652. *Gibberellic Acid. Part XXX.*[1] *The Preparation of 7-Deoxygibberellins from Gibberellic Acid*

By B. E. Cross, J. R. Hanson, and R. N. Speake

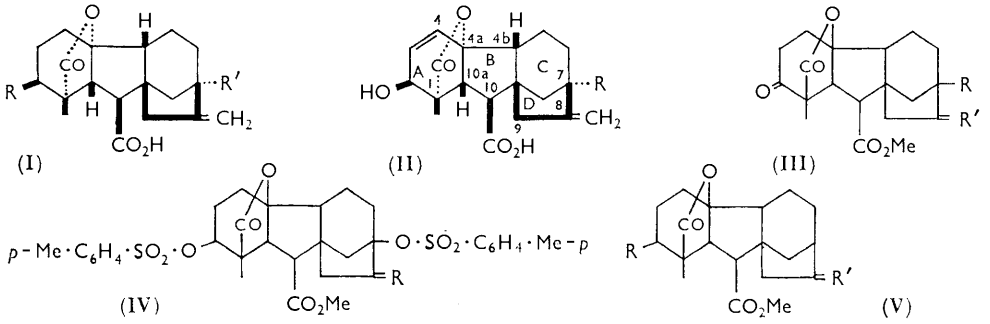
The conversion of gibberellic acid into 7-deoxy-compounds is described. The methyl ester of dihydrogibberellin A_9 has been prepared by a reaction sequence involving the direct removal of the 7-hydroxyl group, whilst a second route utilising the " double inversion " of ring D gave the methyl ester of gibberellin A_4.

The 7-deoxygibberellins, gibberellin A_4 (I; R = OH, R′ = H),[2] gibberellin A_7 (II; R = H),[3] and gibberellin A_9 (I; R = R′ = H)[3] show a high degree of biological specificity;[4] for example, they are much more active than gibberellic acid (II; R = OH) in promoting the growth of cucumber hypocotyls.[4a] The relative inaccessibility of these gibberellins from natural sources prompted studies aimed at removing the 7-hydroxyl group from gibberellic acid or its derivatives. Although reactions at bridgeheads are difficult,[5] two routes have been developed, one involving the direct removal of the 7-hydroxyl group and the other the " double-inversion " of ring D.

The reductive removal of bridgehead halogens with Raney nickel has been reported in model compounds[5] and in the conversion of steviol into (−)-kaurene.[6] In the gibberellin series, bridgehead deoxygenation has been achieved by reduction of 7-toluene-*p*-sulphonates with Raney nickel in carefully purified dioxan. Thus, in a model experiment, reduction of the gummy 7-toluene-*p*-sulphonate of the 8-epi-compound[7] (III; R = OH, R′ = H, Me), a known transformation product of gibberellic acid, gave an alcohol which, without characterisation, was oxidised to a ketone, $C_{20}H_{26}O_5$. The latter was formulated as the 8-epi-2-ketone (III; R = H, R′ = H, Me) since its infrared spectrum was almost identical with that of the mixed C-8 epimers of the 2-ketone (III; R = H, R′ = H, Me).[8] Similarly gibberellin A_1 methyl ester was prepared[9] from gibberellic acid and converted into its crystalline di-toluene-*p*-sulphonate (IV; R = CH_2). Treatment with Raney nickel then afforded a mixture of the 8-epimers of dihydrogibberellin A_9 methyl ester (V; R = H, R′ = H, Me) which was identified by comparison with an authentic sample.[1] To prepare gibberellin A_9 by this route it is necessary to retain the terminal methylene group. Since the nor-ketone of gibberellin A_9 methyl ester has been converted into gibberellin A_9 in good yield[10] the desired result would be achieved if the toluene-*p*-sulphonate groupings

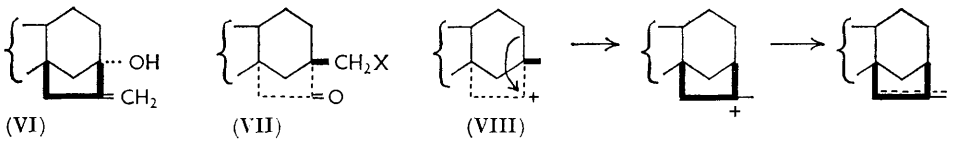
[1] Part XXIX, J. R. Hanson and T. P. C. Mulholland, preceding Paper.
[2] N. Takahashi, Y. Seta, H. Kitamura, and Y. Sumiki, *Bull. Agric. Chem. Soc. Japan*, 1957, **21**, 396; J. F. Grove, J. MacMillan, T. P. C. Mulholland, and W. B. Turner, *J.*, 1960, 3049.
[3] B. E. Cross, R. H. B. Galt, and J. R. Hanson, *Tetrahedron*, 1962, **18**, 451.
[4] (*a*) P. W. Brian, H. G. Hemming, and D. Lowe, *Nature*, 1962, **193**, 946; (*b*) M. Michniewicz and A. Lang, *Planta*, 1962, **58**, 549, and references cited therein.
[5] D. E. Applequist and J. D. Roberts, *Chem. Rev.*, 1954, **54**, 1065; U. Schöllokopf, *Angew. Chem.*, 1960, **72**, 147; P. von R. Schleyer and R. D. Nicholas, *J. Amer. Chem. Soc.*, 1961, **83**, 2700.
[6] F. Dolder, H. Lichti, E. Mosettig, and P. Quitt, *J. Amer. Chem. Soc.*, 1960, **82**, 246.
[7] B. E. Cross, *J.*, 1960, 3022.
[8] Part XXVIII, D. C. Aldridge, J. R. Hanson, and T. P. C. Mulholland, *J.*, 1965, 3539.
[9] D. F. Jones and P. McCloskey, *J. Appl. Chem.*, 1963, 324.
[10] B. E. Cross, R. H. B. Galt, and J. R. Hanson, *J.*, 1964, 295.

could be removed from the nor-ketone (IV; R = O). Ozonolysis of the di-toluene-*p*-sulphonate (IV; R = CH_2) of gibberellin A_1 methyl ester gave a poor yield of the nor-ketone (IV; R = O) but treatment of the di-toluene-*p*-sulphonate (IV; R = CH_2) with osmium tetroxide gave the glycol (IV; R = CH_2·OH, OH) in good yield. Cleavage of the



glycol with sodium periodate readily afforded the required nor-ketone (IV; R = O). However, attempts to hydrogenolyse the toluene-*p*-sulphonate groups of the nor-ketone with Raney nickel gave intractable gums and work on this reaction was discontinued.

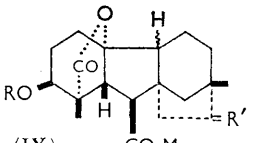
In the presence of a strong electrophile those gibberellins possessing the partial structure (VI) undergo Wagner–Meerwein rearrangement [11,12] to form the 7α-gibbane system (VII; X = H or halogen). The oxygen atom is now more readily available for chemical manipulation, and hence by suitable activation it was envisaged that the rearrangement might be reversed. In particular, if a neopentyl carbonium ion (VIII) could be generated then rearrangement might ensue as shown below.



A suitable derivative with which to test the method would be the diol (IX; R = H, R′ = α-H, β-OH), in which the 8-hydroxyl group is *trans*-antiparallel to the 6,7-bond. When this work was started the hydrogen atom at position 4b in gibberellic acid was believed [13] to have the α-configuration. It was hoped that the diol [14] obtained by conversion of gibberellic acid into the ketone [7] (IX; R = H, R′ = O) followed by reduction with sodium borohydride would be the required 8β-hydroxy-compound (IX; R = H, R′ = α-H, β-OH). However, the configuration of the hydrogen atom at 4b in (IX; R = H, R′ = O) is now known to be β,[15] and inspection of Dreiding models suggests that the product is more likely to be the 8α-epimer (IX; R = H, R′ = β-H, α-OH). As previously reported,[14] reduction of the ketone (IX; R = H, R′ = O, 4bβ) gave only one diol, m. p. 168—169°, except in one experiment from which an isomer (1% yield), m. p. 147—149°, was also isolated. The possibility that this isomer was the 4b-epimer (IX; R = H, R′ = H, OH, 4bα) derived from the ketone (IX; R = H, R′ = O, 4bα), which can only be completely removed from the 4β-epimeric ketone with difficulty, was excluded by reduction of the pure ketone (IX; R = H, R′ = O, 4bα) with sodium borohydride. The major

[11] B. E. Cross, J. F. Grove, J. MacMillan, and T. P. C. Mulholland, *Chem. and Ind.*, 1956, 954.
[12] T. P. C. Mulholland, *J.*, 1958, 2693.
[13] B. E. Cross, J. F. Grove, P. McCloskey, T. P. C. Mulholland, and W. Klyne, *Chem. and Ind.*, 1959, 1345; G. Stork and H. Newman, *J. Amer. Chem. Soc.*, 1959, **81**, 5518.
[14] B. E. Cross, J. F. Grove, and A. Morrison, *J.*, 1961, 2498.
[15] (*a*) F. McCapra, A. I. Scott, G. Sim, and D. W. Young, *Proc. Chem. Soc.*, 1962, 185; (*b*) D. C. Aldridge, J. F. Grove, R. N. Speake, B. K. Tidd, and W. Klyne, *J.*, 1963, 143.

product from this reduction was another isomeric diol, m. p. 196—198°. The diols, m. p. 168—169° and 147—149°, must therefore be epimeric at position 8, and the former is tentatively formulated as the 8α-epimer (IX; R = H, R′ = β-H, α-OH). In support of



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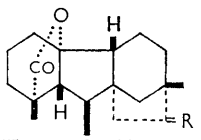

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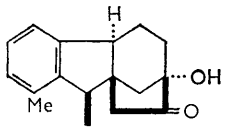

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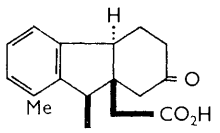

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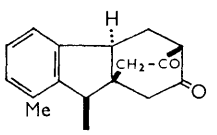

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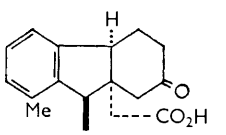

(XIV)

this assignment, reduction of the ketone (IX; R = H, R′ = O, 4bβ) with lithium tri-t-butoxyaluminium hydride, which is claimed to be more stereospecific than sodium borohydride,[16] gave the diol of m. p. 168—169° in good yield. On the other hand, this diol reacted preferentially at the 8-position with toluene-*p*-sulphonyl chloride, which appears to be more consistent with the 8β-configuration. The identity of the toluene-*p*-sulphonate was proved by its conversion into the 2-acetyl-8-toluene-*p*-sulphonate which was also prepared by an unequivocal route from the ketone (IX; R = H, R′ = O, 4bβ).

The diol (IX; R = H, R′ = H, OH, 4bβ), m. p. 168—169°, was recovered from treatment with 3N-hydrochloric acid, aluminium chloride in ether, or boron trifluoride etherate. In refluxing acetic acid containing toluene-*p*-sulphonic acid, the diacetate (IX; R = Ac, R′ = H, $MeCO_2$) was produced. However, brief treatment of the diol in ether with phosphorus pentachloride at room temperature led to the isolation of two products, gibberellin A_4 methyl ester (V; R = OH, R′ = CH_2) (~5%) and a chloro-alcohol, $C_{20}H_{27}ClO_5$ [$\nu_{max.}$ 3520 cm.$^{-1}$ (OH)] (~10%). Although the yield of gibberellin A_4 methyl ester was low, it showed that the synthetic route was feasible and provided a further chemical link between gibberellic acid and the 7-deoxygibberellins (cf. ref. 3). Since the low yield of gibberellin A_4 methyl ester might be due to the presence of the 2-hydroxyl group, the gummy 2-acetyl derivative (IX; R = Ac, R′ = H, OH) was prepared by acetylation of the ketone (IX; R = H, R′ = O, 4bβ) prior to reduction. It was characterised by conversion into the crystalline diacetate (IX; R = Ac, R′ = H, $MeCO_2$). However, treatment of the monoacetate with phosphorus pentachloride in ether gave none of the desired product, but a chloroacetate, $C_{22}H_{29}ClO_6$, together with a small quantity of the above chloro-alcohol, $C_{20}H_{27}ClO_5$. Acetylation of the chloro-alcohol gave the chloroacetate, and hence the chlorine atom is not situated at the 2-position. Therefore, the most likely structures for the chloro-alcohol and its 2-acetyl derivative are (IX; R = H, R′ = H, Cl) and (IX; R = Ac, R′ = H, Cl), respectively, or (V; R = OH, R′ = Me, Cl) and (V; R = $MeCO_2$, R′ = Me, Cl), respectively. The nuclear magnetic resonance (n.m.r.) spectrum of the chloro-alcohol showed $\geq C{\cdot}CH_3$ singlets at τ 8·80 and 8·87 in agreement with structure (IX; R = H, R′ = H, Cl) rather than (V; R = OH, R′ = Me, Cl). In addition, the spectrum showed a quartet at τ 6·85 and 7·41 (J = 15 c./sec.), characteristic [15b] of the hydrogen atoms at positions 10 and 10a, and a two-proton multiplet at τ 6·0 assigned to the >CHOH and >CHCl groups.

A number of experiments were carried out with the intention of preparing gibberellin A_9 methyl ester. The toluene-*p*-sulphonate (IX; R = $SO_2{\cdot}C_6H_4{\cdot}Me$-*p*, R′ = O) was converted [17] into the ketone (X; R = O) and reduced with sodium borohydride to give the

[16] O. H. Wheeler and J. L. Mateos, *Canad. J. Chem.*, 1958, **36**, 1431.
[17] J. MacMillan, J. C. Seaton, and P. J. Suter, *Tetrahedron*, 1960, **11**, 60.

alcohol (X; R = H, OH). Reduction of the 8-ketone (IX; R = SO_2·C_6H_4·Me-*p*, R′ = O) with sodium borohydride, prior to elimination of the toluene-*p*-sulphonate group, gave only gummy products. Treatment of the alcohol (X; R = H, OH) with phosphorus pentachloride in ether gave two compounds. The infrared spectrum of the major product, $C_{20}H_{27}ClO_4$, showed the absence of hydroxyl groups and no evidence for olefinic bonds, whilst it differed from that of gibberellin A_9 methyl ester hydrochloride (V; R = H, R′ = Me, Cl), prepared by the action of hydrogen chloride on the methyl ester of gibberellin A_9. Since the n.m.r. spectrum of the compound $C_{20}H_{27}ClO_4$ contained two $\geq C{\cdot}CH_3$ resonances at τ 8·9 and an ill-defined one-proton multiplet at τ 6·1, it was formulated as (X; R = H, Cl).

The infrared spectrum of the second product from the reaction (~12% yield) contained all the bands due to gibberellin A_9 methyl ester,[3] although the double-bond absorption at 3065 and 1660 cm.$^{-1}$ was diminished and additional bands were present at 3040, 795, and 823 cm.$^{-1}$. It was considered to be a eutectic mixture of gibberellin A_9 methyl ester (V; R = H, R′ = CH_2) and its 8,9-double-bond isomer. The same mixture was produced from gibberellin A_9 methyl ester hydrochloride by the action of sodium iodide in *NN*-dimethylformamide.

These results show that rearrangement of the neopentyl system (VIII) has taken place, but the yields of rearranged products are low. One reason for this must be associated with the configuration at centre 4b. Since the hydrogen at this centre is now known to have the β-configuration [15] the rearrangement involves conversion of the chair form of ring C present in the diol (IX; R = H, R′ = H, OH) into the less favourable boat form of ring C present in the gibberellins.

Hydrogenolysis of 7-hydroxy-8-ketones in the gibberellin series has been reported [18] using zinc dust in acetic anhydride, but attempts to repeat this work were unsuccessful.[19] The nor-ketone (XI) of methyl allogibberate similarly failed to undergo this reaction and gave only the corresponding 7-acetate, also obtained by acetylation with acetic anhydride in pyridine. Since hydrogenolysis of acetoxy-lactols with zinc dust–acetic anhydride might be possible, an attempt was made to prepare such a lactol by the action of acetic anhydride on the keto-acid [12] (XII). However, the neutral product, $C_{18}H_{18}O_4$, did not contain acetoxyl, whilst its infrared absorption in the carbonyl region ($\nu_{max.}$ 1737, 1722, and 1707 cm.$^{-1}$) excluded the presence of an anhydride. Microhydrogenation did not reveal any olefinic unsaturation, hence the compound must be tetracarbocyclic. The structure (XIII) assigned to this Perkin condensation product is also that of the proposed intermediate in the epimerisation [20] of the acetic acid side-chain of the ester (XII). Supporting evidence for structure (XIII) was provided by its n.m.r. spectrum which showed a 4-proton multiplet at 7·0—7·5 τ, assigned to two CH_2·CO groups. Finally, treatment of the β-diketone with alkali, under the conditions used for the inversion of the acetic acid residue in the ester (XII), afforded the dicarboxylic acid (XIV), identical with an authentic specimen.[20]

Experimental

Melting points were determined on a Kofler hot-stage apparatus and were corrected. Unless otherwise stated, Woelm acid alumina grade II and silica gel M.F.C. (Hopkin and Williams) were used in chromatography, and infrared spectra were determined for Nujol mulls. N.m.r. spectra were determined in deuterochloroform with tetramethylsilane as internal standard (τ = 10·0) on a Varian Associates A.60 spectrometer. Light petroleum had b. p. 60—80°. AnalaR dioxan was refluxed over sodium for 8—12 hr., freshly distilled, and filtered through grade I alumina immediately before use.

Preparation of the Toluene-p-*sulphonate of the Keto-ester* (III; R = OH, R′ = H, Me).—The

[18] H. Kitamura, N. Takahashi, Y. Seta, A. Kawarda, and Y. Sumiki, *Bull. Agric. Chem. Soc. Japan*, 1959, **23**, 344.
[19] D. F. Jones, J. MacMillan, and J. F. Grove, *J.*, 1964, 1835.
[20] J. F. Grove and T. P. C. Mulholland, *J.*, 1960, 3007; cf. J. R. Hanson, *J.*, 1963, 5061.

8-epi-keto-ester [7] (480 mg.) and toluene-*p*-sulphonyl chloride (1·16 g.) in dry pyridine (15 ml.) were left to stand for 7 days. The mixture was poured into dilute hydrochloric acid, and the product was recovered in ethyl acetate, and chromatographed on silica gel (19 × 1·6 cm.). Elution with ethyl acetate–light petroleum gave toluene-*p*-sulphonyl chloride, the toluene-*p*-sulphonate as a gum (217 mg.), and starting material (265 mg.).

Treatment of the Toluene-p-*sulphonate* (III; R = O·SO_2·C_6H_4·Me-*p*, R′ = H, Me) *with Raney Nickel.*—Crude toluene-*p*-sulphonate (207 mg.) from the preceding experiment was refluxed in dioxan (20 ml.) with Raney nickel (~2 g.) for 24 hr. The mixture was filtered and the residue washed with hot acetone. Evaporation of the filtrate gave a gum (130 mg.) which showed hydroxyl absorption but no aromatic bands in its infrared spectrum. It was chromatographed on silica gel (14·5 × 1·4 cm.). Elution with ethyl acetate–light petroleum (2 : 3) gave crystals (47 mg.), m. p. 125—135°. Later fractions were intractable. A solution of the crystals in acetone (3 ml.) was cooled to 0°, and oxidised with the 8N-chromic oxide reagent [21] (0·04 ml.) for 30 min. The neutral product (39 mg.), m. p. 85—92°, which showed no hydroxyl absorption in its infrared spectrum, was eluted from silica gel with ethyl acetate–light petroleum (1 : 7) and crystallised from ethyl acetate–light petroleum in prisms (17 mg.), m. p. 104—108°. Recrystallisation gave needles, m. p. 115·5—117°, of *methyl* 1α-*carboxy*-4aα-*hydroxy*-1β,8-*epidimethyl*-2-*oxogibbane*-10β-*carboxylate* 1 ⟶ 4a-*lactone* (III; R = H, R′ = H, Me) (Found: C, 69·6; H, 7·6. $C_{20}H_{26}O_5$ requires C, 69·3; H, 7·6%), $\nu_{max.}$ 1783, 1775sh, 1735sh, and 1730 cm.$^{-1}$; (in $CHCl_3$) 1780 and 1728 cm.$^{-1}$. The infrared spectrum was almost identical with that of the mixed 8-epimers prepared from gibberellin A_4 (see below).

Oxidation of Dihydrogibberellin A_4 *Methyl Ester.*—The ester (50 g.) in acetone (2 ml.) was oxidised with the 8N-chromic oxide reagent (0·2 ml.) for 90 min. The recovered product crystallised from light petroleum in needles, m. p. 116—118°, of the mixed 8-epimers of the ester (III; R = H, R′ = H, Me) (Found: C, 69·5; H, 7·5. Calc. for $C_{20}H_{26}O_5$: C, 69·3; H, 7·6%) (lit.,[1] m. p. 111—113°). Its infrared spectrum was almost identical with that of the 8-epi-compound prepared in the preceding experiment.

Hydrogenation of the Keto-ester (III; R = H, R′ = CH_2).—The ester [1] (36 mg.) and 10% palladised charcoal (75 mg.) in ethyl acetate (15 ml.) were shaken in hydrogen until uptake of hydrogen ceased (15 min.). The product crystallised from acetone–light petroleum in needles, m. p. 118—119°, of the ester (III; R = H, R′ = H, Me). Its infrared spectrum was identical with that of the specimen prepared above by oxidation of dihydrogibberellin A_4 methyl ester.

Gibberellin A_1 *Methyl Ester Di-toluene*-p-*sulphonate.*—Gibberellin A_1 methyl ester (1·97 g.) was prepared [9] from methyl gibberellate (5·4 g.) and then treated with toluene-*p*-sulphonyl chloride (6·0 g.) in dry pyridine (6 ml.) in a sealed tube at room temperature for 25 days. Ethyl acetate (65 ml.) was added and the solution was washed with 3N-hydrochloric acid, water, sodium hydrogen carbonate solution, and water. The product was chromatographed on grade I alumina (28 × 2·6 cm.). After elution of toluene-*p*-sulphonyl chloride with benzene–light petroleum (1 : 1) (800 ml.), elution with benzene (600 ml.) and benzene–chloroform (9 : 1) (2 l.) gave gums which on crystallisation from acetone–light petroleum afforded the *di-toluene*-p-*sulphonate* (IV; R = CH_2) as needles (2·38 g.), m. p. 91—94° (gas evolution). Recrystallisation raised the m. p. to 98·5—100° (Found: C, 61·0; H, 6·2; S, 8·4. $C_{34}H_{36}O_{10}S_2$,2Me_2CO requires C, 61·2; H, 6·2; S, 8·2%). MacMillan, Seaton, and Suter report [17] the di-toluene-*p*-sulphonate as a glass.

Treatment of the Di-toluene-p-*sulphonate* (IV; R = CH_2) *with Raney Nickel.*—The toluene-*p*-sulphonate (210 mg.) in dioxan (20 ml.) was refluxed with Raney nickel (~2 g.) for 27 hr. Recovery as above gave a gum (103 mg.) which was chromatographed on grade I alumina (11 × 1·1 cm.). Elution with benzene–chloroform (4 : 1) gave crystals (57 mg.) which separated from acetone–light petroleum as microcrystals, m. p. 169—180°, $\nu_{max.}$ 1774, 1735, and 1728 cm.$^{-1}$, identified as the mixed 8-epimers of dihydrogibberellin A_9 methyl ester [1] (V; R = H, R′ = H, Me) by its infrared spectrum.

Preparation of the Nor-ketone (IV; R = O).—(a) *By ozonolysis.* The di-toluene-*p*-sulphonate (IV; R = CH_2) (200 mg.) in ethyl acetate was treated with a large excess of ozonised oxygen at −20°. Excess of ozone was removed *in vacuo* at room temperature, 10% palladised charcoal was added, and the solution was hydrogenated until uptake of hydrogen ceased. Recovery in ethyl acetate and separation with sodium hydrogen carbonate solution gave neutral (151 mg.)

[21] R. G. Curtis, I. Heilbron, E. R. H. Jones, and G. F. Woods, *J.*, 1953, 457.

and acidic (30 mg.) gums. The neutral fraction was chromatographed on silica gel (20 × 1·6 cm.). Elution with ethyl acetate–light petroleum (2 : 3) and crystallisation of the product from acetone–light petroleum afforded needles (85 mg.) of the *nor-ketone* (IV; R = O), m. p. 124—129°, which after recrystallisation from methanol had m. p. 144—147° (Found: C, 59·0; H, 5·5. $C_{33}H_{34}O_{11}S_2$ requires C, 59·1; H, 5·1%), $\nu_{max.}$ ~1775, 1765, 1726, 1595 cm.$^{-1}$; (in $CHCl_3$) 1772, 1737, and 1600 cm.$^{-1}$.

In experiments using a small excess of ozone much of the starting material was recovered.

(b) (i) *Preparation of the glycol* (IV; R = OH, CH_2·OH). The ester (IV; R = CH_2) (733 mg.) in pyridine (4 ml.) was treated with osmium tetroxide (300 mg.) at room temperature for 66 hr. Sodium hydrogen sulphite (560 mg.), water (11 ml.), and pyridine (6·5 ml.) were then added and the mixture was left for 1 hr. Water was added, the mixture was extracted with ethyl acetate, and the extract was washed with dilute hydrochloric acid, water, sodium hydrogen carbonate solution, and water. Recovery gave a gum which crystallised from acetone–light petroleum in rods of the *glycol* (IV; R = OH, CH_2·OH), m. p. 187—188° (decomp.) (Found: C, 57·6; H, 5·7. $C_{34}H_{38}O_{12}S_2$ requires C, 58·1; H, 5·45%), $\nu_{max.}$ (KCl disc) 3490, 3410, 1773, 1727, and 1596 cm.$^{-1}$.

(ii) *Oxidation of the glycol* (IV; R = OH, CH_2·OH) *with periodate.* The glycol from (i), in methanol (100 ml.), was treated with 0·25M-sodium periodate solution (7·5 ml.) for 17·5 hr. The methanol was evaporated *in vacuo* and the residue was triturated with water and filtered. The solid was crystallised from methanol, giving the nor-ketone (IV; R = O) as needles (585 mg.), m. p. 144—148°, raised to 148—151° on recrystallisation. Its infrared spectrum was identical with that of the material prepared by ozonolysis (see above).

*Treatment of the Di-toluene-*p*-sulphonate* (IV; R = O) *with Raney Nickel.*—The di-toluene-*p*-sulphonate (196 mg.) in dioxan (20 ml.) was refluxed with Raney nickel (~2 g.) for 40 hr. Work-up, as above, gave a gum (67 mg.) which showed hydroxyl but little aromatic absorption in its infrared spectrum. The gum, in acetone (3 ml.), was oxidised at 0° with the 8N-chromic oxide reagent (0·045 ml.) for 30 min. The neutral fraction (49 mg.) from the oxidation was chromatographed on grade I alumina (15 × 1·0 cm.). Elution with benzene–chloroform (3 : 1) gave a semi-solid product (6 mg.) which failed to crystallise. It showed an infrared spectrum similar to that of the nor-ketone [3] (V; R = H, R′ = O) of gibberellin A_9 methyl ester. Thin-layer chromatography of the product on silica gel G in di-isopropyl ether–acetic acid (97·5 : 2·5), using concentrated sulphuric acid–concentrated nitric acid (95 : 5) as the spray, gave a very faint spot at R_F 0·22. Under these conditions the nor-ketone (V; R = H, R′ = O) gave a spot at R_F 0·23. The other products were intractable gums.

Reduction of the Ketone (IX; R = H, R′ = O, 4bβ).—(a) *With sodium borohydride.* Sodium borohydride (534 mg.) in methanol (50 ml.) was added to the ketone (1·031 g.) in methanol (100 ml.) at 0°. The mixture was left at room temperature for 1 hr., then acetic acid (1 ml.) and water (0·5 ml.) were added. The solvents were evaporated and the residue was chromatographed on alumina. The fractions eluted with ether were recrystallised from ethyl acetate–light petroleum, giving minute needles of the diol [14] (IX; R = H, R′ = H, OH, 4bβ) (525 mg.), m. p. 169—171°, identified by its infrared spectrum.

In one experiment needles (1%), m. p. 147—149°, of an *isomer* were obtained (Found: C, 66·0; H, 8·0. $C_{20}H_{28}O_6$ requires C, 65·9; H, 7·7%).

(b) *With lithium tri-t-butoxyaluminium hydride.* The ketone (106 mg.) in dry tetrahydrofuran (5 ml.) was treated with lithium tri-t-butoxyaluminium hydride (210 mg.) at room temperature for 1·5 hr. A little water was added and the organic solvent evaporated. Dilute hydrochloric acid was added and the solution was extracted with ethyl acetate. Recovery gave a semicrystalline residue which was chromatographed on alumina. Elution with ethyl acetate–light petroleum (2 : 3) gave the diol (IX; R = H, R′ = H, OH, 4bβ) (65 mg.), which crystallised from ethyl acetate–light petroleum as needles, m. p. 167—169°, identified by its infrared spectrum.

Reduction of the Ketone (IX; R = H, R′ = O, 4bα) *with Sodium Borohydride.*—The ketone (43 mg.) in methanol (5 ml.) was treated with sodium borohydride (45 mg.) for 1·5 hr. A little dilute hydrochloric acid was added, the solution was concentrated, diluted with water, and the organic material (35 mg.) recovered in ethyl acetate. The semicrystalline residue was chromatographed on alumina in ethyl acetate–light petroleum (2 : 3) to give *methyl* 1α-*carboxy*-2β,4aα,8ξ-*trihydroxy*-1β,7β-*dimethyl*-4bα,7α-*gibbane*-10β-*carboxylate* 1 ⟶ 4a-*lactone* (IX; R = H, R′ = H, OH, 4bα) (23 mg.) which crystallised from acetone–light petroleum as needles, m. p. 196—

198° (Found: C, 65·6; H, 8·0. $C_{20}H_{28}O_6$ requires C, 65·9; H, 7·7%), $\nu_{max.}$ 3457, 3390, 1746, and 1720 cm.$^{-1}$.

Preparation of the Monoacetate (IX; R = Ac, R′ = H, OH, 4bβ).—Sodium borohydride (204 mg.) in methanol (14 ml.) was added to the acetate [15b] of the ketone (IX; R = H, R′ = O; 4bβ) (291 mg.) in methanol (20 ml.) and the mixture was left at room temperature for 1 hr. It was poured into ether–ethyl acetate and washed with brine. The recovered product was chromatographed on alumina. Elution with ether gave the diol (IX; R = H, R′ = H, OH, 4bβ) (35 mg.); further elution with ethyl acetate containing methanol (5%) gave the acetate (IX; R = Ac, R′ = H, OH, 4bβ) as an intractable gum.

The *diacetate* (IX; R = Ac, R′ = H, $MeCO_2$, 4bβ), prepared with acetic anhydride in pyridine, formed prisms (from ethyl acetate–light petroleum), m. p. 187·5—189° (Found: C, 64·3; H, 7·3. $C_{24}H_{32}O_8$ requires C, 64·3; H, 7·2%), $\nu_{max.}$ 1766, 1737, 1724, 1236, and 1225 cm.$^{-1}$.

On treatment with toluene-*p*-sulphonyl chloride in pyridine at room temperature overnight, the monoacetate (IX; R = Ac, R′ = H, OH, 4bβ) gave the 2-*acetate*-8-*toluene*-p-*sulphonate* (IX; R = Ac, R′ = H, $O{\cdot}SO_2{\cdot}C_6H_4{\cdot}Me$-*p*, 4bβ), m. p. 198—200° (Found: C, 62·35; H, 6·7. $C_{29}H_{36}O_9S$ requires C, 62·2; H, 6·5%), $\nu_{max.}$ 1771, 1723 cm.$^{-1}$.

The Monotoluene-p-*sulphonate* (IX; R = H, R′ = H, $O{\cdot}SO_2{\cdot}C_6H_4{\cdot}Me$-*p*, 4bβ).—The diol (IX; R = H, R′ = H, OH, 4bβ) (69 mg.) and toluene-*p*-sulphonyl chloride (113 mg.) in pyridine (1 ml.) were left at room temperature overnight. Water (0·1 ml.) was added, and after 15 min., the solvents were removed *in vacuo*. The product was chromatographed on alumina, and the major fraction, eluted with benzene–ethyl acetate (4 : 1), crystallised from ethyl acetate–light petroleum as prisms (25 mg.), m. p. 155—158°. Recrystallisation gave prisms, m. p. 158—159°, of the *monotoluene*-p-*sulphonate* (Found: C, 62·1; H, 6·8. $C_{27}H_{34}O_8S$ requires C, 62·5; H, 6·6%), $\nu_{max.}$ 3505, 3380, 1778, 1731, 1708, 1585, and 1177 cm.$^{-1}$.

With acetic anhydride in pyridine the compound gave the 2-acetate-8-toluene-*p*-sulphonate (IX; R = Ac, R′ = H, $O{\cdot}SO_2{\cdot}C_6H_4{\cdot}Me$-*p*, 4bβ), m. p. 198—200°, identified by its infrared spectrum.

Attempted Rearrangement of the Diol (IX; R = H, R′ = H, OH, 4bβ).—(a) *With hydrochloric acid.* The diol (20 mg.) in 3N-hydrochloric acid (1 ml.) was refluxed for 2 hr. The solution was extracted with ethyl acetate, and the extract washed with brine, dried, and the solvent evaporated. The residue crystallised from ethyl acetate–light petroleum in crystals (13 mg.) m. p. 253—261°, which on methylation with diazomethane gave the starting diol, m. p. 168°.

(b) *With aluminium chloride.* The diol (IX; R = H, R′ = H, OH, 4bβ) (63 mg.) was recovered in good yield after treatment in dry ether (10 ml.) with aluminium chloride (75 mg.) at room temperature for 30 min.

(c) *With boron trifluoride etherate.* Boron trifluoride etherate (0·1 ml.) was added at room temperature to a suspension of the diol (IX; R = H, R′ = H, OH, 4bβ) (23 mg.) in ether (1 ml.) and the solution was left for 90 min. The recovered product was eluted from alumina as one fraction (22 mg.) which crystallised from ethyl acetate–light petroleum as needles, m. p. 168—171°, of the starting diol.

(d) *With toluene*-p-*sulphonic acid.* A solution of the diol (IX; R = H, R′ = H, OH, 4bβ) (50 mg.) and toluene-*p*-sulphonic acid (10 mg.) in acetic acid (1 ml.) was heated under reflux for 2 hr. The solvent was evaporated and the residue was chromatographed on alumina. The fractions eluted with benzene–ether (9 : 1) crystallised from ethyl acetate–light petroleum as prisms, m. p. 187·5—189°, of the diacetate (IX; R = Ac, R′ = H, $MeCO_2$, 4bβ), identical with the specimen prepared above.

Treatment of the Diol (IX; R = H, R′ = H, OH, 4bβ) *with Phosphorus Pentachloride.*—Phosphorus pentachloride (40 mg.) was added in one portion to the diol (40 mg.) in ether (3 ml.). The mixture was shaken at room temperature for 10 min., and water was added. The product was recovered in ethyl acetate and chromatographed on alumina. The fractions eluted with benzene–ether (1 : 1) and ether were crystallised several times from ethyl acetate–light petroleum, to give needles (4 mg.), m. p. 208—210°, of the *chloro-alcohol* (IX; R = H, R′ = H, Cl) (Found: C, 62·95; H, 7·3. $C_{20}H_{27}ClO_5$ requires C, 62·7; H, 7·1%), $\nu_{max.}$ 3520, 1748, and 1732 cm.$^{-1}$.

The mother-liquors from the chloro-alcohol (IX; R = H, R′ = H, Cl) gave prisms (4 mg.), m. p. 152—160°, which after crystallisation from ethyl acetate–light petroleum gave prisms (2 mg.), m. p. 171—175°, of gibberellin A_4 methyl ester (IV; R = OH, R′ = CH_2), identified by mixed melting point and infrared spectrum.

Treatment of the Monoacetate (IX; R = Ac, R′ = H, OH, 4bβ) *with Phosphorus Pentachloride*.—The monoacetate (47 mg.) in ether (2 ml.) was cooled to 5° and treated with phosphorus pentachloride (50 mg.). The mixture was shaken at room temperature for 12 min. and then poured into ether–brine. The ether layer gave a gum which was chromatographed on alumina. The first fractions eluted with benzene were crystallised from ethyl acetate–light petroleum, to give needles (12 mg.) of the *chloroacetate* (IX; R = Ac, R′ = H, Cl), m. p. 191—193° (Found: C, 61·6; H, 7·0. $C_{22}H_{29}ClO_6$ requires C, 62·1; H, 6·9%), $\nu_{max.}$ 1766, 1733, and 1723 cm.$^{-1}$.

Later fractions from the column, eluted with benzene–ether (1 : 1), were crystallised from ethyl acetate–light petroleum, to give the chloro-alcohol (IX; R = H, R′ = H, Cl) (2 mg.), m. p. 208—209°, which on acetylation gave the above chloroacetate (IX; R = Ac, R′ = H, Cl), m. p. 191—193°.

The Alcohol (X; R = H, OH).—The ketone [17] (X; R = O) (80 mg.), prepared from the toluene-*p*-sulphonate (IX; R = SO_2·C_6H_4·Me-*p*, R′ = O), was dissolved in methanol (5 ml.) and sodium borohydride (40 mg.) in methanol (2 ml.) was added at 20°. After 50 min., acetic acid (3 drops) and water (5 drops) were added. The solvents were evaporated and the residue was chromatographed on alumina. The major fraction, eluted with benzene–ether (4 : 1) was crystallised from ether–light petroleum to give prisms (43 mg.) of the *alcohol* (X; R = H, OH), m. p. 118—119° (Found: C, 69·2; H, 8·3. $C_{20}H_{28}O_5$ requires C, 68·9; H, 8·1%), $\nu_{max.}$ 3505, 1774, and 1715 cm.$^{-1}$.

Treatment of the Alcohol (X; R = H, OH) *with Phosphorus Pentachloride*.—The alcohol (47 mg.) and phosphorus pentachloride (50 mg.) in ether (10 ml.) were shaken at room temperature for 14 min. The mixture was poured into ethyl acetate–water, and the ethyl acetate solution was evaporated to give a gum which was chromatographed on grade II neutral alumina. The product was eluted in two fractions with light petroleum containing ethyl acetate (5—10%). The first fraction was crystallised twice from aqueous methanol to give prisms (5 mg.) believed to be a mixture of gibberellin A_9 methyl ester (V; R = H, R′ = CH_2) and its Δ^8-isomer, m. p. 144—145°, $[\alpha]_D^{21}$ +44° (*c* 0·2 in ethanol), $\nu_{max.}$ 3065, 3040, 1776, 1733, 1660, 823, and 795 cm.$^{-1}$ (Found: C, 73·0; H, 8·0. Calc. for $C_{20}H_{26}O_4$: C, 72·7; H, 7·9%).

The second fraction (23 mg.) was re-chromatographed and then crystallised from aqueous methanol to give prisms (12 mg.) of the *chloro-compound* (X; R = H, Cl), m. p. 180—181° (Found: C, 65·4; H, 7·45. $C_{20}H_{27}ClO_4$ requires C, 65·4; H, 7·4%), $\nu_{max.}$ 1775 and 1725 cm.$^{-1}$.

The mother-liquors from the chloro-compound (X; R = H, Cl) yielded the above mixture of gibberellin A_9 methyl ester and its Δ^8-isomer (1 mg.).

Gibberellin A_9 Methyl Ester Hydrochloride.—Gibberellin A_9 methyl ester (V; R = H, R′ = CH_2) (150 mg.) in chloroform (10 ml.) was treated with a slow stream of dry hydrogen chloride gas for 4 hr. The solution was diluted with chloroform, air was blown through it, and it was then washed with water and aqueous sodium hydrogen carbonate. The solution was dried and evaporated, giving *methyl* 1α-*carboxy*-8ξ-*chloro*-4a*α*-*hydroxy*-1β,8ξ-*dimethylgibbane*-10β-*carboxylate* 1 ⟶ 4*a*-*lactone* (V; R = H, R′ = Cl, Me) which crystallised from ethyl acetate–light petroleum as needles, m. p. 159—160° (Found: C, 65·6; H, 7·5. $C_{20}H_{27}ClO_4$ requires C, 65·5; H, 7·4%), $\nu_{max.}$ 1772 and 1732 cm.$^{-1}$, τ 8·9, 8·2, 7·54 (doublet, *J* = 15 c./sec.), 7·23 (doublet, *J* = 15 c./sec.), and 6·25.

Dehydrohalogenation of the Chloro-ester (V; R = H, R′ = Cl, Me).—The hydrochloride from the preceding experiment (104 mg.) and sodium iodide (1 g.) in dry dimethylformamide (10 ml.) were heated under reflux for 2 hr. The solution was poured into water and extracted with ethyl acetate. The extract was washed with aqueous sodium thiosulphate and water, dried, and the solvent evaporated. The residue crystallised from acetone–light petroleum as needles (68 mg.), m. p. 138—141°, $[\alpha]_D^{20}$ +40° (*c* 1·0), of the above mixture of gibberellin A_9 methyl ester and its Δ^8-isomer (identified by its infrared spectrum).

Attempted Hydrogenolysis of Methyl Allogibberate Nor-ketone (XI).—The nor-ketone (125 mg.) in acetic anhydride (10 ml.) was heated under reflux while zinc dust (1 g.) was added portionwise during 3 hr. The solution was diluted with ethyl acetate, filtered, washed with water and aqueous sodium hydrogen carbonate, and dried. The solvent was evaporated and the residual gum chromatographed on silica gel (15 × 1 cm.). Elution with ethyl acetate–light petroleum (1 : 4) gave the 7-*acetate* (95 mg.) which crystallised from ether–light petroleum as needles, m. p. 172—173° (Found: C, 70·4; H, 6·5; OAc, 14·9. $C_{20}H_{22}O_5$ requires C, 70·2; H, 6·5; OAc, 13·7%), $\nu_{max.}$ (in $CHBr_3$) 1758, 1736, 1596, and 1230 cm.$^{-1}$.

Acetylation of methyl allogibberate nor-ketone with acetic anhydride in pyridine gave the 7-acetate, m. p. 172—173°, identical (infrared spectra in Nujol mull and bromoform solution) with the above acetate.

Action of Acetic Anhydride on the Keto-acid (XII).—The keto-acid (90 mg.) in acetic anhydride (4 ml.) was refluxed for 2·5 hr. The solution was diluted with ethyl acetate, extracted with aqueous sodium hydrogen carbonate washed with water, and dried. Evaporation of the solvent and crystallisation of the residue (54 mg.) from acetone–light petroleum gave the *diketone* (XIII), m. p. 191—193° (Found: C, 72·6, 72·2; H, 6·3, 6·15; OAc, nil. $C_{18}H_{18}O_4$ requires C, 72·5; H, 6·1%), $\nu_{max.}$ 1727, 1722, and 1701 cm.$^{-1}$. On microhydrogenation there was no rapid uptake of hydrogen.

Action of Alkali on the Diketone (XIII).—The diketone (95 mg.) in 3N-sodium hydroxide (10 ml.) was heated under reflux for 2·5 hr. The solution was diluted, washed with ether, acidified, and extracted with ether. The extract was washed with water, dried, and the solvent evaporated to give a gum (71 mg.) which slowly deposited crystals. Recrystallisation from acetone–light petroleum gave the dicarboxylic acid (XIV) as prisms (17 mg.), m. p. 214—216°, identical (infrared spectrum and mixed m. p.) with an authentic sample.[20]

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