The acid [5,9] (27 mg.) in acetone (3 ml.) was treated with an excess (0·09 ml.) of the above chromium trioxide reagent for 30 min. at room temperature. The mixture was concentrated at room temperature *in vacuo*, diluted with water, and extracted with ethyl acetate. The gummy product (27 mg.) recovered from the extract was chromatographed on Celite (5·0 g.) buffered with the phosphate buffer (5·0 ml.) and made up in chloroform–light petroleum (1 : 1). Elution with chloroform gave a gum (21 mg.) which crystallised from ethyl methyl ketone as prisms (17 mg.), m. p. 255—257° (decomp.) of *4,aα,7-dihydroxy-1β,8-dimethyl-2-oxogibbane-1α,10β-dicarboxylic acid 1→4a-lactone* (III;

[17] Attenburrow, Cameron, Chapman, Evans, Hems, Jansen, and Walker, *J.*, 1952, 1094.

R = H, R′ = O) (Found: C, 66·7; H, 6·95. $C_{19}H_{24}O_6$ requires C, 65·5; H, 6·9%), $\nu_{max.}$ 3516, 1770, 1728 cm.$^{-1}$.

The methyl ester, m. p. 163°, was identical with an authentic specimen.

(ii) *Action of hydrochloric acid* (with Dr. J. F. GROVE). The acid (60 mg.) was boiled with 2N-hydrochloric acid (10 ml.) for 19 hr. The gummy product (55 mg.) recovered in ethyl acetate, was chromatographed on Celite (15 g.) buffered with the phosphate buffer (pH 6·2, 15 ml.) and made up in chloroform. Portionwise elution of the column gave the following main fractions: (i) chloroform (100 ml.) then chloroform–ethyl acetate (9 : 1, 150 ml.) giving a yellow gum (19 mg.) on recovery; (ii) (50 ml.), trace; (iii) (4 : 1, 175 ml.) and (7 : 3, 100 ml.), an intractable gum (17 mg.); (iv) (3 : 2, 50 ml.), trace; (v) (3 : 2, 250 ml.), (1 : 1, 100 ml.), and (2 : 3, 150 ml.), a colourless gum (22 mg.).

Fraction (v) crystallised from ethyl acetate–light petroleum (b. p. 60—80°) as prisms (6·6 mg.) m. p. 241—247° of the 4b-*epimer* (IV; R = H) of tetrahydrogibberellic acid (Found: C, 65·1; H, 7·8. $C_{19}H_{26}O_6$ requires C, 65·1; H, 7·5%). The methyl ester, m. p. 130—135° and 160—162°, was identical with an authentic specimen.[10]

Dehydration of Methyl 8-*Epi-tetrahydrogibberellate* (III; R = Me, R′ = H, β-OH).—A solution of the ester [12] (598 mg.) and methanesulphonyl chloride (209 mg.) in pyridine (15 ml.) was kept at room temperature for 45 hr., then evaporated *in vacuo*. The residue was mixed with ethyl acetate and dilute hydrochloric acid. The product (0·68 g.) recovered from the organic layer was chromatographed in benzene on alumina (25 × 2·2 cm.). The column was washed with benzene (100 ml.) then eluted with portions of benzene–methanol giving the following main fractions (solvent ratio and volume in parentheses): (i) (400 : 1, 200 : 1; 920 ml.) giving gums (45 mg.); (ii) (200 : 1, 80 ml.) giving a gum (67 mg.) consisting essentially of the bismethanesulphonyloxy-derivative and showing no hydroxy absorption in the infrared spectrum; (iii) (60 ml.), trace; (iv) (480 ml.), 273 mg.; (v) (200 : 1, 190 ml.; 100 : 1, 140 ml.; 50 : 1, 160 ml.), 55 mg.; (vi) (50 : 1, 90 ml.), giving starting material (132 mg.).

The product from fraction (iv) was boiled with collidine (40 ml.) for 5·5 hr. The solution was evaporated *in vacuo*, the residue in ethyl acetate was washed with dilute hydrochloric acid and water, dried, and evaporated. The product was chromatographed in benzene on alumina (32 × 2·2 cm.) and the column was eluted with portions of benzene–methanol giving fractions; (i) (400 : 1, 2 l.), yielding 8 mg. on recovery; (ii) (800 ml.), 103 mg. m. p. 185—190°; (iii) (950 ml.), 26 mg.

Crystallisation of fractions (ii) and (iii) from ethyl acetate–light petroleum gave prisms (52 mg.) m. p. 196—198° by recrystallisation of *methyl* 1α-*carboxy*-4aα,7-*dihydroxy*-1β,8-*epi*-*dimethylgibb*-2-*ene*-10β-*carboxylate* 1→4a *lactone* (VI; R = Me) (Found: C, 68·9; H, 7·5. $C_{20}H_{26}O_5$ requires C, 69·3; H, 7·6%), $\nu_{max.}$ 3535, 1761, 1734 cm.$^{-1}$ $\nu_{max.}$ ($CHBr_3$) 3600, 1768, 1729 cm.$^{-1}$. The ester did not react with bromine in chloroform at room temperature and attempts to prepare the 2,3-epoxide failed.

Dehydration of the Mixed 8-*Epimeric Methyl Tetrahydrogibberellates*.—The product (859 mg.), obtained from the mixed esters (749 mg.) with methanesulphonyl chloride, was chromatographed in benzene on alumina (40 × 2·8 cm.) and the column was eluted portionwise with benzene–methanol giving the following main fractions: (i) (400 : 1, 2 l.) yielding a trace of gum on recovery; (ii) (800 ml.) yielding gummy bismethanesulphonyloxy-derivatives (146 mg.); (ii) (400 : 1, 2·8 l. and (300 : 1, 500 ml.), 2 mg.; (iv) (300 : 1, 1200 ml.), a solid (298 mg.); (v) (600 ml.) an intractable mixture (53 mg.); (vi) (1900 ml.), a solid (155 mg.); (vii) (50 : 1 500 ml.), no product; (viii) (750 ml.), starting material (160 mg.). Fraction (iv) crystallised from ethyl acetate–light petroleum as prisms (201 mg.) m. p. 171—173°, of *methyl* 1α-*carboxy*-4aα,7-*dihydroxy*-2β-*methanesulphonyloxy*-1β,8-*epi*-*dimethylgibbane*-10β-*carboxylate* 1→4a-*lactone* (III; R = Me, R′ = H, β-OSO_2Me) (Found: C, 57·1; H, 7·0. $C_{21}H_{30}O_8S$ requires C, 57·1; H, 6·8%), $\nu_{max.}$ 3530, 1783, 1725, 1359 and 1179 cm.$^{-1}$ (SO_2), $\nu_{max.}$ ($CHCl_3$) 1773, 1730 cm.$^{-1}$.

Fraction (vi) crystallised from ethyl acetate–light petroleum giving the 8-*epimeric* 2-*methanesulphonyloxy-derivative* (III; R = Me, R′ = H, β-OSO_2Me) as prisms (143 mg.), m. p. 206—208° (decomp.) (Found: C, 57·0; H, 6·9%), $\nu_{max.}$ 3520, 1782, 1725, 1364, and 1181 cm.$^{-1}$.

In some experiments the fractions of monomethanesulphonyloxy-derivatives were intractable and were treated with collidine (see below, *c*).

Action of Collidine on the Methanesulphonyloxy-derivatives.—(*a*) Methyl 1α-carboxy-4aα,7-dihydroxy-2β-methanesulphonyloxy-1β,8-epi-dimethylgibbane-10β-carboxylate 1→4a-lactone (240 mg.), m. p. 171—173°, was boiled with collidine (25 ml.) for 6 hr. The solid product,

(186 mg.) recovered as described above, crystallised from ethyl acetate–light petroleum as prisms (140 mg.), m. p. 196—198°, of methyl 1α-carboxy-4aα,7-dihydroxy-1β,8-epi-dimethylgibb-2-ene-10β-carboxylate 1→4a-lactone (VI; R = Me) identical with material prepared as described above.

(*b*) The above 8-epimeric 2-methanesulphonyloxy-derivative [201 mg., m. p. 206—208° (decomp.)] was boiled with collidine and the product (95 mg.) was chromatographed in benzene on alumina (32 × 2·0 cm.). The column was eluted with benzene giving fractions (i) (1·9 l.), yielding 5 mg. of gum on recovery; (ii) (500 ml.) giving an impure solid (7 mg.), m. p. <200°; and (iii) (7·3 l.) giving a solid (54 mg.) m. p. >200°.

Fraction (iii) crystallised from ethyl acetate–light petroleum as prisms (46 mg.), m. p. 208—210°, of *methyl* 1α-*carboxy*-4aα,7-*dihydroxy*-1β,8-*dimethylgibb*-2-*ene*-10β-*carboxylate* 1→4a-*lactone* (VI; R = Me) (Found: C, 69·0, H, 7·7. $C_{20}H_{26}O_5$ requires C, 69·3; H, 7·6%), $\nu_{max.}$ 3490, 1779, 1712 cm.$^{-1}$, $\lambda_{max.}$ 220 mμ (log ε 3·19).

(*c*) The product (697 mg.) from collidine treatment of intractable monomethanesulphonyloxy-derivatives of the methyl tetrahydrogibberellates was chromatographed on alumina (45 × 2·0 cm.) and the column was eluted portionwise with benzene–methanol (400 : 1), giving the following main fractions: (i) (4 l.) giving gums (26 mg.) on recovery; (ii) (3·75 l.) giving solid products (214 mg.); (iii) (1 l.) giving intractable gums (64 mg.); (iv) (3·75 l.) giving gums (281 mg.).

Fraction (ii) crystallised from ethyl acetate–light petroleum yielding methyl 1α-carboxy-4aα,7-dihydroxy-1β,8-epi-dimethylgibb-2-ene-10β-carboxylate 1→4a-lactone (VI; R = Me), m. p. 194—196° (157 mg.) identical with authentic material (above).

Fraction (iv) was fractionally crystallised from ethyl acetate–ether giving first 40 mg., m. p. 203—210°, then 136 mg., m. p. 155—165°. The higher-melting product crystallised from ethyl acetate–light petroleum giving methyl 1α-carboxy-4aα,7-dihydroxy-1β,8-dimethylgibb-2-ene-10β-carboxylate 1→4a-lactone (VI; R = Me) (20 mg.), m. p. 208—210°, described above.

The fraction of m. p. 155—165° crystallised from ethyl acetate–light petroleum as prisms (106 mg.), m. p. 169—171° of *methyl* 1α-*carboxy*-2β,4aα-*dihydroxy*-7-*methanesulphonyloxy*-1β,8-*epi-dimethylgibbane*-10β-*carboxylate* 1→4a-*lactone* (V) (Found: C, 57·0; H, 6·9. $C_{21}H_{30}O_8S$ requires C, 57·1; H, 6·8%), $\nu_{max.}$ 3405, 1748, 1725, 1335, 1209, 1172 cm.$^{-1}$. The m. p. was depressed on admixture with the above isomer, m. p. 171—172°. The derivative (103 mg.), m. p. 169—171°, was boiled with 2N-sodium hydroxide (10 ml.) for 5 hr. The cooled solution was washed with ethyl acetate, acidified with dilute hydrochloric acid, and concentrated *in vacuo*. Prisms (52 mg.), m. p. 292—298° (decomp.), of 2-epi-8-epi-tetrahydrogibberellic acid (III; R = H, R′ = H, α-OH) separated.

(*d*) The gummy bismethanesulphonyloxy-derivatives (3·64 g.) from several experiments were boiled with collidine (370 ml.) for 6·5 hr. and the crude gummy product (2·51 g.) hydrolysed with boiling 2N-sodium hydroxide (250 ml.) for 6 hr. The cooled solution was washed with ethyl acetate, acidified with concentrated hydrochloric acid, and the crystals (1·45 g.) which separated were collected.

Part (251 mg.) of the product was chromatographed on Celite (50 g.) buffered with the phosphate buffer (50 ml.) and made up in chloroform–light petroleum (1 : 2). The column was eluted with the solvents (1 : 2, 250 ml.) and (1 : 1, 750 ml.). Further elution with 250 ml. portions of chloroform then gave, on recovery (i) nil; (ii) and (iii), 215 mg. The rest of the crude material was chromatographed in the same way giving a total of 1·37 g. which crystallised from methanol–ethyl acetate as plates or prisms of the 8-epimeric mixture of 4aα,7-*dihydroxy*-1β,8-*dimethylgibb*-2-*ene*-1α,10β-*dicarboxylic acid* 1→4a *lactones* (VI; R = H). (a) 908 mg., m. p. 288—293° (decomp.), $[\alpha]_D^{19}$ −97° (*c* 0·66) (Found: C, 68·7; H, 7·55. $C_{19}H_{24}O_5$ requires 68·65; H, 7·3%); (b) 384 mg., m. p. 280—285° (decomp.), $[\alpha]_D^{19}$ −93° (*c* 0·99).

4aα,7-*Dihydroxy*-1β,8-*epi-dimethylgibb*-2-*ene*-1α,10β-*dicarboxylic Acid* 1→4a-*Lactone* (VI; R = H).—(*a*) Methyl 1α-carboxy-4aα,7-dihydroxy-1β,8-epi-dimethylgibb-2-ene-10β-carboxylate 1→4a-lactone (VI; R = Me) (287 mg.) was heated under reflux for 5 hr. with 2N-sodium hydroxide (29 ml.). The solution was acidified with hydrochloric acid at 25°. The precipitate and material obtained by ethyl acetate extraction of the mother-liquor crystallised from dilute methanol as plates (239 mg.), m. p. ~300° (decomp. variable), $[\alpha]_D^{22}$ −111° (*c* 0·96), of the *acid* (Found: C, 68·4; H, 7·3. $C_{19}H_{24}O_5$ requires C, 68·65; H, 7·3%), $\nu_{max.}$ 3430, 1760, 1751, 1720 cm.$^{-1}$, $\nu_{max.}$ (dioxan) 1783, 1732, 1712 cm.$^{-1}$, $\lambda_{max.}$ 220 mμ (log ε 3·14).

(*b*) 8-Epi-tetrahydrogibberellic acid (III; R = H, R′ = H, β-OH) [12] (301 mg.) was kept

with methanesulphonyl chloride (129 mg.) in pyridine (10 ml.) for 48 hr. at room temperature. The mixture was evaporated *in vacuo* and the residue boiled with collidine (30 ml.) for 6 hr. The gummy product (254 mg.) recovered in the usual way, was chromatographed on Celite (60 g.) buffered with the phosphate buffer (60 ml.) and made up in chloroform. Elution of the column with portions of chloroform gave the following main fractions; (i) (200 ml.), yielding semi-solid products (33 mg.) on recovery; (ii) (500 ml.), gum (5 mg.); further elution with chloroform containing increasing amounts of ethyl acetate gave gums (9 mg.) and impure starting material (85 mg.).

Fraction (i) crystallised from dilute methanol (charcoal) as prisms (17 mg.), m. p. 293—300° (decomp.) of the 8-epi-acid obtained by method (*a*) above. The methyl ester had m. p. 195—197°.

4aα,7-Dihydroxy-1β,8-dimethylgibb-2-ene-1α,10β-dicarboxylic Acid 1→4a-Lactone (VI; R = H).—Methyl 1α-carboxy-4aα,7-dihydroxy-1β,8-dimethylgibb-2-ene-10β-carboxylate 1→4a-lactone (VI; R = Me) (300 mg.) was hydrolysed as described for the 8-epimer (above) giving the *acid* as prisms (252 mg.), m. p. 295—300° (decomp.; variable) (from methanol–ethyl acetate–light petroleum), $[\alpha]_D^{14}$ −83° (*c* 1·09) (Found: C, 69·0; H, 7·5. $C_{19}H_{24}O_5$ requires C, 68·65; H, 7·3%), $\nu_{max.}$ 3425, 1740, 1724 cm.$^{-1}$, $\lambda_{max.}$ 220 mμ (log ε 3·12).

Methylation gave starting material, m. p. 207—209°.

Methyl 1α-Carboxy-4aα,7-dihydroxy-1β,8-epi-dimethylgibbane-10β-carboxylate 1→4a-Lactone (III; R = Me, R′ = H, H).—(*a*) Methyl 1α-carboxy-4aα,7-dihydroxy-1β,8-epi-dimethylgibb-2-ene-10β-carboxylate 1→4a-lactone (VI; R = Me) (68 mg.) was hydrogenated with 10% palladium–carbon (51 mg.) in ethyl acetate (11 ml.) at room temperature (uptake 1·0 mol. in 25 min.). Crystallisation of the product from ethyl acetate–light petroleum gave the *ester* as prisms (50 mg.), m. p. 205—207°, $[\alpha]_D^{23}$ +24° (*c* 1·01) (Found: C, 69·2; H, 8·15. $C_{20}H_{28}O_5$ requires C, 68·9; H, 8·1%), $\nu_{max.}$ 3525, 1781, 1716 cm.$^{-1}$, $\nu_{max.}$ ($CHBr_3$) 3594, 1765, 1728 cm.$^{-1}$, ε (mμ) 373 (210), 366 (215), 352 (220), 290 (225).

(*b*) Methyl 1α-carboxy-4aα,7-dihydroxy-1β,8-epi-dimethyl-2-oxogibbane-10β-carboxylate 1→4a-lactone (III; R = Me, R′ = O) [9] (1·59 g., m. p. 130—133°) in chloroform (25 ml.) was treated with boron trifluoride etherate (1·40 ml.) and ethanedithiol (1·40 ml.). The mixture was kept at room temperature for 48 hr., then diluted with chloroform, washed with water and saturated sodium chloride, dried, and evaporated giving the *thioketal* (III; R = Me, R′ = ·S·CH_2·CH_2·S·) which crystallised from chloroform–ether–light petroleum as prisms (1·78 g.), m. p. 202—204° (Found: C, 60·4; H, 6·9. $C_{22}H_{30}O_5S_2$ requires C, 60·2; H, 6·9%), $\nu_{max.}$ 3525, 1780, 1718 cm.$^{-1}$.

The above thioketal (200 mg.) and Raney nickel (5 g.) were heated together in dioxan (20 ml.) at 100° for 8 hr. The product was recovered and crystallised from ethyl acetate–light petroleum as prisms (135 mg.), m. p. 205—206°, of the 8-epi-ester (III; R = Me, R′ = H, H). The ester prepared by method (*b*) contained a little of the 8-epimer which was separated after hydrolysis (see below).

Hydrolysis of the Ester.—The ester (1·00 g.), m. p. 205—206°, from method (*b*) was boiled with 2N-sodium hydroxide (100 ml.) for 6 hr. The solution was acidified at 10—15° with hydrochloric acid. Filtration after 4 hr. gave solid (A) (814 mg.), and a gum (B) (184 mg.) was recovered from the mother-liquor by extraction with ethyl acetate.

Solid (A) was extracted with portions of boiling ethyl methyl ketone. The undissolved residue (54 mg.) crystallised from methanol as prisms (21 mg.), m. p. 210—221° (decomp.) of *4aα,7-dihydroxy-1β,8-epi-dimethylgibbane-1α,10β-dicarboxylic acid* (IX), $[\alpha]_D^{24}$ +6° (*c* 0·32 in saturated $NaHCO_3$), pK_1 5·35, pK_2 5·60 (in H_2O) (Found: C, 64·3; H, 8·4. $C_{19}H_{28}O_6$ requires C, 64·75; H, 8·0%), $\nu_{max.}$ 3335, ~3200, ~2560, 1794w (? lactonic impurity), 1686s, 1671s cm.$^{-1}$.

With diazomethane in ether–methanol the acid lactonised giving methyl 1α-carboxy-4aα,7-dihydroxy-1β,8-epi-dimethylgibbane-10β-carboxylate 1→4a-lactone (III; R = Me, R′ = H, H), m. p. 203—205°, $[\alpha]_D^{22}$ +25° (*c* 0·60).

The above ethyl methyl ketone extract was concentrated and diluted with light petroleum yielding prisms (521 mg.), m. p. 214—216° of *4aα,7-dihydroxy-1β,8-epi-dimethylgibbane-1α,10β-dicarboxylic acid 1→4a-lactone* (III; R = H, R′ = H, H), $[\alpha]_D^{22}$ +14° (*c* 0·70), $[\alpha]_D^{23}$ +11° (*c* 1·54 in saturated $NaHCO_3$) (Found: C, 68·3; H, 8·0. $C_{19}H_{26}O_5$ requires C, 68·2; H, 7·8%), $\nu_{max.}$ 3460—3200 br, 1773, 1742, 1702 cm.$^{-1}$, $\nu_{max.}$ (dioxan) 3400, 1779, 1730 cm.$^{-1}$. Methylation gave starting material, m. p. 205—206°.

The gum (B) was boiled with N-sodium hydroxide (5 ml.) for 1 hr. Acidification of the

solution gave a precipitate (131 mg.) which, after fractional crystallisation from ethyl methyl ketone, gave prisms (107 mg.), m. p. 252—253° of the 8-epimeric acid (III; R = H, R′ = H, H).

The methyl ester had m. p. 232—234° (see below).

Methyl 1α-*Carboxy*-4aα,7-*dihydroxy*-1β,8-*dimethylgibbane*-10β-*carboxylate* 1→4a-*Lactone* (III; R = Me, R′ = H, H).—(*a*) Methyl 1α-carboxy-4aα,7-dihydroxy-1β,8-dimethylgibb-2-ene-10β-carboxylate 1→4a-lactone (VI; R = Me) (64 mg.) was hydrogenated as described above for the 8-epimer giving, from ethyl acetate–light petroleum, plates or prisms (49 mg.) m. p. 233—235°, $[\alpha]_D^{24}$ +47°, (*c* 0·97) of the *ester* (Found: C, 68·9; H, 8·1. $C_{20}H_{28}O_5$ requires C, 68·9; H, 8·1%) $\nu_{max.}$ 3492, 1776, 1707 cm.$^{-1}$.

(*b*) Methyl 1α-carboxy-4aα,7-dihydroxy-1β,8-dimethyl-2-oxogibbane-10β-carboxylate 1→4a-lactone (III; R = Me, R′ = O) (900 mg.) [9] was converted into the corresponding 2-*thioketal* (III; R = Me, R′ = ·S·CH_2·CH_2·S·) (1·01 g.), needles, m. p. 205—207° (from chloroform–ether–light petroleum) (Found: C, 60·4; H, 7·1. $C_{22}H_{30}O_5S_2$ requires C, 60·2; H, 6·9%), $\nu_{max.}$ 3485, 1783, 1721 cm.$^{-1}$. Treatment of the thioketal (185 mg.) with Raney nickel as described for the 8-epimer gave the ester obtained by method (*a*), as prisms (101 mg.), m. p. 230—233°.

Hydrolysis of the Ester.—The above ester [740 mg., method (*b*)] was hydrolysed as described for the 8-epimer. Acidification of the alkaline solution yielded a solid (587 mg.), and a gum (84 mg.) was recovered in ethyl acetate from the mother-liquor. The combined products crystallised from ethyl methyl ketone–light petroleum giving 4aα,7-*dihydroxy*-1β,8-*dimethylgibbane*-1α,10β-*dicarboxylic acid* 1→4a-*lactone* (III; R = H, R′ = H, H) as prisms (512 mg.), m. p. 252—254°, $[\alpha]_D^{23}$ +37° (*c* 0·72) (Found: C, 68·5; H, 8·0. $C_{19}H_{26}O_5$ requires C, 68·2; H, 7·8%), $\nu_{max.}$ 3485, 1759, 1730 cm.$^{-1}$, $\nu_{max.}$ (dioxan) 3540, 3430, 1779, 1732 cm.$^{-1}$. Methylation gave starting material. Further recovery from the mother-liquor gave (i) the same acid (46 mg.), m. p. 250—253° and (ii) the 8-epimeric acid (26 mg.), m. p. 202—210°.

Reactions with Osmium Tetroxide.—(*a*) Methyl 1α-carboxy-4aα,7-dihydroxy-1β,8-epi-dimethylgibb-2-ene-10β-carboxylate 1→4a-lactone (VI; R = Me) (372 mg.) was kept with osmium tetroxide (372 mg.) in dioxan (45 ml.) in the dark for 68 hr. at room temperature. Hydrogen sulphide was passed through the mixture, which was then filtered, and the filtrate and washings of the cake were evaporated. The residue was chromatographed in benzene on alumina (18 × 2·0 cm.) and the column was eluted with 100 ml. portions of benzene–methanol (ratio in parentheses) giving fractions: (i and ii), (150 : 1), trace; (iii) (150 : 1); (iv)—(vi) (75 : 1), yielding 32 mg. on recovery; (vii) and (viii) (75 : 1), trace; (ix)—(xiii) (10 : 1), 273 mg.

Fractions (ix)—(xiii), a solvated solid partly melting at 110° (gas evolution), setting and re-melting at 193—195°, crystallised from acetone–light petroleum as prisms, m. p. 193—195° of *methyl* 1α-*carboxy*-2β,3β,4aα,7-*tetrahydroxy*-1β,8-*epi-dimethylgibbane*-10β-*carboxylate* 1→4a-*lactone* (X; R = Me) (Found: C, 63·1; H, 7·5. $C_{20}H_{28}O_7$ requires C, 63·1; H, 7·4%), $\nu_{max.}$ 3460, ~3390, 1775, 1710 cm.$^{-1}$.

(*b*) 4aα,7-Dihydroxy-1β,8-epi-dimethylgibb-2-ene-1α,10β-dicarboxylic acid 1→4a-lactone (VI; R = H) (252 mg.) in dioxan (40 ml.) was treated with osmium tetroxide (406 mg.). After storage for 78 hr. the product was recovered as in (*a*) above. Combined product from two identical experiments was chromatographed on Celite (20 g.) buffered with the phosphate buffer (20 ml.) and made up in chloroform. Elution of the column with portions of solvents gave the following main fractions: (i) chloroform (300 ml.) giving a gum (27 mg.) on recovery; (ii) (100 ml.), trace; (iii) chloroform–ethyl acetate (1 : 1; 300 ml.), 21 mg.; (iv) (100 ml.) and ethyl acetate (300 ml.), trace; (v) ethyl acetate (800 ml.) giving 198 mg.

Fraction (v) crystallised from methanol–ethyl acetate as prisms (184 mg.), m. p. 280—293° (decomp., variable) of 2β,3β,4aα,7-*tetrahydroxy*-1β,8-*epi-dimethylgibbane*-1α,10β-*dicarboxylic acid* 1→4a-*lactone* (X; R = H) (Found (on sample dried *in vacuo* at 100° for 4 hr.): C, 60·7; H, 7·3. $C_{19}H_{26}O_7$,0·5H_2O requires C, 60·8; H, 7·25%), $\nu_{max.}$ 3454, 3400, 3350sh, 1769, 1702 cm.$^{-1}$. The methyl ester was identical with the methyl ester, m. p. 193—195°, obtained in (*a*) above.

(*c*) 4aα,7-Dihydroxy-1β,8-dimethylgibb-2-ene-1α,10β-dicarboxylic acid 1→4a-lactone (VI; R = H) (100 mg.) was treated with osmium tetroxide and the product was chromatographed on Celite as described for the 8-epimer in (*b*) above, giving 2β,3β,4aα,7-*tetrahydroxy*-1β-8-*dimethylgibbane*-1α,10β-*dicarboxylic acid* 1→4a-*lactone* (X; R = H), prisms (26 mg.), m. p. 270—274° (decomp.) from methanol–ethyl acetate (Found (on sample dried at 100° for 5 hr. *in vacuo*): C, 61·8; H, 7·1. $C_{19}H_{26}O_7$ requires C, 62·3; H, 7·15%), $\nu_{max.}$ ~3528sh, 1748 1704 cm.$^{-1}$.

Prepared in the same way from an 8-epimeric mixture of the acids (VI; R = H) the mixed product had m. p. 280—285° (decomp.) (Found: C, 61·9; H, 7·3%).

Oxidation of 2β,3β,4aα,7-*Tetrahydroxy*-1β,8-*epi*-*dimethylgibbane*-1α,10β-*dicarboxylic Acid* 1→4a-*Lactone* (X; R = H).—The acid (190 mg.) in methanol (5 ml.) was treated with 0·02M-aqueous sodium metaperiodate (32·0 ml.) and the solution was kept for 24 hr. at room temperature. Extraction of the solution with ethyl acetate and recovery from the extract gave a gummy aldehyde (193 mg.) which restored the colour to Schiff's reagent and gave a precipitate with Brady's reagent. The gum, in acetone (10 ml.), was treated at 5° with the chromium trioxide–sulphuric reagent (0·43 ml.; 8N) and after 1·5 hr. at 0° the mixture was concentrated *in vacuo* at room temperature, diluted with water, and extracted with ethyl acetate. Recovery from the extract and crystallisation of the gummy product (193 mg.) from ethyl acetate gave prisms (97 mg.), m. p. 145—150° (decomp.) of 4aα,7-*dihydroxy*-1β,8-*epi*-*dimethyl*-2,3-*secogibbane*-1α,2,3,10β-*tetraoic acid* 1→4a-*lactone* (XI; R = H, R′ = CO_2H) (Found: dried at 77° *in vacuo* for 8 hr., C, 57·1; H, 6·1%; Equiv., 163. $C_{19}H_{24}O_9$ requires C, 57·6; H, 6·1%; Equiv., 132), $\nu_{max.}$ 3582, ~3480, 1775—1694br cm.$^{-1}$.

The *methyl ester*, prepared with diazomethane, crystallised from ethyl acetate–light petroleum as prisms, m. p. 141—144° (Found: OMe, 19·5. $C_{22}H_{30}O_9$ requires 3OMe, 21·2%).

Oxidation of the mixed 8-epimeric acids (X; R = H) (36·4 mg.) as described above gave the corresponding mixture of 8-*epimeric seco-acids* (XI; R = H, R′ = CO_2H) as prisms (17 mg.), m. p. 147—150° (decomp.) (Found (on sample dried at 77° *in vacuo*): C, 56·2; H, 6·35%; Equiv., 139. $C_{19}H_{24}O_9$,0·5H_2O requires C, 56·3; H, 6·2%; Equiv., 135).

Oxidation of Methyl 1α-*Carboxy*-2β,3β,4aα,7-*tetrahydroxy*-1β,8-*epi*-*dimethylgibbane*-10β-*carboxylate* 1→4a-*Lactone* (X; R = Me).—The ester (138 mg.) was oxidised with sodium metaperiodate followed by chromium trioxide, as described above, giving a gum (143 mg.). The gum was chromatographed on a column of Celite (20 g.) buffered with the phosphate buffer (20 ml.) and made up in chloroform–light petroleum (1 : 5). The column was eluted with 100 ml. portions of the solvents (ratio in parentheses) giving fractions: (i)—(iii), (1 : 5); (iv)–(vi), (1 : 2); (vii), (1 : 1); (viii), (2 : 1), giving gums (20 mg.) on recovery; (ix)—(xii) (2 : 1) giving a gum (92 mg.) which crystallised from ethyl acetate–light petroleum as prisms (21 mg.), m. p. 248—253°, of 4aα,7-*dihydroxy*-1β,8-*epi*-*dimethyl*-10β-*methoxycarbonyl*-1,2-*seco*-*A*-*norgibbane*-1α,2-*dioic acid* 1→4a-*lactone* (XI; R = Me, R′ = H) [Found: C, 62·5; H, 7·15%; Equiv. 171. $C_{19}H_{26}O_7$ requires C, 62·3; H, 7·15% Equiv. (dibasic, lactone fission), 183], $\nu_{max.}$ 3530, 3490, ~1772, 1753sh, 1710 cm.$^{-1}$.

The *methyl ester* was a gum (Found: OMe, 17·15. $C_{20}H_{28}O_7$ requires 2OMe, 16·3%).

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