177. *Synthesis of Compounds Related to Gibberellic Acid. Part II.* (±)-Gibberic Acid.*[1]

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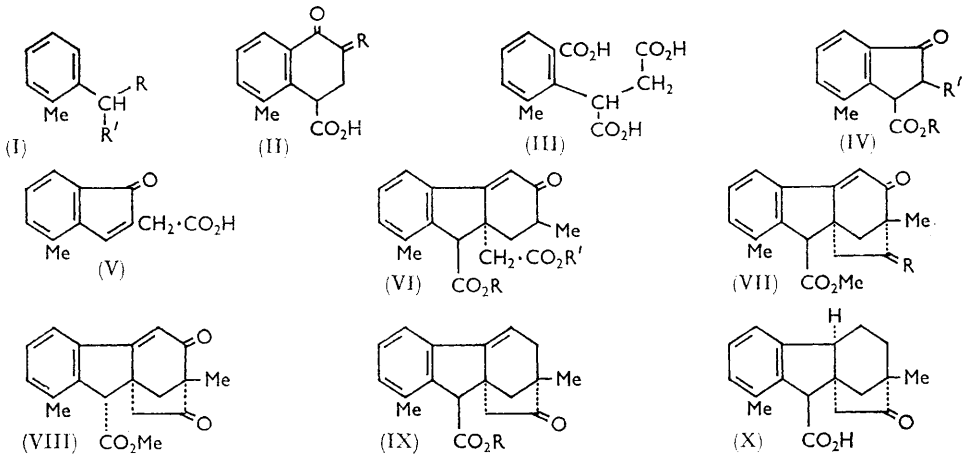
(±)-Gibberic acid, a key degradation product of gibberellic acid, has been synthesised, starting from *o*-tolylacetonitrile.

In the work described in Part I of this series the key step in the formation of the quadricyclic gibbane system[2] found in gibberellic acid and its degradation products was the internal electrophilic cyclisation of a suitable unsaturated keto-acid to a bicyclo[3,2,1]-octane derivative. The question now arose whether this type of cyclisation could be used in a synthesis of (±)-gibberic acid (X). Such a synthesis would also demand the correct introduction of two asymmetric centres in the gibbane system at C-4b and C-10, whose steric relationship to the two-carbon bridge has been established[3,4] as shown in (X). One of the groups of workers has shown[2] that in gibberic acid the *trans*-configuration of the carboxyl group relative to the bridge is unstable, as is evident from the facile epimerisation of methyl gibberate by base. On the other hand, a change in the conformation of ring C by the introduction of a double bond at position 4b stabilised the above *trans*-relationship since methyl dehydrogibberate (IX; R = Me) was not epimerised on alkaline hydrolysis. This, and the fact that the hydrogenation of dehydrogibberic acid to gibberic

* Part I, Kos and Loewenthal, *J.*, 1963, 605.

[1] Preliminary communication, Loewenthal and Malhotra, *Proc. Chem. Soc.*, 1962, 230.
[2] Grove and Mulholland, *J.*, 1960, 3007.
[3] Grove, MacMillan, Mulholland, and Turner, *J.*, 1960, 3049.
[4] Stork and Newman, *J. Amer. Chem. Soc.*, 1959, **81**, 3168.

acid is stereospecific,[3] appeared *a priori* to solve our steric problem; even if an epimer of dehydrogibberic acid were to result from our projected sequence, equilibration would probably lead to the correct stereochemistry. However, the synthesis happened to be stereospecific throughout in the desired direction.



The key intermediate, 3-carboxy-4-methyl-1-oxoindan-2-ylacetic acid (IV; R = H, R′ = CH_2·CO_2H), was obtained as follows. Condensation of *o*-tolylacetonitrile with diethyl carbonate in the presence of sodium ethoxide [5] gave the nitrile-ester (I; R = CO_2Et, R′ = CN). This was cyanoethylated and the product subjected to acid hydrolysis and decarboxylation to give α-(*o*-tolyl)glutaric acid, whose anhydride was cyclised by means of polyphosphoric acid to give the keto-acid (II; R = H_2) in which the alicyclic ring was now cleaved by ozonolysis of its furfurylidene derivative [6] to give the tricarboxylic acid (III). Dieckmann cyclisation of the derived trimethyl ester, followed by alkylation of the resulting β-keto-ester (IV; R = Me, R′ = CO_2Me) with ethyl bromoacetate, acid hydrolysis, and decarboxylation led to the desired intermediate. Unsuccessful routes involved (a) the reaction of the bromo-ester (IV; R = Me, R′ = Br) with diethyl sodiomalonate, and (b) the addition of cyanide ion to the indenone (V), itself obtained by a Stobbe reaction from *o*-tolualdehyde.

The dimethyl ester (IV; R = Me, R′ = CH_2·CO_2Me) reacted smoothly with isopropenyl methyl ketone in the presence of an excess of sodium methoxide in methanol, giving the half-ester of an unsaturated keto-dicarboxylic acid (VI; R = Me, R′ = H) whose structure was clear from its subsequent reactions, and whose formation was expected on the basis of a mechanism involving an aldol-lactone intermediate as proposed in Part I of this series. Cyclisation of this compound with the boron trifluoride–ether complex in acetic acid–acetic anhydride led in excellent yield to the diketo-ester (VII; R = O).

The assumed *trans*-stereochemistry of this and subsequent products has been confirmed by Mori and his collaborators.[7] Acting upon information communicated by us in advance of publication of this Paper they used the same intermediate and converted the *trans*-dicarboxylic acid (VI; R = R′ = H) into a *cis*-anhydride which they cyclised to a *cis*-diketo-carboxylic acid whose methyl ester (VIII) was clearly different from our *trans*-epimer.

Ketalisation of the latter compound gave as main product the monoketal [VII; R = $(O{\cdot}CH_2)_2$] which was subjected to Huang-Minlon reduction. This led to (±)-dehydrogibberic acid (IX; R = H) which showed the expected characteristic ultraviolet spectrum.[8]

[5] Horning and Finelli, *J. Amer. Chem. Soc.*, 1949, **71**, 3204.
[6] Johnson, Bannister, and Pappo, *J. Amer. Chem. Soc.*, 1956, **78**, 6333.
[7] Mori, Matsui, and Sumuki, *Agric. and Biol. Chem.* (*Japan*), 1962, **26**, 783; 1963, **27**, 537.
[8] Birnbaum, Cookson, and Lewin, *J.*, 1961, 1224.

A by-product, resulting from decarboxylation, was (±)-gibberone ethylene ketal (Part I). Catalytic reduction of (±)-dehydrogibberic acid furnished (±)-gibberic acid (X), whose infrared spectrum in solution was identical with that of (—)-gibberic acid produced by degradation.[9]

Experimental

Infrared spectra refer to chloroform solutions, and ultraviolet spectra to methanol solutions.

Ethyl o-*Tolylcyanoacetate* (I; R = CO_2Et, R′ = CN).—*o*-Tolylacetonitrile (40 g.), diethyl carbonate (200 ml.), and dry toluene (80 ml.) were added to dry sodium ethoxide (from 8 g. of sodium), and the mixture was slowly distilled with stirring, the volume being maintained by the addition of more toluene, until the distillation temperature reached 111°. The mixture was cooled, acidified with dilute acetic acid, and extracted several times with ether. The extracts were dried ($MgSO_4$) and concentrated. The residue distilled at 149—150°/1·8 mm., giving the *ester* (50 g.) (Found: C, 71·25; H, 6·65. $C_{12}H_{13}NO_2$ requires C, 70·9; H, 6·45%), $\lambda_{max.}$ 4·50 and 5·80 μ.

α-*Ethoxycarbonyl*-α-(o-*tolyl*)*glutaronitrile*.—Acrylonitrile (14 g.) in t-butyl alcohol (15 ml.) was added to a solution of the above ester (26 g.) in t-butyl alcohol (50 ml.) at 40—45°; 30% methanolic potassium hydroxide (1 ml.) was added after the first few ml. of the acrylonitrile solution and again after about one half had been added. The cloudy mixture was set aside at room temperature overnight, after which it was diluted with water and acidified with dilute hydrochloric acid. The product was isolated with ether and distilled *in vacuo*, the *nitrile-ester* being collected at 200—203°/1 mm. (29 g.) (Found: C, 70·8; H, 6·55; N, 10·55. $C_{15}H_{16}N_2O_2$ requires C, 70·3; H, 6·3; N, 10·95%).

1,2,3,4-*Tetrahydro*-8-*methyl*-4-*oxo*-1-*naphthoic Acid* (II; R = H_2).—The above nitrile-ester (29 g.) was refluxed with a mixture of conc. hydrochloric acid (225 ml.) and acetic acid (50 ml.) for 15 hr. To the cooled mixture water was added and the product isolated with ether. Removal of the solvent gave crude α-(o-*tolyl*)*glutaric acid* which was used directly for the next step. A sample, recrystallised from benzene, had m. p. 110—112° (Found: C, 64·8; H, 6·05. $C_{12}H_{14}O_4$ requires C, 64·85; H, 6·35%).

The above crude acid was refluxed with acetic anhydride (50 ml.) for 2 hr. After removal of acetic acid and excess of anhydride the residue was distilled to give the anhydride which distilled at 215—220°/1·8 mm. (23 g.). On cooling it solidified, m. p. 98—100°, $\lambda_{max.}$ 5·55 and 5·70 μ. This (20 g.) was heated in polyphosphoric acid, prepared from phosphoric oxide (40 g.) and orthophosphoric acid (85%; 20 ml.), at 90—100° for 5 min., after which a further 60 g. of polyphosphoric acid, prepared as above, was added and heating continued for another 15 min. After cooling, ice was added and the mixture extracted with ether. The ether layer was extracted with sodium hydrogen carbonate solution and the extracts acidified, giving the *keto-acid*, m. p. 146—147° (16 g.) (from benzene) (Found: C, 70·5; H, 6·1. $C_{12}H_{12}O_3$ requires C, 70·55; H, 5·9%), $\lambda_{max.}$ 5·9 and 6·0 μ.

1,2,3,4-*Tetrahydro*-3-*furfurylidene*-8-*methyl*-4-*oxo*-1-*naphthoic Acid* (II; R = CH·C_4H_3O).—To the above keto-acid (12 g.) in ethanol (300 ml.) furfuraldehyde (freshly distilled; 8 ml.) was added, followed by 15% potassium hydroxide (72 ml.). The mixture was heated at 100° for 2 min., left at room temperature for 1 hr., acidified with dilute hydrochloric acid, and extracted with ether. The dried ($MgSO_4$) extract was concentrated and the residue crystallised from benzene, giving the *derivative*, m. p. 184—186° (13 g.) (Found: C, 72·15; H, 5·0. $C_{17}H_{14}O_4$ requires C, 72·35; H, 5·0%).

(2-*Carboxy*-6-*methylphenyl*)*succinic Acid* (III).—A solution of the above derivative (3 g.) in ethyl acetate (50 ml.) was ozonised at −70° until a blue colour developed. Most of the solvent was removed at reduced pressure and the residue was dissolved in acetic acid (100 ml.). Hydrogen peroxide (30%; 30 ml.) and concentrated hydrochloric acid (4 ml.) were added and the whole left at room temperature overnight. Most of the solvent was again removed *in vacuo* and the residue dissolved in an excess of sodium hydrogen carbonate solution. The solution was washed with ether, acidified, and the product extracted with ether. The extract was dried ($MgSO_4$), and the residue obtained after removal of solvent crystallised from benzene to give the *tricarboxylic acid* (1·87 g.), m. p. 156—157° (Found: C, 57·25; H, 4·8. $C_{12}H_{12}O_6$ requires C, 57·15; H, 4·8%).

[9] Cross, *J.*, 1954, 4670.

7-*Methyl*-3-*oxoindane*-1-*carboxylic Acid* (IV; R = R′ = H).—*o*-Tolylsuccinic acid (9·5 g.) was heated with acetyl chloride (80 ml.) under reflux for 2 hr. Excess of acetyl chloride and acetic acid were removed *in vacuo* and the residue was distilled at 140—160°/0·4—0·8 mm., to give the corresponding anhydride (85%). A solution of this anhydride (7·3 g.) in dry benzene (15 ml.) was added with stirring to a solution of aluminium chloride (15 g.) in nitrobenzene (40 ml.), and the resulting solution was left at room temperature for 48 hr. The customary working-up gave the *acid* (4·0 g.), m. p. 154—155° (from benzene) (Found: C, 69·75; H, 5·35. $C_{11}H_{10}O_3$ requires C, 69·45; H, 5·3%). The methyl ester of this acid, prepared with ethereal diazomethane, was caused to react with one mol equiv. of bromine in ether solution; however, from the reaction of the resulting bromo-derivative with ethyl sodiomalonate in benzene no useful product could be obtained.

γ-(o-*Tolyl*)*itaconic Acid*.—Diethyl succinate (27·6 g.) was added to a mixture of *o*-tolualdehyde (6·0 g.) and sodium hydride (3·6 g.) in benzene (25 ml.), and the reaction was initiated by the addition of a few drops of absolute ethanol. The mixture was warmed to 40° and kept at this temperature for 2 hr., after which it was cooled and acetic acid (12 ml.) was added. The organic layer was extracted with sodium hydrogen carbonate solution, the extract was acidified and the half-ester obtained isolated with ether. After removal of the solvent it was hydrolysed by heating under reflux with 20% sodium hydroxide in aqueous ethanol (50%) for 0·5 hr. Acidification and isolation with ether gave the *dicarboxylic acid* (2·45 g.), m. p. 186° (from methylene chloride) (Found: C, 65·65; H, 5·35. $C_{12}H_{12}O_4$ requires C, 65·45; H, 5·5%).

Attempted Preparation of **4-*Methyl*-1-*oxoinden*-2-*ylacetic Acid*** (V).—Concentrated sulphuric acid (5 g.) was added dropwise at −10° to the above dicarboxylic acid (0·5 g.), and the mixture was kept at this temperature for 5 hr. It was then cautiously diluted with water and extracted with ether. The ether layer was extracted with sodium hydrogen carbonate solution. Acidification of the extract and isolation with ether gave the *keto-acid* (0·125 g.), m. p. 249—250° (decomp.) (from benzene), $\lambda_{max.}$ 247 mμ (ε 19,000). However, no satisfactory analysis could be obtained, and attempted addition of cyanide ion to this compound was unsuccessful.

Dimethyl **7-*Methyl*-3-*oxoindan*-1,2-*dicarboxylate*** (IV; R = Me, R′ = CO_2Me).—The tricarboxylic acid (III) (7·9 g.) was converted into its oily trimethyl ester by treatment with an excess of ethereal diazomethane. The ester was dissolved in benzene (30 ml.) and the solution was added to a suspension of sodium hydride (1·44 g.) in benzene (60 ml.) and dimethylformamide (10 ml.) to which methanol (5 ml.) had previously been added. The stirred suspension was slowly distilled during 7 hr. through a short column until the total volume was reduced to *ca.* 50 ml. It was then cooled and acetic acid (5 ml.) was added. The organic layer was separated, dried ($MgSO_4$), and the solvent removed. The residue crystallised from isopropyl ether to give the *keto-ester* (6·0 g.) which after further crystallisation from the same solvent had m. p. 97—99° (Found: C, 64·3; H, 5·5. $C_{14}H_{14}O_5$ requires C, 64·1; H, 5·4%), $\lambda_{max.}$ 255 (ε 11,000) and 297 mμ (ε 8700), and 5·85—5·95, 6·1, and 6·24 μ. Acid hydrolysis of this compound gave the keto-acid (IV; R = R′ = H), identified by m. p. and mixed m. p.

3-*Carboxy*-4-*methyl*-1-*oxoindan*-2-*ylacetic Acid* (IV; R = H, R′ = CH_2·CO_2H).—The above keto-ester (6·0 g.) was added to a suspension of sodium hydride (0·63 g.) in benzene (30 ml.) and dimethylformamide (10 ml.), and the mixture was stirred at room temperature under nitrogen until hydrogen evolution ceased. Ethyl bromoacetate (3·5 ml.) was added, and the mixture was refluxed for 12 hr., water added, and the benzene layer separated. Removal of solvent from the latter gave a residue which was refluxed with acetic acid (40 ml.) and 6N-hydrochloric acid (150 ml.) for 12 hr., after which the solvents were removed *in vacuo*. The solid obtained was dissolved in ether, the solution was treated with charcoal, filtered, and concentrated, and benzene was added, whereupon the *dicarboxylic acid* crystallised (5·1 g.), m. p. 173—175° (Found: C, 62·55; H, 5·05. $C_{13}H_{12}O_5$ requires C, 62·9; H, 4·85%), $\lambda_{max.}$ 251 (ε 11,000) and 292 mμ (ε 2800), and 5·85—5·9 and 6·24 μ.

1,2,3,9a-*Tetrahydro*-2,8-*dimethyl*-9β-*methoxycarbonyl*-3-*oxofluoren*-9aα-*ylacetic Acid* (VI; R = Me, R′ = H).—The above dicarboxylic acid (5·0 g.) was converted by ethereal diazomethane into its oily dimethyl ester which was added in benzene (10 ml.) to a solution of sodium (1·18 g.) in methanol (50 ml.) at 0° under nitrogen. Isopropenyl methyl ketone (3·65 g.) was then added dropwise with stirring, after which the mixture was left at room temperature overnight. Acetic acid (5 ml.) and water were added and the methanol removed *in vacuo*, giving the *half-ester* (5·7 g.), m. p. 200—201° (decomp.) (from chloroform–cyclohexane) (Found: C, 69·8; H, 6·2. $C_{19}H_{20}O_5$ requires C, 69·5; H, 6·15%), $\lambda_{max.}$ 231 (ε 9500), 236 (ε 9500), and 296 mμ (ε 22,000),

and 5·8—5·85, 6·05, and 6·12 μ. The corresponding *dimethyl ester* (VI; R = R′ = Me), prepared with ethereal diazomethane, had m. p. 137·5—138° (from methylene chloride–isopropyl ether) (Found: C, 70·1; H, 6·35. $C_{20}H_{22}O_5$ requires C, 70·15; H, 6·5%).

Methyl (±)-1,7-*Dimethyl*-6,8-*dioxogibba*-A,4b-*tetraene*-10β-*carboxylate* (VII; R = O).—The half-ester (VI; R = Me, R′ = H) (1·50 g.) was dissolved in a mixture of acetic acid (7·5 ml.) and acetic anhydride (1·5 ml.), and boron trifluoride–ether complex (redistilled; 3·0 ml.) was added. After standing overnight at room temperature, ice and ether–benzene were added. The organic layer was separated and washed thoroughly with water and then with ice-cold 2% sodium hydrogen carbonate solution until its pink colour had changed to yellow. It was dried ($MgSO_4$), and the solvents were removed *in vacuo* at room temperature. The solid residue was recrystallised from isopropyl ether, to give the *diketo-ester* (1·20 g.), m. p. 148·5—149° (Found: C, 73·65; H, 6·0. $C_{19}H_{18}O_4$ requires C, 73·55; H, 5·85%), $\lambda_{max.}$ 205 (ε 17,000), 238 (ε 8450), 299 (ε 21,000), and 324 mμ (ε 14,500), and 5·75, 6·02, and 6·16 μ.

Methyl (±)-8,8-*Ethylenedioxy*-1,7-*dimethyl*-6-*oxogibba*-A,4b-*tetraene*-10β-*carboxylate* [VII; R = (·O·CH_2·)$_2$].—The above diketo-ester (1·20 g.) was refluxed in benzene (60 ml.) with ethylene glycol (9 ml.) and toluene-*p*-sulphonic acid (100 mg.) for 15 hr., water being removed azeotropically. The crude product (1·52 g.), obtained after the usual working-up, was dissolved in methanol (25 ml.) and 20% sodium hydroxide (20 ml.), and the solution was kept at 40° for 1 hr. The methanol was removed *in vacuo* and the remaining solution was acidified at 0° under a layer of benzene. The latter was washed with water, dried ($MgSO_4$), and the solvent removed *in vacuo*. The residue was esterified with ethereal diazomethane and the product chromatographed on alumina (Alcoa F-20; 30 g.) using hexane–methylene chloride as solvent and eluant, giving, in order of elution, (a) the keto-diester (VI; R = R′ = Me), identified by m. p. and mixed m. p., and (b) the *monoketal-ester*, m. p. 141·5—142° (from isopropyl ether) (523 mg.) (Found: C, 70·75; H, 6·0. $C_{21}H_{22}O_5$ requires C, 71·15; H, 6·25%), $\lambda_{max.}$ 229 (ε 9700), 235 (ε 9550), and 298 mμ (ε 20,600), and 5·8, 6·05, and 6·15 μ.

(±)-*Dehydrogibberic Acid* (IX; R = H).—The above monoketal-ester (675 mg.) was refluxed with hydrazine hydrate (80%; 1·58 ml.) in ethylene glycol (12 ml.) for 2 hr. After cooling, potassium hydroxide (1·50 g.) was added and the solution was distilled until the temperature reached 180°. It was then heated under reflux for 1·5 hr. After cooling, water was added and the product was separated into neutral (100 mg.) and acidic (467 mg.) fractions. The former, after chromatography and recrystallisation from ether–methanol, was identified as (±)-gibberone ethylene ketal by m. p. and mixed m. p. and infrared spectrum. The acidic fraction was heated with 80% acetic acid (5 ml.) at 100° for 0·5 hr., followed by removal of solvents *in vacuo*. The residue was esterified with ethereal diazomethane and the product was chromatographed on alumina (Alcoa F-20; 8 g.), using hexane–methylene chloride as solvent and eluant. After a small oily fraction there was obtained the *methyl ester* of the above acid, m. p. 155—157° (from pentane) (165 mg.) (Found: C, 77·25; H, 6·45. $C_{19}H_{20}O_3$ requires C, 77·0; H, 6·8%), $\lambda_{max.}$ 213 (ε 25,000), 260 (ε 17,000), 269·5 (ε 14,500), 287·5 (ε 3200), and 298 mμ (ε 2800). Hydrolysis of this ester (120 mg.) in methanol (3 ml.) with 20% sodium hydroxide (1·5 ml.) under reflux for 1 hr. gave the *acid* which after recrystallisation from ether and then from chloroform–isopropyl ether had m. p. 220—222° (decomp.) (86 mg.) (Found: C, 76·25; H, 6·6. $C_{18}H_{18}O_3$ requires C, 76·55; H, 6·4%), $\lambda_{max.}$ 260 (ε 15,500), 270 (ε 15,500), 290 (ε 4100), and 301 mμ (ε 4100).

(±)-*Gibberic Acid* (X).—The above acid (82 mg.) was hydrogenated in ethyl acetate (10 ml.) in the presence of palladium on carbon (10%; 50 mg.). The theoretical amount of hydrogen was absorbed in 3 min. The residue obtained after filtration and removal of solvent was recrystallised three times from isopropyl ether–hexane, giving the *acid* (45 mg.), m. p. 176—177° (Found: C, 76·1; H, 7·3. $C_{18}H_{20}O_3$ requires C, 76·05; H, 7·1%).

Gibberellic acid was degraded by treatment with dilute hydrochloric acid, as described by Cross,[9] giving (−)-gibberic acid, m. p. 155—155·5°. The infrared spectra, in chloroform, of this and of the foregoing racemate were identical.

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