

**514. Gibberellic Acid. Part VIII.<sup>1</sup> Synthesis of Methyl ( $\pm$ )- $\alpha$ - and - $\beta$ -3 : 5-Dimethoxycarbonyl-6-(2-methoxycarbonyl-6-methylphenyl)-3-methylhexanoate.**

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The structures methyl  $\alpha$ - and  $\beta$ -3 : 5-dimethoxycarbonyl-6-(2-methoxycarbonyl-6-methylphenyl)-3-methylhexanoate assigned to products obtained by degradation of gibberic acid have been confirmed by the synthesis of their racemates.

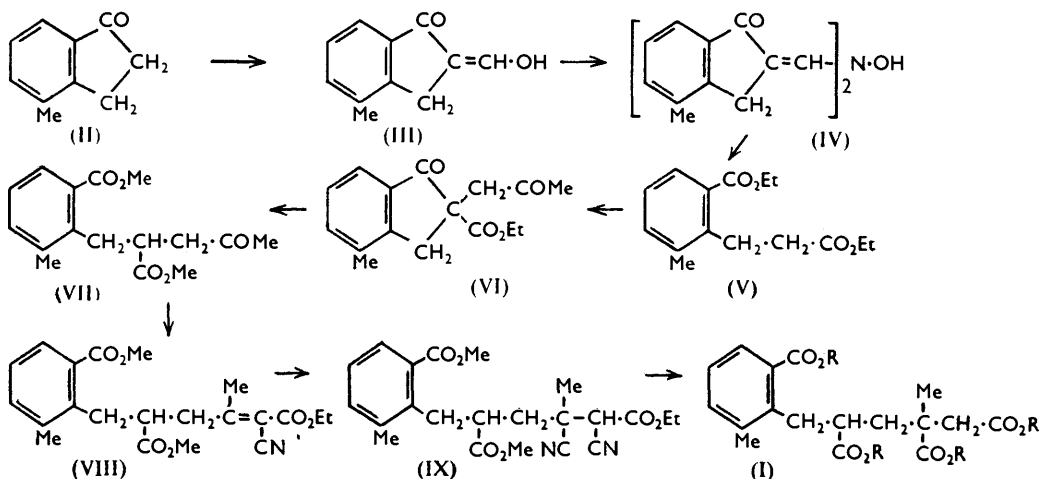
STEPWISE degradation <sup>1</sup> of gibberic acid has been shown to yield a tetracarboxylic acid, from which two crystalline methyl esters  $C_{21}H_{28}O_8$  were obtained. The formation of the two esters, which differed in optical rotatory power, was considered to be due to racemisation of one of two centres of asymmetry during the formation of the acid. The structure (I; R = H) proposed for the acid <sup>1</sup> has been confirmed by the synthesis of racemates of both methyl esters.

4-Methylindan-1-one (II) was converted into 2-formyl-4-methylindan-1-one (III) which with hydroxylamine hydrochloride <sup>2</sup> gave the disubstituted hydroxylamine (IV). Chakravarti <sup>2</sup> considered this compound to be the 2-cyano-derivative but comparison of its

<sup>1</sup> Part VII, Cross, Grove, MacMillan, and Mulholland, preceding paper.

<sup>2</sup> Chakravarti, *J. Indian Chem. Soc.*, 1943, **20**, 393.

properties with those of related compounds<sup>3</sup> showed that it was the disubstituted hydroxylamine. Hydrolysis and esterification then gave ethyl  $\beta$ -(2-ethoxycarbonyl-6-methylphenyl)propionate (V) which on treatment with sodium followed by bromoacetone was converted into ethyl ( $\pm$ )-2-acetonyl-4-methyl-1-oxindane-2-carboxylate (VI).



Attempts to condense the last compound with ethyl cyanoacetate failed even under vigorous conditions;<sup>4</sup> it was therefore hydrolysed and the product esterified, to give the methyl ester (VII) which condensed satisfactorily. Addition of potassium cyanide across the ethylenic bond of the product (VIII), followed by hydrolysis of the resulting dinitrile (IX), gave the required acid (I; R = H).

Methylation of this acid gave a mixture which was separated into methyl ( $\pm$ )- $\alpha$ -3 : 5-dimethoxycarbonyl-6-(2-methoxycarbonyl-6-methylphenyl)-3-methylhexanoate, m. p. 78—80°, and the ( $\pm$ )- $\beta$ -isomer, m. p. 36—38°, from which the corresponding tetracarboxylic acids (I; R = H), m. p. 202—205° and 176°, respectively, were prepared by hydrolysis. The synthetic esters did not depress the m. p.s of the corresponding ( $-$ )- $\alpha$ -, m. p. 83—84°, and ( $-$ )- $\beta$ -ester, m. p. 46—48°, obtained by degradation<sup>1</sup> and were shown to be racemates of the natural compounds by comparison of their infrared spectra in carbon tetrachloride solution.

#### EXPERIMENTAL

M. p.s are corrected. Microanalyses are by Messrs. W. Brown and A. G. Olney. Alumina for chromatography and absorption spectra were obtained as described previously.<sup>5</sup>

**4-Methylindan-1-one** (with Mr. P. J. SUTER).— $\beta$ -*o*-Tolylpropionic acid (1.00 g.) was covered with hydrogen fluoride and kept in a Polythene container for 6 hr. at room temperature. The hydrogen fluoride was allowed to evaporate, the residue was made alkaline with sodium hydrogen carbonate and extracted with ether. The extract was washed with sodium carbonate, then water, dried, and evaporated, giving the indanone (805 mg.) which crystallised from light petroleum (b. p. 60—80°) in needles (690 mg.), m. p. 101—104° (Found: C, 82.2; H, 7.0. Calc. for C<sub>10</sub>H<sub>10</sub>O: C, 82.2; H, 6.9%) (lit., m. p.'s 96°,<sup>6</sup> 102°,<sup>2</sup> 103—104°<sup>7</sup>).

**2-Formyl-4-methylindan-1-one**.—4-Methylindan-1-one (9.7 g.) in benzene (80 ml.) was added with shaking during 10 min. to a mixture of ethyl formate (9.7 g.), benzene (50 ml.) and powdered sodium methoxide (from sodium, 3.0 g.), which was cooled in ice. The mixture was kept in ice

<sup>3</sup> Johnson, Anderson, and Shelberg, *J. Amer. Chem. Soc.*, 1944, **66**, 218; Johnson and Shelberg, *ibid.*, 1945, **67**, 1745.

<sup>4</sup> Cope, Hofmann, Wyckoff, and Hardenbergh, *ibid.*, 1941, **63**, 3452; Cragoe, Robb, and Sprague, *J. Org. Chem.*, 1950, **15**, 381.

<sup>5</sup> Mulholland and Ward, *J.*, 1954, 4676.

<sup>6</sup> Plattner and Wyss, *Helv. Chim. Acta*, 1940, **23**, 907.

<sup>7</sup> Mercer and Robertson, *J.*, 1936, 288.

for 15 min., then at room temperature overnight, and was then shaken with ice-water. Ether was added and the combined aqueous layer and water washings of the organic layer were washed with ether and acidified with ice-cold dilute hydrochloric acid. The *formyl derivative* (11.1 g.), m. p. 166—168° (decomp.), was filtered off and used for further work without purification. A specimen crystallised from benzene in pale yellow prisms, m. p. 168—170° (decomp.) (Found: C, 75.8; H, 5.95.  $C_{11}H_{10}O_2$  requires C, 75.8; H, 5.8%).

The compound has been obtained in crude form <sup>2</sup> but an attempt to repeat this preparation, which involved the use of a large excess of sodium, gave a very low yield.

*NN-Di-(4-methyl-1-oxo-2-indanylidene-methyl)hydroxylamine* (IV).—Reaction of the above compound with hydroxylamine hydrochloride in acetic acid <sup>2</sup> gave the hydroxylamine derivative as an orange-red powder (85%), m. p. 220—222° (decomp.), which was not purified. The product was soluble in, and gave a blue colour with, dilute aqueous sodium hydroxide and was therefore not the simple cyano-ketone.<sup>2</sup> It appeared to form an acetate (cf. Johnson *et al.*<sup>3</sup>) but this was not obtained pure.

*β-(2-Carboxy-6-methylphenyl)propionic Acid*.—The above hydroxylamine derivative (33.0 g.) and hydroxylamine hydrochloride (6.8 g.) were heated under reflux with aqueous 3% potassium hydroxide solution (7 l.) for 12 days in nitrogen. The volume was reduced to *ca.* 2 l. by distillation at atmospheric pressure, and the residual solution was washed with ether and acidified with hydrochloric acid. The combined product obtained by filtration and ether-extraction of the filtrate was dissolved in aqueous sodium hydrogen carbonate, recovered by acidification, and then crystallised from water (charcoal), giving pale yellow needles of the acid (21.2 g.), m. p. 167—169°. A specimen, sublimed *in vacuo* and recrystallised, formed colourless needles, m. p. 173—174° (Chakravarti <sup>2</sup> gives m. p. 172°) (Found: C, 63.6; H, 5.75. Calc. for  $C_{11}H_{12}O_4$ : C, 63.45; H, 5.8%),  $\lambda_{max.}$  (in EtOH) 232, 277—282  $m\mu$  ( $\log \epsilon$  3.85, 3.26 respectively).

The diethyl ester <sup>2</sup> distilled as a colourless oil, b. p. 120—121°/10<sup>-1</sup> mm. (86%).

*Ethyl (±)-2-Acetyl-4-methyl-1-oxoindane-2-carboxylate* (VI).—The above diethyl ester (22.7 g.) in benzene (120 ml.) was added to powdered sodium (2.37 g.) in benzene (*ca.* 20 ml.) and heated under reflux in nitrogen for 4 hr. After cooling, a solution of bromoacetone (14.2 g.) in benzene (50 ml.) was added at 0° with shaking. The mixture was kept at 0° for 1 hr., at room temperature overnight and then heated under reflux in nitrogen for 15 hr. After cooling, shaking with ice-water, and dilution with ether, the organic fraction was separated, combined with ether washings of the aqueous fraction, washed with water, dried, treated with charcoal, and filtered. Evaporation and treatment of the residual gum with small amounts of ether gave crystals of the sparingly soluble *ketone* (15.4 g.), m. p. 103—108°. Chromatography of the mother-liquor in ether on alumina gave more product (705 mg.). Crystallisation of a specimen from benzene-light petroleum and dilute ethanol gave prisms, m. p. 110—111° (Found: C, 70.2; H, 6.6.  $C_{18}H_{18}O_4$  requires C, 70.05; H, 6.6%),  $\lambda_{max.}$  (in EtOH) 256, 300  $m\mu$  ( $\log \epsilon$  4.08, 3.25 respectively).

The *semicarbazone*, prepared in pyridine, crystallised from ethanol in needles, m. p. 183—185° (decomp.) (Found: C, 61.55; H, 6.5; N, 12.2.  $C_{17}H_{21}O_4N_3$  requires C, 61.6; H, 6.4; N, 12.7%).

Attempts to condense the ketone with ethyl cyanoacetate failed.

*(±)-2-(2-Carboxy-6-methylbenzyl)-4-oxopentanoic Acid* ( $CO_2H = 1$ ).—A mixture of the above ketone (16.1 g.) and a 20% solution of potassium hydroxide in 50% aqueous ethanol (805 ml.) was heated under reflux for 3 hr. The ethanol was removed *in vacuo* and the residue was washed with ether, treated with charcoal, filtered, and acidified with hydrochloric acid. After storage overnight at 0° the *keto-acid* (9.45 g.; m. p. 171—174°) was filtered off, and a further crop (274 mg.) was recovered from the mother-liquor by ether-extraction followed by crystallisation from ethyl methyl ketone-light petroleum (b. p. 60—80°). A specimen recrystallised as needles, m. p. 173—174° [Found: C, 63.5; H, 6.05%; equiv., 136.  $C_{14}H_{16}O_5$  requires C, 63.6; H, 6.1%; equiv. (dibasic), 132],  $\lambda_{max.}$  (in EtOH) 232, 282—283  $m\mu$  ( $\log \epsilon$  2.77; 2.11 respectively). The yellow 2 : 4-dinitrophenylhydrazone, crystallised from dilute acetic acid, had m. p. 248—250° (Found: C, 54.4; H, 4.6; N, 12.5.  $C_{20}H_{20}O_8N_4$  requires C, 54.05; H, 4.5; N, 12.6%). The *methyl ester* (VII), prepared with ethereal diazomethane, crystallised from dilute methanol in needles, m. p. 49—51°, but consistent analyses were not obtained. Recrystallisation from ether-light petroleum (b. p. 40—60°) gave prisms, m. p. 50—52° (Found: C, 65.9; H, 7.1; OMe, 20.7.  $C_{16}H_{20}O_5$  requires C, 65.7; H, 6.9; 2OMe, 21.2%).

*Methyl (±)-3 : 5-Dimethoxycarbonyl-6-(2-methoxycarbonyl-6-methylphenyl)-3-methylhexanoate*

(I; R = Me).—(i) A mixture of the above methyl ester (7.00 g.), ethyl cyanoacetate (4.05 g.), acetic acid (2.31 g.), and ammonium acetate (0.50 g.) in benzene (40 ml.) was heated under reflux for 20 hr. in an apparatus fitted with a Dean and Stark<sup>8</sup> water separator. After each 4-hr. period more ammonium acetate ( $4 \times 0.4$  g.) was added. The cooled mixture was diluted with ether, washed with water, dried, and evaporated, giving an oil (10.1 g.). Distillation *in vacuo* gave unchanged ethyl cyanoacetate (bath-temp. up to  $140^\circ/10^{-2}$  mm.) and a very viscous yellow oil (7.71 g.) of b. p.  $176\text{--}184^\circ/15 \times 10^{-3}$  mm. consisting essentially of ethyl ( $\pm$ )-2-cyano-5-methoxycarbonyl-6-(2-methoxycarbonyl-6-methylphenyl)-3-methylhex-2-enoate (VIII).

(ii) The above nitrile (7.70 g.) in ethanol (50 ml.) was treated slowly at  $10^\circ$  with potassium cyanide (2.6 g.) in water (20 ml.). The mixture was kept at room temperature for 1 hr., heated under reflux for 30 min., cooled to  $0\text{--}5^\circ$ , and acidified with dilute hydrochloric acid (70 ml.; 1 : 1). The crude ethyl ( $\pm$ )-2 : 3-dicyano-5-methoxycarbonyl-6-(2-methoxycarbonyl-6-methylphenyl)hexanoate (IX) (6.9 g.) was recovered in ether as a gum, which was not purified.

(iii) The above dinitrile (6.9 g.) and 50% sulphuric acid (300 ml.) were heated under reflux in a stream of nitrogen until evolution of carbon dioxide ceased (50 hr.). On cooling, an oil separated which solidified. After removal of a globule of tar (*ca.* 0.1 g.) the mixture was extracted with ether. Recovery from the extract gave ( $\pm$ )- $\alpha$ - and - $\beta$ -3 : 5-dicarboxy-6-(2-carboxy-6-methylphenyl)-3-methylhexanoic acid (I; R = H) as a pale yellow gum (6.8 g.). Pure specimens were prepared from the methyl esters (see below).

(iv) Esterification of the above acid (6.8 g.) with diazomethane gave a neutral yellow gum (6.0 g.) which was chromatographed on alumina ( $18 \times 2.5$  cm.) in ether and eluted with the same solvent (150 ml. fractions) until the last fraction gave only 3 mg. on recovery. The product (5.4 g.) crystallised from ether–light petroleum (b. p.  $40\text{--}60^\circ$ ), giving a sticky solid (3.4 g.), m. p.  $48\text{--}64^\circ$ , and a gum which was distilled, b. p.  $175\text{--}185^\circ/10^{-1}$  mm. (1.58 g.). Recrystallisation of the solid product from ether–light petroleum and then from light petroleum (b. p.  $60\text{--}80^\circ$ ) gave needles (1.83 g.) of methyl ( $\pm$ )- $\alpha$ -3 : 5-dimethoxycarbonyl-6-(2-methoxycarbonyl-6-methylphenyl)-3-methylhexanoate (I; R = Me), m. p.  $78\text{--}79^\circ$ , raised to  $79\text{--}80^\circ$  by further crystallisation (Found: C, 61.85; H, 7.0; OMe, 30.0.  $C_{21}H_{28}O_8$  requires C, 61.75; H, 6.9; 4OMe, 30.4%).

After the recovery of a small amount of the  $\alpha$ -ester from the crystallisation mother-liquors the gummy fractions were combined and separated from most of a ketonic impurity with Girard's reagent  $\tau$  in methanol (Girard's reagent  $p$  or chromatography on alumina was ineffective). The material recovered was only weakly ketonic to Brady's reagent. Colour was removed by passage of an ethereal solution through alumina ( $16 \times 1.4$  cm.). The gum (2.59 g.) which was recovered crystallised on addition of light petroleum (b. p.  $40\text{--}60^\circ$ ) to an ethereal solution at  $-10^\circ$  to  $0^\circ$ . Three crops of crystals (2.02 g.), m. p. range  $35\text{--}50^\circ$ , were combined and fractionally crystallised, giving the ( $\pm$ )- $\beta$ -ester as small needles (180 mg.), m. p.  $34\text{--}36^\circ$  (Found: C, 61.7; H, 6.9; OMe, 29.1%). From the mother-liquors two further batches of less pure material were obtained: (a) 984 mg., m. p.  $39\text{--}42^\circ$ ; (b) 124 mg., m. p.  $37\text{--}40^\circ$ . The infrared spectra of the ( $\pm$ )- $\alpha$ - and - $\beta$ -racemate in solution in carbon tetrachloride were identical with those of the  $\alpha$ - and  $\beta$ -ester respectively obtained from gibberic acid.

*Hydrolysis.*—A solution of the above ( $\pm$ )- $\alpha$ -ester (400 mg.) in 6% ethanolic potassium hydroxide (10 ml.) was heated under reflux for 2 hr. The potassium salt which separated was filtered off, washed with ethanol, and dissolved in water. Acidification of the solution with hydrochloric acid followed by recovery of the product in ether gave ( $\pm$ )- $\alpha$ -3 : 5-dicarboxy-6-(2-carboxy-6-methylphenyl)-3-methylhexanoic acid (I; R = H) (215 mg.), m. p.  $202\text{--}204^\circ$  (decomp.). This separated from ethyl methyl ketone–light petroleum (b. p.  $60\text{--}80^\circ$ ) as an amorphous white powder (155 mg.), m. p.  $204\text{--}205^\circ$  (decomp.) [Found: C, 58.2; H, 5.9%; equiv., 88.  $C_{17}H_{20}O_8$  requires C, 57.95; H, 5.7%; equiv. (4  $CO_2H$ ), 88].

The ( $\pm$ )- $\beta$ -ester (500 mg.), hydrolysed in the same way, gave the ( $\pm$ )- $\beta$ -acid as an amorphous white powder (202 mg.), m. p.  $176^\circ$  (decomp.) (Found: C, 58.0; H, 5.9%; equiv., 84).

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<sup>8</sup> Dean and Stark, *Ind. Eng. Chem.*, 1920, **12**, 486.