771. *An Alternative Synthetic Approach to (±)-Gibberone.*

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A synthetic route is described to 1,2,3,10-tetrahydro-2,8-dimethyl-3-oxofluoren-10-ylacetic acid (IX), which has earlier been converted into (±)-gibberone.

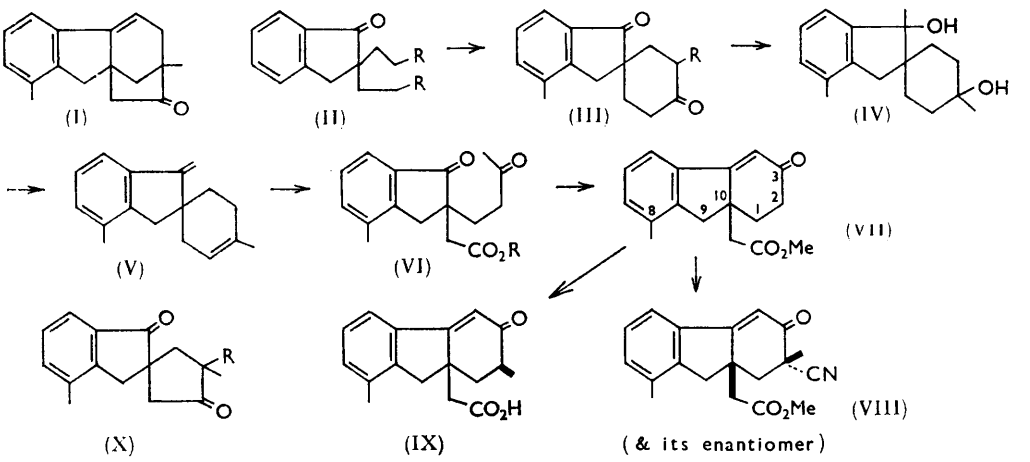
A synthesis of (±)-gibberone [1] (I), a transformation product of gibberellic acid which retains the characteristic tetracyclic system, has recently been described [2] which uses as its key intermediate the tetrahydrofluorenone (IX). We have independently obtained this compound in another way as follows.

The starting material, 4-methylindan-1-one,[3] was prepared from β-*o*-tolylpropionic acid by an improvement of Bachmann's procedure.[4] Treatment of the indanone with acrylonitrile in the presence of base produced the expected dicyanoethylated compound (II; R = CN), which by hydrolysis gave the keto-dicarboxylic acid (II; R = CO_2H). Esterification and Dieckmann cyclisation of the derived diester (II; R = CO_2Et) gave the spiro-β-keto-ester (III; R = CO_2Et) which was converted by acid hydrolysis and decarboxylation into a spirodiketone with light absorption compatible with structure (III; R = H).

An excess of methylmagnesium bromide converted the spirodiketone smoothly into the di-tertiary diol (IV), as shown by the complete disappearance of carbonyl absorption in the infrared, and indanone absorption in the ultraviolet, region. The diol was dehydrated by toluene-*p*-sulphonic acid in boiling benzene to a crystalline diene which was shown to possess structure (V), rather than that of its di-exo-isomer, by absorption maxima at 790 (trisubstituted double bond [5]) as well as 890 cm.$^{-1}$ (CH_2= double bond). Confirmation was provided by low-temperature ozonisation-oxidation of the diene, which afforded, with the loss of one methylene-carbon atom, the diketo-acid (VI; R = H). The corresponding methyl ester (VI; R = Me) showed the expected light absorption at

[1] Cross, Grove, MacMillan, and Mulholland, *J.*, 1958, 2520.
[2] Loewenthal, *Proc. Chem. Soc.*, 1960, 355.
[3] Young, *Ber.*, 1892, **25**, 2102.
[4] Bachmann and Raunio, *J. Amer. Chem. Soc.*, 1950, **72**, 2530.
[5] Bellamy, " The Infra-red Spectra of Complex Molecules," Methuen, London, 1958.

1735 (ester C=O) and at 1715 cm.$^{-1}$ and 250 and 295 mμ (indanone chromophore).[1,6,7] The third ring was then introduced by an internal aldol condensation of the diketo-ester in the presence of sodium methoxide. The resulting material showed bands at 1735



(ester C=O), 1670 (cyclohexenone), and 1630 cm.$^{-1}$ (styrene C=C) and at 238 and 300 mμ (ε 8300 and 19,500) in accord with those expected for the tricyclic product (VII).

Our first attempt at construction of the fourth ring involved the introduction of nitrile and methyl groups vicinal to the carbonyl group of compound (VII). Conversion into the α-cyano-ketone was achieved by Johnson and Shelberg's isoxazole procedure,[8] and subsequent methylation produced a compound for which formula (VIII) represents one possible stereoisomer. Attempted cyclisations of this product to form the required tetracyclic cyclopentanone were uniformly unsuccessful and, for this reason, the relative stereochemistry depicted in (VIII) is tentatively assigned, in which the methoxycarbonylmethyl and nitrile groups are *trans*-situated.

Attempted direct monomethylation of the ketone (VII) led to intractable mixtures but the required product (IX) was obtained by conversion into the hydroxymethylene derivative followed by treatment with sodium hydride and methyl iodide in dimethylformamide. Hydrolysis of the product furnished the acid (IX), at which point our route and Loewenthal's [2] converged. A mixed melting point of this acid (m. p. 169·5—170°) with that (m. p. 171—172°) obtained by courtesy of Dr. Loewenthal showed no depression and the infrared and mass spectra of the two samples were identical.

For comparison with an acid (X; R = CH_2·CO_2H),[1] another degradation product of gibberellic acid, the closely similar tricyclic diketone (X; R = H) was obtained from the keto-ester (III; R = CO_2Et). Methylation, hydrolysis, and decarboxylation converted it into the spirodiketone (III; R = Me) which was subjected to ring contraction *via* the furfurylidene derivative, ozonolysis, and Dieckmann cyclisation in the obvious manner. The properties of the resulting spirodiketone were in full accord with the structure (X; R = H) and closely resembled those of the tricyclic degradation product (X; R = CH_2·CO_2H).

Experimental

M. p.s were determined on the Kofler block. Infrared spectra were taken with a Perkin–Elmer Infracord spectrometer for solutions in carbon tetrachloride; ultraviolet spectra with a Unicam S.P. 500 spectrophotometer for solutions in ethanol. Microanalyses are by Mr. J. M. L. Cameron, B.Sc., and his staff. The light petroleum used had b. p. 60—80°. The

[6] See Brian, Grove, and MacMillan, *Fortschritte Chem. org. Naturstoffe*, 1960, **18**, 350, for leading references.

[7] Friedel and Orchin, "Ultraviolet Spectra of Aromatic Compounds," Wiley, New York, 1959.

[8] Johnson and Shelberg, *J. Amer. Chem. Soc.*, 1945, **67**, 1745.

phrase " in the usual way " refers to dilution with water, extraction with ether, washing successively with aqueous sodium hydrogen carbonate, dilute hydrochloric acid, and water, and, after drying ($MgSO_4$), concentration on the steam bath *in vacuo*. When necessary, benzene or chloroform was added to remove final traces of water.

4-*Methylindan*-1-*one*.—The following modification of the recorded method [4] was found most convenient. 2-Methylcinnamic acid (20 g.) in 10% aqueous sodium hydroxide (120 c.c.) containing 5% palladium–charcoal (3 g.) was shaken under hydrogen. Uptake of 1 mol. was complete in 2 hr., whereupon filtration and acidification gave β-*o*-tolylpropionic acid as plates (18·5 g., 90%), m. p. 102—104° (from light petroleum; lit.,[3] m. p. 102°).

A mixture of this acid (8 g.) and polyphosphoric acid (150 g.) was stirred vigorously at 100° for 3 hr. The resultant syrup was added to water (400 c.c.). Working up in the usual way afforded 4-methylindan-1-one (5·5 g., 79%) as pale yellow needles, m. p. 98—101° (from light petroleum; lit.,[4] m. p. 98—101°).

4-*Methyl*-1-*oxoindan*-2-*ylidenedi*-β-*propionic Acid* (II; R = CO_2H).—Acrylonitrile (2·2 g.) was added at room temperature to a solution of 4-methylindan-1-one (3 g.) in dry benzene (30 c.c.) containing Triton B (300 mg.) with stirring. After 16 hr., working up in the usual way gave the crude oily dinitrile (II; R = CN). When this had been refluxed for 8 hr. with 10% aqueous potassium hydroxide (100 c.c.), isolation of the acidic fraction and crystallisation from hot water gave the keto-dicarboxylic acid (II; R = CO_2H) as plates (4·5 g., 75%), m. p. 160—164°, $\nu_{max.}$ (in Nujol) 1720 (indanone C=O) and 1700 cm.$^{-1}$ (CO_2H) (Found: C, 66·0; H, 6·25. $C_{16}H_{18}O_5$ requires C, 66·2; H, 6·25%).

Ethyl 4-*Methyl*-1-*oxoindan*-2-*spiro*-1′-(4′-*oxocyclohexane*-3′-*carboxylate*) (III; R = CO_2Et).—The foregoing acid was esterified (ethanol–sulphuric acid; 8 hours' refluxing) in the usual way. The crude keto-ester (II; R = CO_2Et) showed the expected infrared bands at 1735 and 1715 cm.$^{-1}$ (ester and indanone C=O). This ester (21·6 g.) was added dropwise during 1 hr. with stirring to a refluxing mixture of powdered sodium (1·44 g.) and dry benzene (175 c.c.). Stirring and refluxing were maintained for 12 hr. after the addition. Then the mixture was cooled, treated with ice-cold dilute hydrochloric acid, and worked up in the usual way to furnish needles of the *spiro*-β-*keto-ester* (III; R = CO_2Et) (13·2 g., 70%) which, after recrystallisation from ethanol, had m. p. 131—133°, $\nu_{max.}$ 1720 (ester and indanone C=O), 1670 (chelated ester C=O), and 1615 cm.$^{-1}$ (enol C=C), $\lambda_{max.}$ 250—252 and 295—300 mμ (ε 26,200 and 3080) (Found: C, 71·8; H, 6·85. $C_{18}H_{20}O_4$ requires C, 72·0; H, 6·7%).

4-*Methyl*-1-*oxoindane*-2-*spiro*-1′-(*cyclohexan*-4′-*one*) (III; R = H).—A solution of the spiro-β-keto-ester (III; R = CO_2Et) (10 g.) in " AnalaR " acetic acid (40 c.c.) containing concentrated hydrochloric acid (10 c.c.) and water (6 c.c.) was heated under reflux in a nitrogen atmosphere for 5 hr. The cooled solution was added to ice-water (150 c.c.), and the resultant white solid filtered off and dried (7 g., 92%). Crystallized from aqueous ethanol the spiro-diketone (III; R = H) formed prisms, m. p. 123—126°, ν 1720 cm.$^{-1}$ (indanone and cyclohexanone C=O), $\lambda_{max.}$ 250—255 and 298 mμ (ε 12,700 and 2420) (Found: C, 79·2; H, 7·2. $C_{15}H_{16}O_2$ requires C, 78·9; H, 7·05%).

1-*Hydroxy*-1,4-*dimethylindane*-2-*spiro*-1′-(4′-*methylcyclohexan*-4′-*ol*) (IV).—Methylmagnesium bromide was prepared by adding methyl bromide (20 c.c.) in dry ether (25 c.c.) to a stirred mixture of magnesium turnings (2 g.) and dry ether (10 c.c.). Loss of methyl bromide in the nitrogen stream was minimised by attachment of a methanol–carbon dioxide condenser. The latter was then replaced by a water-condenser and a solution of spirodiketone (III; R = H) (4·6 g.) in ether–tetrahydrofuran (1 : 1; 100 c.c.) added dropwise to the stirred, refluxing Grignard reagent. After 3 hr. the complex was decomposed by saturated ammonium chloride solution (50 c.c.). Isolation in the usual way gave a colourless gum (5·1 g., 97%) which had ν 3400 (OH), 1600 (C=C aromatic) cm.$^{-1}$, $\lambda_{max.}$ 265 mμ (ε 430) and was used directly for the next step.

4-*Methyl*-1-*methyleneindane*-2-*spiro*-1′-(4′-*methylcyclohex*-3′-*ene*) (V).—A solution of the crude diol (IV) (5·1 g.) in dry benzene (150 c.c.) containing toluene-*p*-sulphonic acid (400 mg.) was heated under reflux for 3 hr. under a Dean and Stark apparatus. The benzene solution was processed in the usual way to furnish an oil (4·3 g.) which was chromatographed in light petroleum over alumina (Brockmann grade III). Elution with light petroleum gave the *spirodiene* (V) as prisms (from light petroleum), m. p. 67—69°, $\nu_{max.}$ 1635 (styrene C=C) and 1600 cm.$^{-1}$ (aromatic C=C), $\lambda_{max.}$ 255, 290, and 300 mμ (ε 15,500, 3940, 3520) (Found: C, 90·7; H, 9·2. $C_{17}H_{20}$ requires C, 91·0; H, 9·0%).

Methyl 4-*Methyl*-1-*oxo*-2-3′-*oxobutylindan*-2-*ylacetate* (VI; R = Me).—A solution of the spiro-diene (V) (1 g.) in " AnalaR " ethyl acetate (50 c.c.) was ozonised for 2 hr. at −70°. The solvent was removed *in vacuo* at 40°, and the residue treated with glacial acetic acid (15 c.c.) containing 30% hydrogen peroxide (5 c.c.) and dilute hydrochloric acid (2 drops). After 16 hr. at room temperature the solution was heated on the steam bath for 10 min., and the acetic acid neutralised with sodium hydrogen carbonate solution. Removal of neutral material in ether, followed by acidification of the alkaline extract and isolation of the acid in ethyl acetate, gave an oil (1 g., 82%) which had $\nu_{max.}$ 1700 and 1600 cm.$^{-1}$. Esterification with diazomethane gave the diketo-ester (VI; R = Me) which had $\nu_{max.}$ 1735 (ester C=O) and 1715 cm.$^{-1}$ (indanone C=O), $\lambda_{max.}$ 250 and 295 mμ (ε 7200 and 1400) and was used directly for the next step.

Methyl 1,2,3,10-*Tetrahydro*-3-*oxofluoren*-10-*ylacetate* (VII).—A solution of the oily diketo-ester (VI; R = Me) (800 mg.) in methanol (100 c.c.) containing sodium (1 g.) was heated under reflux in a nitrogen atmosphere for 4 hr. The resultant solution was concentrated to 30 c.c. and water (75 c.c.) added. Acidification with dilute hydrochloric acid and extraction with ethyl acetate furnished an oil (600 mg.) which on trituration with ether gave the amorphous tricyclic enone-acid (250 mg., 33%), m. p. 218—225°. The corresponding *methyl ester* (VII) formed prisms, m. p. 109—111°, from ethyl acetate–light petroleum (Found: C, 75·35; H, 6·25. $C_{17}H_{16}O_3$ requires C, 75·55; H, 6·7%).

Methyl 2-*Cyano*-1,2,3,10-*tetrahydro*-2,8-*dimethyl*-3-*oxofluoren*-10-*ylacetate* (VIII).—To a stirred suspension of sodium methoxide (450 mg.) in dry benzene (15 c.c.) was added a solution of ethyl formate (600 mg.) in dry benzene (5 c.c.). The mixture was stirred for 40 min. at room temperature under nitrogen and then cooled in ice. A solution of the enone-ester (VII) (1 g.) in dry benzene (35 c.c.) was added to the suspension at 0° and the mixture maintained at this temperature for 30 min. The greenish-brown mixture was stirred overnight at room temperature. Acidification with dilute sulphuric acid and extraction with ether gave the hydroxymethylene derivative as a red oil (900 mg., 81%) which showed a purple ferric reaction and $\nu_{max.}$ 1760 (ester), 1670 (cyclohexenone), and 1640 (enolised β-dicarbonyl, enol, and styrene C=C) cm.$^{-1}$, $\lambda_{max.}$ 238 and 300 mμ (ε 7400 and 12,800), $\lambda_{max.}$ (in 0·1N-alcoholic sodium ethoxide) 232, 295, and 390—395 mμ (ε 7900, 13,000, and 5150). A solution of this compound (900 mg.) in " AnalaR " acetic acid (25 c.c.) containing hydroxylamine hydrochloride (900 mg.) was refluxed under nitrogen for 25 min. The red solution was cooled, diluted with water (200 c.c.), and extracted with ethyl acetate. Working up in the usual way gave the isoxazole as an oil (700 mg., 78%) showing no colour with alcoholic ferric chloride and having $\nu_{max.}$ 1730 (ester) and 1630 cm.$^{-1}$ (styrene C=C and C=N), $\lambda_{max.}$ 238 and 320 mμ (ε 7200 and 11,700). The crude isoxazole (700 mg.) in benzene (18 c.c.) was added under nitrogen to an ice-cold solution from sodium (150 mg.) in dry methanol 5 c.c.). After 30 min. at room temperature, the mixture was refluxed for 10 min. After cooling, methyl iodide (1 c.c.) was added and the stirred solution kept at 20° for 1 hr., then refluxed for 2 hr. after addition of a further amount (0·5 c.c.) of methyl iodide. Working up in the usual way gave the methylated α-cyano-ketone (VIII) as plates (250 mg., 34%) from ethyl acetate), m. p. 191—195°, $\nu_{max.}$ 2250 (C≡N), 1740 (ester), 1675 (cyclohexenone), and 1640 cm.$^{-1}$ (styrene C=C), $\lambda_{max.}$ 240 and 302—310 mμ (ε 8150 and 20,300) [Found: C, 73·8; H, 5·95; N, 4·6%; *M* (mass spectrometer), 309. $C_{19}H_{19}O_3N$ requires C, 73·75; H, 6·2; N, 4·55%; *M*, 309].

Attempted cyclisation of the cyano-ketone (VIII) with potassium t-butoxide in t-butyl alcohol gave intractable products.

1,2,3,10-*Tetrahydro*-2,8-*dimethyl*-3-*oxofluoren*-10-*ylacetic Acid* (IX).—To a solution of the hydroxymethylene compound (100 mg.) (prepared as above) in dry dimethylformamide (1·5 c.c.) was added sodium hydride (30 mg.). The suspension was stirred for 1·5 hr. under nitrogen and then methyl iodide (0·7 c.c.) added with ice-cooling. Stirring at 0° was maintained for 1 hr. and the solution allowed to reach room temperature and stirred for 4 hr. Working up in the usual way gave an oil which was directly hydrolysed in refluxing ethanol (5 c.c.) containing 60% potassium hydroxide solution (1 c.c.) during 3·5 hr. Neutral products were removed in ether, and the acidified solution was extracted with ether to give an oil which solidified slowly on trituration with isopropyl ether. Chromatography in benzene over silica gel gave a fraction, eluted with benzene–ether (19 : 1), which crystallised from isopropyl ether as prisms, m. p. 169·5—170° alone or mixed with the authentic sample (m. p. 171°). A comparison of mass and infrared spectra confirmed the identity of the acids.

4-*Methyl*-1-*oxoindane*-2-*spiro*-1′-(3′-*methylcyclohexan*-4′-*one*) (III; R = Me).—A solution of

the spiro-β-keto-ester (III; R = CO_2Et) (6 g.) in dry benzene (30 c.c.) was added dropwise to a stirred mixture of powdered sodium (500 mg.) and dry benzene (5 c.c.). After 30 min. at room temperature the stirred mixture was heated under reflux for 1 hr., then methyl iodide (2 c.c.) was added to the cooled suspension and refluxing maintained for a further 8 hr. Working up in the usual way gave a viscous oil (6 g.) which showed no colour with ferric chloride solution. When this oil was refluxed for 6 hr. under nitrogen in acetic acid (20 c.c.) containing concentrated hydrochloric acid (8 c.c.) and water (4 c.c.), addition of ice-water (120 c.c.) gave a yellow solid (4 g.) which recrystallised from aqueous methanol as prisms, m. p. 112—114°, $\nu_{max.}$ 1710 cm.$^{-1}$ (indanone and cyclohexanone C=O), $\lambda_{max.}$ 252 and 299 mμ (ε 12,500 and 2300) (Found: C, 79·2; H, 7·65. $C_{16}H_{18}O_2$ requires C, 79·3; H, 7·5%).

4-Methyl-1-oxoindane-2-spiro-1'-(4'-methylcyclopentan-3'-one) (X; R = H).—The furfurylidene derivative of the ketone (III; R = Me) was prepared in the usual way by means of sodium hydroxide–ethanol but was obtained only as an oil, $\lambda_{max.}$ 250 and 325 mμ (ε 13,000, 17,500). The crude furfurylidene compound (600 mg.) was ozonised in ethyl acetate (40 c.c.) at −70° for 30 min., the solvent removed, and oxidation carried out in " AnalaR " acetic acid (5 c.c.) containing 30% hydrogen peroxide (2 c.c.) and dilute hydrochloric acid (1 c.c.). The acidic product was isolated and esterified as described above for the diketo-ester (VI; R = Me). The oily keto-diester (320 mg.) obtained in this way had $\lambda_{max.}$ 250 and 295 (ε 1200 and 1800), $\nu_{max.}$ 1735 and 1700 cm.$^{-1}$ (indanone and ester C=O). Dieckmann cyclisation was carried out on the latter ester in 79% yield. This resultant keto-ester had $\nu_{max.}$ 1720 (indanone and ester C=O), 1665 (chelated ester C=O) and 1620 cm.$^{-1}$ (enol C=C). Hydrolysis and decarboxylation, as in the preparation of the methylated spirodiketone (III; R = Me) above, gave the new *spirodiketone* (X; R = H), b. p. 140°/0·4 mm., $\nu_{max.}$ 1745 (cyclopentanone) and 1715 cm.$^{-1}$ (indanone), $\lambda_{max.}$ 252 and 299 (ε 12,300 and 2200) (Found: C, 78·4; H, 7·4. $C_{15}H_{16}O_2$ requires C, 78·9; H, 7·05%).

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