## 472. *Phthalaldehydes and Related Compounds. Part VII.* Further Applications of the N-Bromosuccinimide Preparative Method.*

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A new synthesis of gladiolic acid from 5-methoxy-6-methylphthalan-4-carboxylic acid is described which uses the *N*-bromosuccinimide method. Opianic acid and 3-bromo- and 3-methyl-opianic acid have been similarly prepared from the corresponding phthalides, and 4 : 5-dimethoxyphthalaldehyde from 4 : 5-dimethoxyphthalyl alcohol.

ALTHOUGH gladiolic acid (I; R = Me, R' = H) † had been synthesised [1] by oxidation of 4-formyl-7-methoxy-6-methylphthalide (II; R = Me, R' = H, R'' = CHO) with periodate, the synthesis could not be achieved [2] from the analogous 4-chloromethyl compound (II; R = Me, R' = H, R'' = $CH_2Cl$) by treatment with *N*-bromosuccinimide and subsequent hydrolysis. The latter method had been effective [3] for the preparation of 3-formylopianic acid (I; R = OMe, R' = H) from 4-chloromethylmeconin (II; R = OMe, R' = H, R'' = $CH_2Cl$), but failed also for two other 4-chloromethylphthalides (II; R = OMe, R' = Me [4] or OMe, R'' = $CH_2Cl$). However, application of the *N*-bromosuccinimide method to phthalancarboxylic acids, which had previously been used [3,4] to convert the acids (III; R = OMe, R' = H, Me, or OMe) into the respective phthalaldehydecarboxylic acids (I; R = OMe, R' = H, Me or OMe), has now been successful for the synthesis of gladiolic acid.

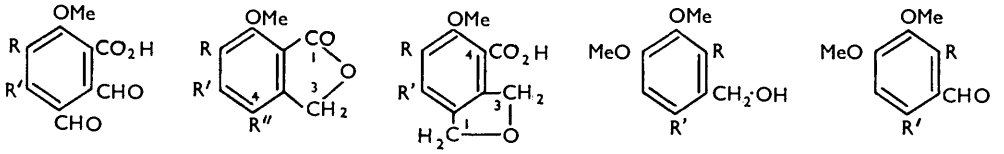
The requisite 5-methoxy-6-methylphthalan-4-carboxylic acid (III; R = Me, R' = H) was obtained by isomerisation of 4-hydroxymethyl-7-methoxy-6-methylphthalide [5] (II; R = Me, R' = H, R'' = $CH_2$·OH) with methanolic sodium methoxide, a further example of the hydroxymethylphthalide–phthalancarboxylic acid rearrangement.[3,4] Treatment of this acid (III; R = Me, R' = H) with *N*-bromosuccinimide and subsequent hydrolysis of the intermediate was followed by isolation of gladiolic acid as its hydrate triacetate (3-acetoxy-4-diacetoxymethyl-7-methoxy-6-methylphthalide). The last compound has been hydrolysed to gladiolic acid by hot mineral acid.[1] The yield of gladiolic acid hydrate triacetate was 11% as compared with 10% in the less convenient periodate method.[1]

Three further phthalaldehydic acids and one *o*-phthalaldehyde have also been prepared by the *N*-bromosuccinimide method. Of special interest was the preparation of opianic acid (5 : 6-dimethoxyphthalaldehydic acid) (V; R = $CO_2H$, R' = H) from meconin (II; R = OMe, R' = R'' = H) in spite of the presence of an easily substituted 4-position in the latter. 4-Bromomeconin (II; R = OMe, R' = H, R'' = Br), the product obtained when meconin is treated with bromine in acetic acid,[6] was also converted by *N*-bromosuccinimide into 3-bromo-opianic acid [7] (V; R = $CO_2H$, R' = Br), which was reduced by sodium borohydride back to the parent phthalide. The phthalide was also converted into 3-bromo-opianic acid by successive reaction with dimethylamine, oxidation by chromic

* Part VI, *J.*, 1954, 3935.
† For convenience only this tautomeric form is shown.

[1] Brown and Newbold, *J.*, 1954, 1076.
[2] *Idem*, *J.*, 1953, 3648.
[3] *Idem*, *J.*, 1952, 4878.
[4] Blair and Newbold, *J.*, 1954, 3935.
[5] Brown and Newbold, *J.*, 1953, 1285.
[6] Perkin and Robinson, *J.*, 1911, **99**, 775.
[7] Prinz, *J. prakt. Chem.*, 1881, **24**, 353; Wegscheider, *Monatsh.*, 1883, **4**, 267.

acid, and hydrolysis following the method of Blair, Brown, and Newbold.[8] 4-Methylmeconin[9] (II; R = OMe, R' = H, R'' = Me) was smoothly converted into 3-methylopianic acid (V; R = $CO_2H$, R' = Me) by the *N*-bromosuccinimide method. Both 4-methylmeconin and 3-methylopianic acid gave 3-methylhemipinic anhydride (3 : 4-dimethoxy-6-methylphthalic anhydride) on oxidation with alkaline permanganate. We have been unable to transform this anhydride into 3-methylhemipinic acid; the anhydride




separates on acidification of an alkaline solution of the acid. This behaviour is not without precedent since certain other 3 : 6-disubstituted phthalic acids pass readily into their anhydrides.[10]

*m*-Meconin (the lactone of IV; R = H, R' = $CO_2H$) was reduced by lithium aluminium hydride to 4 : 5-dimethoxyphthalyl alcohol (IV; R = H, R' = $CH_2$·OH), oxidation of which with *N*-bromosuccinimide, following the usual procedure, gave 4 : 5-dimethoxyphthalaldehyde (V; R = H, R' = CHO) in good yield. The phthalaldehyde was characterised by the formation of its *iso*naphthazarin derivative (2 : 3-dihydroxy-6 : 7-dimethoxy-1 : 4-naphthaquinone); the latter compound has been obtained [11] from the crude product of reduction of 4 : 5-dimethoxyphthalic bis-*N*-methylanilide by lithium aluminium hydride but detailed experimental directions were not given. In contrast with the behaviour of 4 : 5-dimethoxyphthalyl alcohol, the 3 : 4-dimethoxy-alcohol (IV; R = $CH_2$·OH, R' = H), readily obtained by reduction of meconin with lithium aluminium hydride, did not yield a crystalline product on reaction with *N*-bromosuccinimide and subsequent hydrolysis under the same conditions.

## Experimental

Ultraviolet absorption spectra were determined in EtOH solution unless otherwise stated; for other general directions see *J.*, 1954, 3935. All *N*-bromosuccinimide reactions were carried out with irradiation from an adjacent 60 w lamp.

*5-Methoxy-6-methylphthalan-4-carboxylic Acid* (III; R = Me, R' = H).—4-Hydroxymethyl-7-methoxy-6-methylphthalide (600 mg.) was heated under reflux for 7 hr. with a solution of methanolic sodium methoxide from sodium (328 mg.) and methanol (15 c.c.). Isolation of the product as described under the preparation of 5 : 6-dimethoxyphthalan-4-carboxylic acid [4] gave *5-methoxy-6-methylphthalan-4-carboxylic acid* (560 mg.) which separated from water as needles, m. p. 131—132° (Found: C, 63·8; H, 5·6%; equiv., 207. $C_{11}H_{12}O_4$ requires C, 63·45; H, 5·8%; equiv. 208). It had p$K_a$ 3·13. Light absorption: Max. at 2140 (ε 16,000) and 2970 (ε 3000), inflexion at 2350 Å (ε 6000).

*Gladiolic Acid Hydrate Triacetate.*—The foregoing acid (200 mg.) in dry benzene (12 c.c.) and dry carbon tetrachloride (12 c.c.) was heated under reflux for 15 min. with *N*-bromosuccinimide (385 mg.). The cooled solution was filtered and the filtrate evaporated under reduced pressure, to yield a brown oil which was heated on the steam-bath with water (10 c.c.) for 1½ hr. with frequent shaking. The cooled solution was extracted with chloroform (3 × 25 c.c.), and the combined extracts were washed with 10% aqueous sodium hydrogen carbonate (3 × 50 c.c.). The combined aqueous washings were acidified and the crude gladiolic acid was isolated and converted [1] into the hydrate triacetate, which separated from aqueous ethanol as needles (39 mg.), m. p. and mixed m. p. 130—131° (lit.,[1] m. p. 131—132°) (Found: C, 55·6; H, 5·3.

[8] Blair, Brown, and Newbold, *J.*, 1955, 708.
[9] Manske and Ledingham, *Canad. J. Res.*, 1944, **22**, *B*, 115.
[10] Freund and Fleischer, *Annalen*, 1916, **411**, 14; Alder and Vogt, *ibid.*, 1951, **571**, 137; Parker and Goldblatt, *J. Amer. Chem. Soc.*, 1950, **72**, 2151; Graves and Adams, *ibid.*, 1923, **45**, 2439; Helferich and Bodenbender, *Ber.*, 1923, **56**, 1112.
[11] Weygand, Eberhardt, Linden, Schäfer, and Eigen, *Angew. Chem.*, 1953, **65**, 525.

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 3400), inflexion at 2320 Å (ε 9000).

4 : 5-*Dimethoxyphthalyl Alcohol.*—*m*-Meconin (2·8 g.) in tetrahydrofuran (30 c.c.) was added during 15 min. to a refluxing part-solution of lithium aluminium hydride (1·5 g.) in tetrahydrofuran (80 c.c.) and refluxing was continued for 4 hr. The cooled mixture was treated with ice, the organic layer separated, and the aqueous phase extracted with ether (100 c.c.). The combined organic layers were dried ($Na_2SO_4$) and evaporated under reduced pressure, to give a gum which crystallised from benzene, yielding 4 : 5-*dimethoxyphthalyl alcohol* (2·01 g.) as needles, m. p. 111° (Found: C, 60·7; H, 7·4. $C_{10}H_{14}O_4$ requires C, 60·6; H, 7·1%). Light absorption: Max. at 2100 (ε 24,600), 2350 (ε 10,200) and 2870 Å (ε 2900).

3 : 4-*Dimethoxyphthalyl Alcohol.*—Meconin (10 g.) was reduced as in the preceding experiment, to 3 : 4-*dimethoxyphthalyl alcohol* (7·0 g.) which separated from benzene–light petroleum (b. p. 60—80°) as needles, m. p. 68° (Found: C, 60·4; H, 7·5. $C_{10}H_{14}O_4$ requires C, 60·6; H, 7·1%). Light absorption: Max. at 2080 (ε 20,400), 2240 (ε 7700), and 2800 Å (ε 2000). The *diacetate*, prepared by the action of acetic anhydride–pyridine at room temperature for 5 days, separated from light petroleum (b. p. 60—80°) as needles, m. p. 58° (Found: C, 59·75; H, 6·55. $C_{14}H_{18}O_6$ requires C, 59·6; H, 6·4%). Light absorption: Max. at 2080 (ε 21,500), 2300 (ε 7100), and 2820 Å (ε 2200).

4 : 5-*Dimethoxyphthalaldehyde.*—4 : 5-Dimethoxyphthalyl alcohol (114 mg.) and *N*-bromosuccinimide (2·1 mols.) in benzene (10 c.c.) and carbon tetrachloride (30 c.c.) were refluxed for 15 min., during which a transient red colour appeared. The mixture was cooled, filtered, and evaporated under reduced pressure and the residual gum heated with water (40 c.c.) for ¾ hr. on the steam-bath with stirring. The solution was extracted with chloroform (2 × 25 c.c.), and the combined extracts were washed with 10% aqueous sodium hydrogen carbonate (20 c.c.) and dried ($Na_2SO_4$). Removing the solvent and crystallising the residue from benzene–light petroleum (b. p. 60—80°) provided 4 : 5-*dimethoxyphthalaldehyde* (80 mg.) as needles, m. p. 165° (Found: C, 62·0; H, 5·5. $C_{10}H_{10}O_4$ requires C, 61·85; H, 5·2%). Light absorption: Max. at 2050 (ε 6500), 2520 (ε 28,000), and 3200 Å (ε 7800). Acidification (Congo-red) of the sodium hydrogen carbonate washings with 5N-hydrochloric acid and isolation by chloroform gave *m*-opianic acid (20 mg.) which separated from water as needles, m. p. and mixed m. p. 185° (lit.,[12] m. p. 187—188°).

2 : 3-*Dihydroxy*-6 : 7-*dimethoxy*-1 : 4-*naphthaquinone.*—A mixture of 4 : 5-dimethoxyphthalaldehyde (120 mg.), glyoxal sodium hydrogen sulphite (150 mg.) and potassium cyanide (25 mg.) was treated with 2N-sodium carbonate (3 c.c.) and kept at 20° for 2 hr. with constant shaking and free access to air. The deep blue solution was made acid (Congo-red) with 3N-hydrochloric acid, and the resulting red solution kept overnight at 0°. The product (40 mg.) which separated crystallised from water as needles, m. p. 260° (decomp.) (lit.,[11] m. p. 268°) (Found: C, 57·3; H, 4·5. Calc. for $C_{12}H_{10}O_6$: C, 57·6; H, 4·0%). Light absorption: in water, max. at 2030 (ε 40,500), 2600 (ε 38,000), and 3160 (ε 10,900) and inflexion at 2100—2160 Å (ε 10,900); in 0·05N-sodium hydroxide, max. at 2160 (ε 18,000), 2370 (ε 18,000), and 2850 (ε 7000) and inflexion at 3050—3200 Å (ε 5000).

*Opianic Acid.*—Meconin (500 mg.) in benzene (12 c.c.) and carbon tetrachloride (12 c.c.) was refluxed with *N*-bromosuccinimide (1·69 g., 1·5 mols.). The succinimide was removed, the filtrate evaporated, and the remaining gum heated with water (50 c.c.) on the steam-bath with stirring for ½ hr. The solid which separated on cooling crystallised from water, to give opianic acid (300 mg.) as needles, m. p. and mixed m. p. 147° (Found: equiv., 215. Calc. for $C_{10}H_{10}O_5$: equiv., 210).

3-*Bromo-opianic Acid.*—(*a*) Under the same conditions as in the preceding experiment 4-bromomeconin [6] (500 mg.) gave 3-bromo-opianic acid (280 mg.) which separated from water as needles, m. p. and mixed m. p. 202° (lit.,[7] m. p. 204°) (Found: C, 41·5; H, 3·4. Calc. for $C_{10}H_9O_5Br$: C, 41·5; H, 3·1%). Light absorption in 0·05N-NaOH: Max. at 2380 (ε 19,000) and 2860 Å (ε 14,000).

(*b*) 4-Bromomeconin (300 mg.) was heated at 80° in an autoclave with dimethylamine (35 c.c.) and ethanol (30 c.c.) for 3 hr. The mixture was then treated according to Blair, Brown, and Newbold [8] involving oxidation and hydrolysis, to give 3-bromo-opianic acid (120 mg.) as needles, m. p. and mixed m. p. 204°.

4-*Bromomeconin.*—A solution of 3-bromo-opianic acid (100 mg.) in saturated aqueous sodium hydrogen carbonate (10 c.c.) was kept overnight at room temperature with sodium borohydride

[12] Brown and Newbold, *J.*, 1952, 4397.

(100 mg.). The crystalline precipitate obtained on acidification with 5N-hydrochloric acid was once recrystallised from ethanol, to give 4-bromomeconin (90 mg.) as needles, m. p. and mixed m. p. 176°.

3-*Methylopianic Acid* (3 : 4-*Dimethoxy*-6-*methylphthalaldehydic Acid*).—4-Methylmeconin [9] (150 mg.) in benzene (12 c.c.) and carbon tetrachloride (12 c.c.) was refluxed for 1½ hr. with *N*-bromosuccinimide (164 mg., 1·3 mols.). Filtration, evaporation, and aqueous hydrolysis for 1½ hr., followed by isolation of the product by chloroform and purification through aqueous sodium hydrogen carbonate, gave 3-*methylopianic acid* (85 mg.) as needles, m. p. 191—191·5° (Found : C, 58·7; H, 5·4. $C_{11}H_{12}O_5$ requires C, 58·9; H, 5·4%). Light absorption in water : Max. at 2130 (ε 29,000) and 3120 (ε 3300), and inflexion at 2490 Å (ε 4800).

3-*Methylhemipinic Anhydride* (3 : 4-*Dimethoxy*-6-*methylphthalic Anhydride*).—(*a*) 4-Methylmeconin (200 mg.) was dissolved in hot 2N-sodium hydroxide (10 c.c.), and the solution cooled, treated with 5% aqueous potassium permanganate (17·6 c.c.), and heated on the steam-bath for 10 min. After addition of methanol the mixture was cooled and filtered from manganese dioxide. The filtrate and washings were concentrated under reduced pressure to *ca.* 5 c.c. and acidified (Congo-red) with hydrochloric acid (*d* 1·16). After being kept overnight the solid which had separated was collected and crystallised from aqueous ethanol, to give 3-*methylhemipinic anhydride* (102 mg.) as needles, m. p. 186—187° (Found : C, 59·45; H, 4·8. $C_{11}H_{10}O_5$ requires C, 59·5; H, 4·5%).

(*b*) By the same method 3-methylopianic acid (186 mg.) gave 3-methylhemipinic anhydride (105 mg.), needles, m. p. 186—187° alone or mixed with preparation (*a*).

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