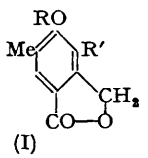
734. *Gladiolic Acid. Part IV.* Synthesis of 5-Methoxy-6-methylphthalide.*

By D. Gardner and John Frederick Grove.

The synthesis is described of 5-methoxy-6-methylphthalide, the methyl ether of a degradation product of gladiolic acid (Grove, *Biochem. J.*, 1952, **50**, 648).

The hydroxy-methyl-phthalide, m. p. 244°, obtained by decarboxylation of *iso*gladiolic acid (Grove, *Biochem. J.*, 1952, **50**, 648) and nor*iso*gladiolic acid (I; R = H, R′ = CO_2H) (Duncanson, Grove, and Zealley *) has now been shown to be 5-hydroxy-6-methylphthalide (I; R = R′ = H) by synthesis of the methyl ether. The method of synthesis is essentially that devised by Brown and Newbold (*J.*, 1953, 1285) for 7-methoxy-6-methylphthalide, and required as intermediate 5-hydroxy-2-nitro-*p*-toluic acid.†



(I)

Nitration of 3-hydroxy-*p*-toluic acid (Borsche and Böcker, *Ber.*, 1903, **36**, 4357) gives the 2 : 6-dinitro-compound, even under mild conditions and mononitration of 3-methoxy-*p*-toluic acid gives exclusively the 2-nitro-derivative (Simonsen and Rau, *J.*, 1921, **119**, 1339). However, by nitration of 3-hydroxy-*p*-tolunitrile Borsche and Böcker obtained two mononitro-compounds, m. p. 141—142° and 191—193°, believed to be the 3-hydroxy-2-nitro- and 5-hydroxy-2-nitro-*p*-tolunitrile respectively although their structures were not firmly established.

In the present investigation, nitration of 3-hydroxy-*p*-tolunitrile gave a mixture of two nitro-compounds, m. p. 144—145° and 210—211° respectively, whose orientation was established by hydrolysis to the corresponding toluic acids, the lower-melting isomer giving 3-hydroxy-2-nitro-*p*-toluic acid previously obtained by demethylation of its methyl ether, whose structure was proved by Simonsen and Rau. Catalytic reduction of 5-methoxy-2-nitro-*p*-toluic acid yielded the corresponding amine which furnished 2-amino-5-methoxy-4-methylbenzyl alcohol on further reduction with lithium aluminium hydride. Diazotisation, treatment with cuprous cyanide, and hydrolysis, without isolation of the intermediate nitrile, then gave the desired phthalide (I; R = Me, R′ = H).

Experimental

M. p.s are corrected. Microanalyses are by Messrs. W. Brown and A. G. Olney.

Nitration of 3-*Hydroxy*-p-*toluic Acid.*—The acid (1 g.) was added to nitric acid (*d* 1·42) as described below for 3-hydroxy-*p*-tolunitrile. Crystallisation of the product from ethanol furnished yellow needles, m. p. 215°, of 3-hydroxy-2 : 6-dinitro-*p*-toluic acid, identical (mixed m. p.) with a specimen prepared according to Borsche and Böcker's method (*loc. cit.*) (Borsche and Böcker give m. p. 200°) (Found: C, 39·7; H, 2·5; N, 11·6. Calc. for $C_8H_6O_7N_2$: C, 39·7; H, 2·5; N, 11·6%).

Nitration of 3-*Hydroxy*-p-*tolunitrile.*—The nitrile, m. p. 99° (1 g.; Borsche and Böcker, *loc. cit.*) was added in portions to nitric acid (*d* 1·42; 2 g.) at −5° with vigorous stirring. After 10 min. the mixture was poured over cracked ice (20 g.), and the solid collected and crystallised from ethanol, giving the fractions (i), m. p. 142—145° (370 mg.), (ii) m. p. 130—180° (140 mg.), (iii) m. p. 190—195° (280 mg.), and (iv) gum. Recrystallisation of (i) and (ii) from ethanol furnished 3-*hydroxy*-2-*nitro*-p-*tolunitrile* (410 mg., 31%), lemon-yellow needles, m. p. 144—145° (Found: C, 54·1; H, 3·3; N, 15·8. $C_8H_6O_3N_2$ requires C, 53·9; H, 3·4; N, 15·7%). Recrystallisation of (iii) from benzene, in which it was only sparingly soluble, furnished 5-*hydroxy*-2-*nitro*-p-*tolunitrile* (250 mg., 19%), pale yellow needles, m. p. 210—211° (decomp.) (Found: C, 54·0; H, 3·3; N, 15·4%). The 5-hydroxy-compound was readily soluble in ethanol and darkened appreciably on prolonged exposure to daylight. The yields (%) of the 3- and 5-hydroxy-compounds were unaltered in an experiment with 6 g. of 3-hydroxy-*p*-tolunitrile.

3-*Hydroxy*-2-*nitro*-p-*toluic Acid.*—(a) *By demethylation of* 3-*methoxy*-2-*nitro*-p-*toluic acid.* 3-Methoxy-2-nitro-*p*-toluic acid (0·1 g.; m. p. 172—173°) (Simonsen and Rau, *loc. cit.*, give m. p. 165—166°) and hydrobromic acid (*d* 1·25; 4 ml.) were heated under reflux for 40 min.

* Part III, preceding paper.

† Toluic acids are now numbered with CO_2H = 1 (see *J.*, 1952, 5088, footnote 13).

Crystallisation of the product from water and finally from benzene furnished *3-hydroxy-2-nitro-p-toluic acid*, lemon-yellow plates (56 mg.), m. p. 186—188° (Found: C, 48·6; H, 3·3; N, 7·0. $C_8H_7O_5N$ requires C, 48·7; H, 3·6; N, 7·1%).

(b) *By hydrolysis of 3-hydroxy-2-nitro-p-tolunitrile.* The nitrile (0·2 g.) was heated under reflux for 2 hr. with 2N-sodium hydroxide (5 ml.), and the dark solution acidified (Congo-red) and extracted with ether. Sublimation of the pitch-like extract at 120—130°/10^{-1} mm. yielded a lemon-yellow solid (0·14 g.; m. p. 164—170°) which crystallised from benzene in plates, m. p. 182—184° undepressed by the acid obtained as in (a).

5-Hydroxy-2-nitro-p-toluic Acid.—5-Hydroxy-2-nitro-*p*-tolunitrile (450 mg.) was heated under reflux for 10 hr. with 2N-sodium hydroxide (10 ml.). Acidification yielded a clear solution which furnished the crude *acid* as a brown solid (360 mg.; m. p. 150—170°) on ether-extraction and recovery. A portion (200 mg.) was sublimed at 130—140°/10^{-1} mm. and crystallised from toluene (50 ml.), forming yellow prisms (160 mg.), m. p. 182° depressed to 150° by the 3-hydroxy-isomer (Found: C, 48·8; H, 3·7; N, 7·1. $C_8H_7O_5N$ requires C, 48·7; H, 3·6; N, 7·1%). It was readily soluble in water, ethanol, acetic acid, acetone and ethyl acetate, but sparingly soluble in benzene.

Hydrolysis of the nitrile for 2 hr. gave mainly the corresponding *amide*, prisms, m. p. 221° (decomp.), from ether (Found: C, 49·1; H, 4·3. $C_8H_8O_4N_2$ requires C, 49·0; H, 4·1%).

Methylation of the toluic acid with methyl sulphate and alkali in the usual way and sublimation of the product at 145°/10^{-1} mm. followed by crystallisation from benzene gave the *methyl ether*, colourless prisms or needles, m. p. 172° depressed to 145° on admixture with the 3-hydroxy-isomer (Found: C, 50·85; H, 4·4; N, 6·7. $C_9H_9O_5N$ requires C, 51·2; H, 4·3; N, 6·6%).

2-Amino-5-methoxy-p-toluic Acid.—5-Methoxy-2-nitro-*p*-toluic acid (0·2 g.) in ethanol (10 ml.) was hydrogenated at 20° in the presence of a Raney nickel catalyst. Reduction ceased after the uptake of 3 mols. and after removal of the catalyst the product was recovered by evaporation. Sublimation at 130°/10^{-2} mm. and crystallisation from ethanol gave colourless prisms (130 mg.), m. p. 202° (decomp.) with darkening above 195°, of *2-amino-5-methoxy-p-toluic acid* (Found: C, 59·6; H, 5·9. $C_9H_{11}O_3N$ requires C, 59·7; H, 6·1%). It dissolved in 2N-hydrochloric acid, and an ethanol solution showed a violet fluorescence. It gave a transient green colour with ferric chloride in ethanol, changing on dilution with water to deep bluish-purple which soon faded to red-brown. The *acetate*, obtained by 1 hour's heating under reflux with acetic anhydride, crystallised from ethanol in colourless prisms, m. p. 208° (Found: C, 59·1; H, 6·0. $C_{11}H_{13}O_4N$ requires C, 59·2; H, 5·9%).

2-Amino-5-methoxy-4-methylbenzyl Alcohol.—The above aminotoluic acid (50 mg.) in ether (10 ml.) was added dropwise during 10 min. to lithium aluminium hydride (0·2 g.) in ether (10 ml.). After 3 hours' heating under reflux, excess of hydride was destroyed by water, and then 10% sodium hydroxide (25 ml.) was added. Extraction of the aqueous alkaline layer with ether (3 × 10 ml.) and recovery furnished a gum, purified by sublimation at 90°/10^{-1} mm. and crystallisation from light petroleum (b. p. 60—80°). The *2-amino-5-methoxy-4-methylbenzyl alcohol* (40 mg.) formed colourless needles, m. p. 112° (Found: C, 64·6; H, 7·6; N, 8·2. $C_9H_{13}O_2N$ requires C, 64·65; H, 7·8; N, 8·4%). It gave a green colour with ferric chloride in ethanol.

5-Methoxy-6-methylphthalide.—2-Amino-5-methoxy-4-methylbenzyl alcohol (40 mg.) in hydrochloric acid (0·5 ml.; *d* 1·18) and water (0·5 ml.) was diazotised at 0° with sodium nitrite (30 mg.) in water (0·5 ml.). The cold diazo-solution was added with stirring to a solution of potassium cyanide (0·16 g.) and cupric sulphate (0·14 g.) in water (2 ml.) at 80°, heated for 30 min. at 100°, cooled, and extracted with ether. The red-brown oil obtained on recovery was heated under reflux with 2N-sodium hydroxide (1 ml.) for 7 hr. Acidification (Congo-red), ether-extraction, and recovery yielded a gum, purified by sublimation at 100°/10^{-1} mm. The sublimate (6·5 mg.) crystallised from water in needles, m. p. 144°, of *5-methoxy-6-methylphthalide* (Found: C, 67·7; H, 6·0. $C_{10}H_{10}O_3$ requires C, 67·4; H, 5·7%). The m. p. was depressed to 115—120° on admixture with 6-methoxy-5-methylphthalide, m. p. 143—145°. The infra-red spectrum was identical with that of the methoxy-methyl-phthalide obtained by methylation of the decarboxylation product of nor*iso*gladiolic acid (Duncanson, Grove, and Zealley, *loc. cit.*). A mixed m. p. determination with the two specimens showed no depression.

IMPERIAL CHEMICAL INDUSTRIES LIMITED, BUTTERWICK RESEARCH LABORATORIES,
THE FRYTHE, WELWYN, HERTS. [*Received, July 28th*, 1953.]