Phthalaldehydes and Related Compounds. Part IV. Synthesis of Gladiolic Acid.*

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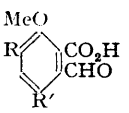
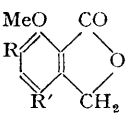
Gladiolic acid has been obtained by periodate oxidation of deoxygladiolic acid (4-formyl-7-methoxy-6-methylphthalide) (cf. *Chem. and Ind.*, 1953, 1151).

The structure of gladiolic acid, an antifungal metabolic product from *Penicillium gladioli* Machacek, is represented by (I; R = Me, R′ = CHO) tautomeric with (III; R = Me, R′ = CHO, R″ = H) as a result of analytical and degradation evidence (Grove, *Biochem. J.*, 1952, **50**, 648; *J.*, 1952, 3345; Raistrick and Ross, *Biochem. J.*, 1952, **50**, 635). In Part III *



(I)



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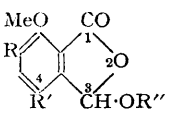

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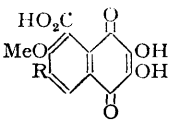

(IV)

we described a synthesis of deoxygladiolic acid (II; R = Me, R′ = CHO) (Grove, *Biochem. J.*, 1952, 648) by the action of *N*-bromosuccinimide on 4-hydroxymethyl-7-methoxy-6-methylphthalide (II; R = Me, R′ = CH_2·OH), followed by hydrolysis (Brown and Newbold, *J.*, 1953, 1285). An attempt to convert (II; R = Me, R′ = CH_2Cl) into gladiolic acid by the same reagent (*idem*, *J.*, 1953, 3648) was unsuccessful, the products being deoxygladiolic acid and *iso*gladiolic acid (II; R = Me, R′ = CO_2H) (Grove, *loc. cit.*); a trace of gladiolic acid, insufficient for isolation, was also formed. Thus negligible attack by *N*-bromosuccinimide on the methylene group of (II; R = Me, R′ = CH_2Cl) occurred, in marked contrast to the behaviour of 4-chloromethylmeconin (II; R = OMe, R′ = CH_2Cl) which under these conditions gave a good yield of 3-formylopianic acid (I; R = OMe, R′ = CHO) tautomeric with (III; R = OMe, R′ = CHO, R″ = H) (Brown and Newbold, *J.*, 1952, 4878).

Dihydrogladiolic acid, also produced by *Penicillium gladioli* Machacek, has been shown to be (I; R = Me; R′ = CH_2·OH), tautomeric with (III; R = Me, R′ = CH_2·OH,

* Part III, *J.*, 1953, 3648.

R'' = H) (Duncanson, Grove, and Zealley, *J.*, 1953, 3637; Brown and Newbold, *J.*, 1953, 3648). Raistrick and Ross (*loc. cit.*) oxidised it by periodate to gladiolic acid, *i.e.*, a phthalaldehyde was formed from an *o*-hydroxymethylbenzaldehyde. Since deoxygladiolic acid (II; R = Me, R' = CHO) has the related 4-formylphthalide system, attention was turned to periodate oxidation of this compound. Prolonged oxidation with sodium metaperiodate in boiling dilute sulphuric acid partly converted it into gladiolic acid and *iso*gladiolic acid. Deoxygladiolic acid (73%) was recovered, and the gladiolic acid was isolated as its hydrate triacetate [III; R = Me, R' = $CH(OAc)_2$, R'' = Ac] which was obtained in 10% yield calculated on the deoxygladiolic acid converted. The triacetate was smoothly hydrolysed to gladiolic acid by hot mineral acid. Both the latter and the triacetate were indistinguishable from the natural material (supplied by Mr. J. F. Grove) and its derivative respectively. *iso*Gladiolic acid was isolated, in 40% yield calculated on the deoxygladiolic acid converted, from the acid fraction of the acetylation mixture. Gladiolic acid has been transformed into dihydrogladiolic acid (I; R = Me, R' = CH_2·OH) by successive acetylation [to give (III; R = Me, R' = CHO, R'' = Ac)], hydrogenation [to (III; R = Me, R' = CH_2·OH, R'' = Ac)], and hydrolysis of the 3-acetoxy-group (Duncanson, Grove, and Zealley, *loc. cit.*); our synthesis of gladiolic acid is therefore a formal synthesis of dihydrogladiolic acid.

Oxidation of 4-formylmeconin (II; R = OMe, R' = CHO), whose preparation was described in Part III, with periodate proceeded much more rapidly than that of deoxygladiolic acid; 71% of the material was recovered and 3-formylopianic acid (I; R = OMe, R' = CHO) was readily isolated in 40% yield calculated on the 4-formylmeconin transformed. This again illustrates the greater reactivity of the lactone methylene group towards an oxidising agent in the dimethoxy-series. Presence of the phthalaldehyde system in 3-formylopianic acid has been proved directly by reaction with glyoxal in mildly alkaline solution in the presence of cyanide, which gave 2 : 3-dihydroxy-6 : 7-dimethoxynaphtha-1 : 4-quinone-5-carboxylic acid (IV; R = OMe). This reaction of phthalaldehydes, to give *iso*naphthazarin derivatives, was developed by Weygand and his collaborators (*Ber.*, 1942, **75**, 625; 1943, **76**, 818; *Chem. Ber.*, 1947, **80**, 391). The preparation of the corresponding *iso*naphthazarin derivative (IV; R = Me) from gladiolic acid has been carried out independently (Weygand, Weber, and Grove, *Chem. and Ind.*, 1954, 106).

Experimental

Ultra-violet absorption spectra were determined in ethanol solution unless otherwise stated.

Gladiolic Acid Hydrate Triacetate.—Deoxygladiolic acid (300 mg.) (Brown and Newbold, *J.*, 1953, 3648) and sodium metaperiodate (3·0 g.) in N-sulphuric acid (20 c.c.) were refluxed for 40 hr. The cooled solution, which deposited crystals, was extracted with chloroform (3 × 25 c.c.), and the combined extracts were washed with water (20 c.c.), aqueous sodium hydrogen carbonate (3 × 20 c.c.; 10%), and water (20 c.c.) and dried (Na_2SO_4). Evaporation of the chloroform and crystallisation of the residue from benzene–light petroleum (b. p. 60—80°) gave deoxygladiolic acid (220 mg.) as needles, m. p. and mixed m. p. 173—174°. The combined sodium hydrogen carbonate extracts were acidified (Congo-red) with 3N-hydrochloric acid and extracted with chloroform (3 × 25 c.c.), and the combined chloroform extracts were washed with water (20 c.c.) and dried (Na_2SO_4). Evaporation of the chloroform gave a pale yellow solid (50 mg.) which gave a strong positive test for gladiolic acid (Grove, *Biochem. J.*, 1952, **50**, 648) with ammonia. The solid was heated on the steam-bath for 10 min. with acetic anhydride (2 c.c.) and sulphuric acid (1 drop; *d* 1·84), and the solution poured on crushed ice (5 g.); an oil separated, rapidly solidifying. This was extracted with chloroform (3 × 15 c.c.), the combined extracts were washed with aqueous sodium hydrogen carbonate (2 × 10 c.c.; 10%) (combined to give solution A) and with water (10 c.c.), dried (Na_2SO_4), and evaporated. Crystallisation of the residue from aqueous ethanol gave gladiolic acid hydrate triacetate (12 mg.) as needles, m. p. 131—132° undepressed on admixture with a specimen prepared from natural gladiolic acid (Found: C, 55·4; H, 5·1. Calc. for $C_{17}H_{18}O_9$: C, 55·7; H, 4·95%). Light absorption: Max. at 2140 (ε 37,000) and 2980 (ε 3100), inflexion at 2340 Å (ε 7000).

Gladiolic Acid.—The triacetate (19 mg.) was heated under reflux for 1 hr. with 2N-sulphuric acid (2·5 c.c.). The gladiolic acid which crystallised from the cooled solution recrystallised

from water as needles (11 mg.), m. p. 159—160° alone or mixed with a specimen of natural gladiolic acid kindly supplied by Mr. J. F. Grove (Found : C, 59·7; H, 4·8. Calc. for $C_{11}H_{10}O_5$: C, 59·5; H, 4·5%). Light absorption : Max. at 2140 (ε 18,500), 2710 (ε 6900) and 3040 Å (ε 3200). The 2 : 4-dinitrophenylhydrazone separated from glacial acetic acid as orange needles, m. p. and mixed m. p. 231—233° (decomp.).

iso*Gladiolic Acid.*—Solution A from the triacetate formation was acidified (Congo-red) with 3N-hydrochloric acid, and the solution extracted with chloroform (3 × 10 c.c.). The extracts were washed with water (10 c.c.) and dried (Na_2SO_4). Evaporation, and crystallisation of the resulting solid from aqueous ethanol, gave *iso*gladiolic acid (33 mg.) as needles, m. p. and mixed m. p. 232—233° (Found : C, 59·8; H, 4·8. Calc. for $C_{11}H_{10}O_5$: C, 59·5; H, 4·5%). Light absorption : Max. at 2180 (ε 33,000) and 3000 (ε 4400) and inflexion at 2450 Å (ε 8600).

3-*Formylopianic Acid.*—4-Formylmeconin (140 mg.) (Brown and Newbold, *loc. cit.*) was heated under reflux for 3 hr. with a solution of sodium metaperiodate (1·5 g.) in N-sulphuric acid (10 c.c.). The cooled solution was extracted with chloroform (3 × 15 c.c.), the combined extracts were washed with aqueous sodium hydrogen carbonate (2 × 10 c.c.; 10%) and water (10 c.c.), dried (Na_2SO_4), and evaporated, and the residue crystallised from methanol to give 4-formylmeconin (100 mg.) as blades, m. p. and mixed m. p. 193—195°. The combined aqueous washings were acidified (Congo-red) with 3N-hydrochloric acid and extracted with chloroform (3 × 20 c.c.). Evaporation of the dried (Na_2SO_4) chloroform extracts followed by crystallisation of the residue from water gave 3-formylopianic acid (17 mg.) as fine needles, m. p. 173—174° undepressed on admixture with a specimen prepared by Brown and Newbold (*J.*, 1952, 4878) (Found : C, 55·6; H, 4·5. Calc. for $C_{11}H_{10}O_6$: C, 55·5; H, 4·2%). Light absorption : Max. at 2110 (ε 21,000), 2750 (ε 4400) and 3190 Å (ε 3900). The pK_a value, 5·1, which we gave for this acid (*loc. cit.*) was determined in 50% aqueous ethanol; in water it has pK_a 4·3.

2 : 3-*Dihydroxy*-6 : 7-*dimethoxynaphtha*-1 : 4-*quinone*-5-*carboxylic Acid* (with J. Blair).—A mixture of 3-formylopianic acid (250 mg.), glyoxal sodium bisulphite (300 mg.), and potassium cyanide (50 mg.) was treated with 2N-sodium carbonate (7 c.c.), and the mixture kept for 1 hr. at room temperature with frequent shaking and free access of air. The deep purple solution was made acid (Congo-red) with 3N-hydrochloric acid, and the red solution kept at 0° for 2 days. 2 : 3-*Dihydroxy*-6 : 7-*dimethoxynaphtha*-1 : 4-*quinone*-5-*carboxylic acid* which separated crystallised from water as small red needles (100 mg.), m. p. 249—253° (decomp.) (Found, after drying at 110° for 5 hr. : C, 53·0; H, 3·7. $C_{13}H_{10}O_8$ requires C, 53·1; H, 3·4%). The compound is very soluble in methanol and ethanol, slightly soluble in ether, benzene, and chloroform, and insoluble in light petroleum. It dissolves in aqueous sodium hydroxide giving a blue solution, and in aqueous sodium hydrogen carbonate with effervescence to give a violet solution. Light absorption : in H_2O, max. at 2700 (ε 13,600), 2940 (ε 5700) and 4400 Å (ε 280); in 0·05N-NaOH, max. at 2160 (ε 34,000) and 5450 (ε 370), inflexion at 2450—2500 Å (ε 12,000).

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