258. *Phthalaldehydes and Related Compounds. Part II.* Synthesis of* iso*Gladiolic Acid.*

By J. J. Brown and G. T. Newbold.

The structure of *iso*gladiolic acid, the alkali rearrangement product of gladiolic acid, has been confirmed as 7-methoxy-6-methylphthalide-4-carboxylic acid by synthesis.

The structure of gladiolic acid (I; R = Me),† an antifungal metabolic product of *Penicillium gladioli* Machacek, has been elucidated by Grove (*Biochem. J.*, 1952, **50**, 648) and Raistrick and Ross (*ibid.*, p. 635). Supporting evidence was obtained by Brown and Newbold (*J.*, 1952, 4878) by examination of 3-formylopianic acid (I; R = OMe) synthesised by treatment of 4-chloromethylmeconin (II; R = OMe, R′ = CH_2Cl) with *N*-bromosuccinimide and subsequent hydrolysis.

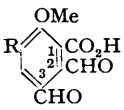
Treatment of gladiolic acid with alkali gives *iso*gladiolic acid, which was formulated by Grove (*loc. cit.*) as (II; R = Me, R′ = CO_2H), though the structure (III), involving lactonisation in the alternative direction, was considered a possibility. Although the alkaline rearrangement product of 3-formylopianic acid (I; R = OMe) was shown to be 4-carboxymeconin (II; R = OMe, R′ = CO_2H) by Brown and Newbold (*loc. cit.*) since it was also formed by oxidation of 4-hydroxymethylmeconin (II; R = OMe, R′ = CH_2·OH) it was apparent that a synthesis of *iso*gladiolic acid was necessary in order to decide between the possible structures (II; R = Me, R′ = CO_2H) and (III). This has now been carried out.

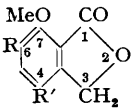
The synthetical route envisaged required the preparation of 7-methoxy-6-methylphthalide (II; R = Me, R′ = H) as an intermediate. In a first attempt to prepare this

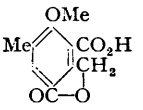
* Part I, *J.*, 1952, 4878.

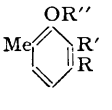
† For brevity the other, tautomeric form of this structure (see Grove, *J.*, 1952, **3345**) has been omitted.

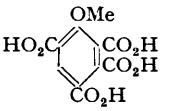
compound 2-hydroxy-*p*-toluic acid (IV; R = CO_2H, R′ = R″ = H)* was reduced by lithium aluminium hydride to 3-hydroxy-4-methylbenzyl alcohol (IV; R = CH_2·OH, R′ = R″ = H); a number of variants of the Kolbe procedure were tried in order to carboxylate the latter compound to the lactone of (IV; R = CH_2·OH, R′ = CO_2H, R″ = H) but all failed to give this product. Attention was then turned to 2-methoxy-*p*-


(I)


(II)


(III)


(IV)


(V)

toluic acid (IV; R = CO_2H, R′ = H, R″ = Me) as starting material. This compound is readily obtained by methylation of 2-hydroxy-*p*-toluic acid (Perkin and Weizmann, *J.*, 1906, **89**, 1649) but was also prepared by carboxylation of the Grignard reagent from 4-bromo-2-methoxytoluene (IV; R = Br, R′ = H, R″ = Me), the latter compound being obtained by methylation of the known 4-bromo-*o*-cresol (Hodgson and Moore, *J.*, 1926, 2036). Simonsen and Rau (*J.*, 1921, **119**, 1339) showed that nitration of (IV; R = CO_2H, R′ = H, R″ = Me) gave 2-methoxy-3-nitro-*p*-toluic acid (IV; R = CO_2H, R′ = NO_2, R″ = Me), the orientation of the nitro-group being proved by conversion of the nitro-acid into 3-nitro-*o*-cresol (Me = 1). The same authors reduced (IV; R = CO_2H, R′ = NO_2, R″ = Me) to 3-amino-2-methoxy-*p*-toluic acid (IV; R = CO_2H, R′ = NH_2, R″ = Me) using ferrous sulphate and ammonia; a more satisfactory reagent for this reaction is sodium hydrosulphite (dithionite). Reduction of the amino-acid (IV; R = CO_2H, R′ = NH_2, R″ = Me) with lithium aluminium hydride gave 2-amino-3-methoxy-4-methylbenzyl alcohol (IV; R = CH_2·OH, R′ = NH_2, R″ = Me) which was diazotised and treated with cuprous cyanide. The nitrile was not isolated in the pure state; the crude product on alkaline hydrolysis gave 7-methoxy-6-methylphthalide (II; R = Me, R′ = H).

Treatment of 7-methoxy-6-methylphthalide with formaldehyde and hydrochloric acid gave a product which we formulate as 4-chloromethyl-7-methoxy-6-methylphthalide (II; R = Me, R′ = CH_2Cl), the position of the entering group being inferred by analogy with the chloromethylation of meconin (Brown and Newbold, *loc. cit.*); in general the chloromethyl group preferentially enters in the *para*-position to a methoxyl group if this is free and the methoxyl group exerts a much more powerful directive influence than the methyl group, *e.g.*, the reaction of methyl *o*-tolyl ether to give 4-methoxy-3-methylbenzyl chloride (Quelet and Anglade, *Bull. Soc. chim.*, 1937, **4**, 620) and the formation of 6-methoxy-5-methylphthalide from 2-methoxy-*p*-toluic acid (Charlesworth, Rennie, Sinder, and Yan, *Canad. J. Res.*, 1945, **23**, *B*, 17). Hydrolysis of 4-chloromethyl-7-methoxy-6-methylphthalide by aqueous sodium carbonate gave 4-hydroxymethyl-7-methoxy-6-methylphthalide (II; R = Me, R′ = CH_2·OH), oxidised by dilute, acid potassium permanganate to 7-methoxy-6-methylphthalide-4-carboxylic acid (II; R = Me, R′ = CO_2H) which was identical with *iso*gladiolic acid. (We are indebted to Mr. J. F. Grove, Imperial Chemical Industries Limited, Butterwick Research Laboratories, for the mixed m. p. determination and for comparison of the infra-red spectra of these preparations.)

Grove (*loc. cit.*) oxidised *iso*gladiolic acid to 4-methoxybenzene-1 : 2 : 3 : 5-tetracarboxylic acid (V) whose structure was proved by synthesis; it follows that chloromethylation of 7-methoxy-6-methylphthalide took place in the 4-position. The structure of *iso*gladiolic acid is thus established as (II; R = Me, R′ = CO_2H), and the structure (III) eliminated.

Experimental

Ultra-violet absorption spectra were determined in ethanol solution.

*2-Hydroxy-*p*-toluic Acid* (Me = 1).—2-Nitro-*p*-tolunitrile (50 g.; Pfeiffer, *Ber.*, 1918, **51**, 554) was added in portions with stirring to a solution of stannous chloride (250 g.) in hydrochloric acid (500 c.c.; *d* 1·19) initially at 60°, the temperature being kept below 70°. The mixture

* Toluic acids and cresols are numbered with Me = 1, throughout.

was made strongly alkaline with sodium hydroxide solution (20%) at <40° and extracted with ether (4 × 500 c.c.). The combined ethereal extracts were washed with water (3 × 250 c.c.) and dried (Na_2SO_4); removal of the ether gave 2-amino-*p*-tolunitrile (37 g., 91%), m. p. 77—78°, which was used directly for the next stage [cf. reduction of 2-nitro-*p*-tolunitrile with tin and hydrochloric acid (Borsche and Böcker, *Ber.*, 1903, **36**, 4357) who claim a 50% yield]. 2-Hydroxy-*p*-tolunitrile was prepared from 2-amino-*p*-tolunitrile in 72% yield (*loc. cit.*); no details appear in the literature for its hydrolysis to 2-hydroxy-*p*-toluic acid which was accomplished by heating the nitrile (40 g.) under reflux with sodium hydroxide solution (500 c.c.; 10%) for 4 hours. The solution was acidified with hydrochloric acid (*d* 1·19) to Congo-red and extracted with ether (3 × 250 c.c.). Removal of the ether and crystallisation of the residue from aqueous acetic acid gave 2-hydroxy-*p*-toluic acid (37 g., 80%) as needles, m. p. 205—207° (Meldrum and Perkin, *J.*, 1908, 1416, gave m. p. 206—207° for the same acid obtained by sulphonation and alkali fusion from *p*-toluic acid).

4-Bromo-2-methoxytoluene.—4-Amino-2-nitrotoluene was converted into 4-bromo-2-nitrotoluene after Gibson and Johnson (*J.*, 1929, 1229) in 70% yield and 4-bromo-*o*-cresol prepared from the latter in 40% yield (Hodgson and Moore, *loc. cit.*). A solution of 4-bromo-*o*-cresol (6·0 g.) in sodium hydroxide solution (30 c.c.; 10%) at room temperature was treated with methyl sulphate (7 c.c.), stirred for 30 min., and then slowly heated to 100° and maintained thereat for 30 minutes. The mixture was steam-distilled until 300 c.c. of distillate had been collected, and *4-bromo-2-methoxytoluene* was isolated by ether as a colourless oil (5·2 g., 80%), b. p. 108°/15 mm., n_D^{16} 1·5632 (Found: C, 48·0; H, 4·7. C_8H_9OBr requires C, 47·8; H, 4·5%). Light absorption: Max. at 210 (ε = 12,000), 222 (ε = 9000), and 276 mμ (ε = 13,000).

*2-Methoxy-*p*-toluic Acid* (Me = 1).—4-Bromo-2-methoxytoluene (10 g.) was added with a crystal of iodine to magnesium turnings (5·0 g.) under dry ether (50 c.c.), and the mixture heated, with stirring, under reflux. A further 26 g. of the bromo-compound in dry ether (100 c.c.) were added dropwise during 2 hours; reflux and stirring were continued for a further 2 hours, most of the magnesium then dissolving. The mixture was cooled to −10° with stirring and a stream of dry carbon dioxide gas directed on the surface at such a rate as to keep the temperature below −2°. When the temperature dropped again an excess of sulphuric acid (25%) was added with cooling, the ethereal layer separated, and the aqueous phase extracted with ether (3 × 50 c.c.). The combined ethereal extracts were washed with sodium hydroxide solution (3 × 50 c.c.; 25%), and the alkaline extract was washed with ether (3 × 25 c.c.), boiled, cooled, and acidified to Congo-red with sulphuric acid (50%). The crude acid was crystallised from aqueous acetic acid, to give 2-methoxy-*p*-toluic acid (57%) as needles, m. p. 156°, undepressed by a specimen, m. p. 156°, prepared by methylation of 2-hydroxy-*p*-toluic acid (Perkin and Weizmann, *loc. cit.*) (Found: C, 65·0; H, 6·1. Calc. for $C_9H_{10}O_3$: C, 65·05; H, 6·1%). Light absorption: Max. at 212 (ε = 55,000), 245 (ε = 20,400), and 292 mμ (ε = 8000).

Demethylation. Anhydrous aluminium bromide (10 g.) in warm dry benzene (60 c.c.) was added to a solution of 2-methoxy-*p*-toluic acid (2·0 g.) in dry benzene (70 c.c.), and the solution refluxed for 4½ hours. Hydrochloric acid (100 c.c.; *d* 1·19) was added to the cooled solution, and 2-hydroxy-*p*-toluic acid (1·7 g.) isolated by ether-extraction, alkali-washing, and acidification. It separated from water (charcoal) as needles, m. p. 207—208°, undepressed by an authentic specimen (Found: C, 63·3; H, 5·5. Calc. for $C_8H_8O_3$: C, 63·15; H, 5·3%). Light absorption: Max. at 206 (ε = 46,500), 244 (ε = 12,000), and 298 mμ (ε = 4500).

3-Hydroxy-4-methylbenzyl Alcohol.—Commercial lithium aluminium hydride (10 g.) was refluxed with dry ether for 30 min., cooled to 15°, and treated with a solution of 2-hydroxy-*p*-toluic acid (6·0 g.) in dry ether (200 c.c.) added dropwise during 1 hour, with stirring. The mixture was then refluxed for 3 hours, cooled, and poured on ice. The mixture was acidified (Congo-red) with sulphuric acid (350 c.c.; 4N), and the aqueous phase saturated with sodium chloride and extracted with ether (4 × 200 c.c.) The combined ethereal solutions were washed with water (2 × 50 c.c.), dried (Na_2SO_4), and evaporated. The residual *3-hydroxy-4-methylbenzyl alcohol* crystallised from benzene as needles (4·7 g.; 86%), m. p. 102—103° (Found: C, 69·55; H, 7·5. $C_8H_{10}O_2$ requires C, 69·5; H, 7·3%). The compound sublimed readily at 90°/10^{-3} mm. and had light absorption: Max. at 220 (ε = 6300) and 278 mμ (ε = 2200). Attempts to carboxylate this compound by using potassium hydrogen carbonate in glycerol at 120—130°, 150°, 170°, or 190° for 4 hours with a stream of carbon dioxide were unsuccessful; starting material was recovered at the three lower temperatures and charring occurred at the highest. 3-Hydroxy-4-methylbenzyl alcohol was unchanged after 6 hours at 100° or 24 hours at 130° in an autoclave with water, potassium hydrogen carbonate, and carbon dioxide.

*3-Amino-2-methoxy-*p*-toluic Acid* (Me = 1).—Reduction of 2-methoxy-3-nitro-*p*-toluic

acid, prepared by nitration of 2-methoxy-*p*-toluic acid (Simonsen and Rau, *loc. cit.*), using ferrous sulphate and ammonia, gave a low yield in our hands. The following method proved satisfactory: sodium hydrosulphite (dithionite) (40 g.) was added in portions during 20 min. to a stirred solution of 2-methoxy-3-nitro-*p*-toluic acid (10 g.) in a solution of potassium hydroxide (10 g.) in water (100 c.c.), the temperature being kept below 40°. The solution was made acid (Congo-red) with dilute hydrochloric acid and stored overnight. The solid which separated was crystallised once from water, giving 3-amino-2-methoxy-*p*-toluic acid (7·5 g.) as needles, m. p. 161—162° (lit., 162°).

2-Amino-3-methoxy-4-methylbenzyl alcohol.—Commercial lithium aluminium hydride (2 g.) was heated under reflux with dry ether (70 c.c.) for 30 min., cooled, and treated with 3-amino-2-methoxy-*p*-toluic acid (1·0 g.) in dry ether (70 c.c.) dropwise during 30 min. The mixture was refluxed for 3 hours, cooled, poured on ice, and acidified (Congo-red) with sulphuric acid (90 c.c.; 4N). The solution was then made strongly alkaline with sodium hydroxide and extracted with ether (3 × 50 c.c.). The combined extracts were washed with water (25 c.c.), dried (Na_2SO_4), and evaporated to a dark brown oil which was extracted with boiling light petroleum (b. p. 40—60°) (8 × 50 c.c.). Concentration of the combined extracts to 150 c.c. and storage gave *2-amino-3-methoxy-4-methylbenzyl alcohol* (400 mg.) which separated from benzene–light petroleum (b. p. 40—60°) as needles, m. p. 48—49° (Found: C, 64·9; H, 7·6. $C_9H_{13}O_2N$ requires C, 64·65; H, 7·8%). Light absorption: Max. at 211 (ε = 26,000), 240 (ε = 6300), and 289 mμ (ε = 2100). The compound sublimed rapidly at 50°/10^{-3} mm.

7-Methoxy-6-methylphthalide.—A solution of 2-amino-3-methoxy-4-methylbenzyl alcohol (400 mg.) in hydrochloric acid (3 c.c.; *d* 1·19) and water (10 c.c.) was diazotised at 0° with sodium nitrite (0·4 g.) in water (5 c.c.). After the addition of urea the filtered solution was added to potassium cyanide (1·6 g.) and copper sulphate (1·4 g.) in water (20 c.c.) at 70°, heated on the steam-bath for 15 min., cooled, and extracted with ether (4 × 25 c.c.). The combined ethereal extracts were washed with water (25 c.c.), dried (Na_2SO_4), and evaporated. The residual oil was heated with potassium hydroxide solution (10 c.c.; 10%) under reflux for 2 hours. The solution was acidified (Congo-red) with hydrochloric acid (*d* 1·19), and the precipitated *7-methoxy-6-methylphthalide* crystallised from water as needles (0·2 g.), m. p. 120° (Found: C, 67·5; H, 5·8. $C_{10}H_{10}O_3$ requires C, 67·4; H, 5·7%). Light absorption: Max. at 213 (ε = 26,000), 237 (ε = 7500), and 295 mμ (ε = 2800). The compound sublimed rapidly at 80°/10^{-3} mm.

4-Chloromethyl-7-methoxy-6-methylphthalide.—The above phthalide (250 mg.) rapidly dissolved in hydrochloric acid (5 c.c.; *d* 1·19) and aqueous formaldehyde (3 c.c.; 40%) under reflux (45 min.), and an oil separated. The mixture was diluted with water (10 c.c.) and extracted with chloroform (5 × 10 c.c.), and the combined extracts were washed with water (10 c.c.), saturated sodium hydrogen carbonate solution (10 c.c.), and water (10 c.c.), and dried (Na_2SO_4). Removal of the chloroform gave a light yellow gum (250 mg.) which partly crystallised; the solid was separated with the aid of a little methanol and crystallised from ether–light petroleum (b. p. 40—60°) to give *4-chloromethyl-7-methoxy-6-methylphthalide* as needles, m. p. 88—90° (Found: C, 58·6; H, 5·2. $C_{11}H_{11}O_3Cl$ requires C, 58·3; H, 4·9%). Light absorption: Max. at 216 (ε = 29,400) and 298 (ε = 3000); inflexion at 240 mμ (ε = 7300).

4-Hydroxymethyl-7-methoxy-6-methylphthalide.—The crude chloromethyl compound (200 mg.) obtained after evaporation of the chloroform extract in the previous experiment was heated under reflux with sodium carbonate (0·5 g.) in water (5 c.c.) for 30 min. The solution was made acid (Congo-red) with dilute hydrochloric acid and extracted with chloroform (20 c.c.), and the chloroform extract was dried (Na_2SO_4) and evaporated. The solid residue crystallised from benzene, to give *4-hydroxymethyl-7-methoxy-6-methylphthalide* (150 mg.) as needles, m. p. 119° (Found: C, 63·5; H, 5·9. $C_{11}H_{12}O_4$ requires C, 63·45; H, 5·8%). Light absorption: Max. at 212 (ε = 31,000) 238 (ε = 6500), and 298 mμ (ε = 3000). A mixture of the compound with 7-methoxy-6-methylphthalide had m. p. 105—110°.

7-Methoxy-6-methylphthalide-4-carboxylic Acid.—A solution of 4-hydroxymethyl-7-methoxy-6-methylphthalide (50 mg.) in sulphuric acid (25 c.c.; N) at 70° was treated with aqueous potassium permanganate (7 c.c.; 1%). After 10 min. at 70° the solution was decolorised by sulphur dioxide and kept at 0° for 1 hour. The solid was separated and crystallised from aqueous ethanol, to give 7-methoxy-6-methylphthalide-4-carboxylic acid (25 mg.) as needles, m. p. 230—232°, undepressed when mixed with *iso*gladiolic acid (Found: C, 59·7; H, 4·6. Calc. for $C_{11}H_{10}O_5$: C, 59·5; H, 4·5%). Light absorption: Max. at 216 (ε = 33,000) and 298 (ε = 5000) inflexion at 244 mμ (ε = 9000)

The authors thank Professor F. S. Spring, F.R.S., for his kind encouragement, the Governors of The Royal Technical College for the award of the Nobel Scholarship (to J. J. B.), and Mr. John Blair, B.Sc., for some experimental assistance. The microanalyses were by Mr. Wm. McCorkindale and the ultra-violet absorption spectra were measured by Miss Norma Caramando.

THE ROYAL TECHNICAL COLLEGE, GLASGOW. [*Received, January 21st,* 1953.]