951. *Phthalaldehydes and Related Compounds. Part I. The Preparation of 3-Formylopianic Acid.*

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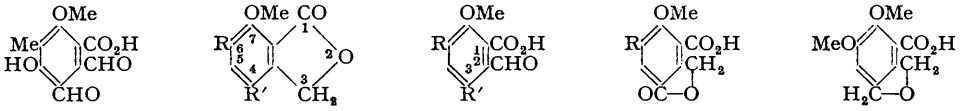
Chloromethylation of meconin (II; R = OMe, R′ = H) gives 4-chloromethylmeconin (II; R = OMe, R′ = CH_2Cl) which on treatment with *N*-bromosuccinimide followed by hydrolysis produces 3-formylopianic acid (III; R = OMe, R′ = CHO). Some reactions of the latter compound are discussed and compared with those of the mould product, gladiolic acid (III; R = Me, R′ = CHO).

Recently Raistrick and Ross (*Biochem. J.*, 1952, **50**, 635) and Grove (*ibid.*, p. 648) elucidated the structure of gladiolic acid (III; R = Me, R′ = CHO),* a metabolic product of *Penicillium gladioli*. The vicinal carboxy-*o*-phthalaldehyde system is found also in cyclopaldic acid (I) obtained from culture fluids of *Penicillium cyclopium* Westling (Birkinshaw, Raistrick, Ross, and Stickings, *ibid.*, p. 610). In view of our interest in the closely related fields of phthalaldehydic acids and phthalides (see Dijksman and Newbold, *J.*, 1951, 1213; 1952, 13; Brown and Newbold, *J.*, 1952, 4397) our attention was turned to the possibility of elaborating the vicinal carboxy-*o*-phthalaldehyde system from the readily available opianic acid (III; R = OMe, R′ = H). This involved the preparation of 3-formylopianic acid (III; R = OMe, R′ = CHO).

4-Chloromethylmeconin (II; R = OMe, R′ = CH_2Cl) was used as the starting material. Manske and Ledingham (*Canad. J. Res.*, 1944, **22**, *B*, 115) obtained it by the action of formaldehyde and hydrochloric acid on *o*-veratric acid (2 : 3-dimethoxybenzoic acid) and proved its structure by reduction to 4-methylmeconin (II; R = OMe, R′ = Me) which was synthesised by an unambiguous route. *o*-Veratric acid being somewhat inaccessible, the chloromethylation of meconin (II; R = OMe, R′ = H), obtained in good yield by reduction of opianic acid by sodium amalgam, was examined and found to proceed in 50% yield and to give the 4-chloromethylmeconin prepared by Manske and Ledingham (*loc. cit.*). Treatment of this meconin with three mols. of *N*-bromosuccinimide in carbon



(I) (II) (III) (IV) (V)

tetrachloride (cf. Brown and Newbold, *loc. cit.*) followed by hot water gave 3-formylopianic acid (III; R = OMe, R′ = CHO), which titrated as a monobasic acid, pK_a 5·1, and gave only a mono-2 : 4-dinitrophenylhydrazone. 3-Formylopianic acid gives a number of characteristic colour tests (see Experimental) also given by gladiolic acid (Raistrick and Ross, *loc. cit.*; Grove, *loc. cit.*).

Another possible route to 3-formylopianic acid appeared to be the direct oxidation of 4-hydroxymethylmeconin (II; R = OMe, R′ = CH_2·OH) readily obtained by hydrolysis of 4-chloromethylmeconin (II; R = OMe, R′ = CH_2Cl). Oppenauer oxidation of the former compound with benzophenone as hydrogen acceptor gave an isomeric acidic product, $C_{11}H_{12}O_5$, later shown to be obtained by refluxing 4-hydroxymethylmeconin

* For brevity the other tautomeric form of compounds having the vicinal carboxy-*o*-phthalaldehyde system has been omitted.

in benzene with aluminium *tert.*-butoxide alone. We formulate it as 5 : 6-dimethoxyphthalan-4-carboxylic acid (1 : 3-dihydro-5 : 6-dimethoxybenzo[*c*]furan-4-carboxylic acid) (V) since it is stable to alkali but isomerised by acid to 4-hydroxymethylmeconin, properties which would be expected of an ether. (V) formed a methyl ester and was reduced to 4-methylmeconin (II; R = OMe, R′ = Me) by the Clemmensen procedure. Reaction of (V) with two molecular proportions of *N*-bromosuccinimide followed by hydrolysis gave 3-formylopianic acid (III; R = OMe, R′ = CHO).

Heating 3-formylopianic acid with sodium hydroxide solution converted it into an isomeric monobasic acid, which we regard as meconin-4-carboxylic acid (II; R = OMe, R′ = CO_2H) since it is also formed by the oxidation of 4-hydroxymethylmeconin (II; R = OMe, R′ = CH_2·OH) with neutral permanganate. Gladiolic acid (III; R = Me, R′ = CHO) on similar treatment gives *iso*gladiolic acid (Raistrick and Ross, *loc. cit.*; Grove, *loc. cit.*) which is formulated by Grove as (II; R = Me, R′ = CO_2H) though he does not entirely discount the structure (IV; R = Me) in which lactonization has proceeded in the alternative direction. We believe that the formation of (IV; R = OMe) in our oxidation of 4-hydroxymethylmeconin is excluded because the alkalinity of the medium is insufficient to open the lactone ring in (II; R = OMe, R′ = CO_2H); Stevens and Robertson's observation (*J.*, 1927, 2790) that the oxidation of α-6-hydroxymethylpiperonylcinnamolactone under identical conditions gives 5 : 6-methylenedioxyphthalide which separates directly from the reaction mixture would support this hypothesis; in addition, meconin-4-carboxylic acid titrates sharply in the cold as a monobasic acid, indicating that the stability of the lactone ring has not been lessened by the proximity of the carboxyl group.

The ultra-violet absorption spectra of gladiolic and *iso*gladiolic acid are compared with those of 3-formylopianic and meconin-4-carboxylic acid in the Table.

Compound	Solvent	Max. (mμ) and $\varepsilon_{max.}$
3-Formylopianic acid [1]	H_2O	278 (ε = 4300), 324 (ε = 2800)
	0·1N-NaOH	284 (ε = 2500)
Gladiolic acid [2]	H_2O	269 (ε = 11,000), 307 (ε = 4500)
	0·1N-NaOH	275 (ε = 3400), 343 (ε = 6600)
Meconin-4-carboxylic acid [1]	EtOH	218 (ε = 27,600), 316 (ε = 6000)
*iso*Gladiolic acid [2]	EtOH	298 (ε = 5350)

[1] This paper. [2] Grove (*loc. cit.*).

The properties and reactions of 3-formylopianic acid discussed above support the formulation of gladiolic acid by Raistrick and Ross (*loc. cit.*) and Grove (*loc. cit.*) as (III; R = Me, R′ = CHO).

Experimental

Meconin.—No details are given by Matthiessen and Foster (*J.*, 1863, **16**, 342) for the preparation of this compound by sodium amalgam reduction of opianic acid. The following procedure was used: Opianic acid (65 g.) in 2N-sodium hydroxide (150 c.c.) was stirred for 3 hours with sodium amalgam (650 g.; 3½%) and left overnight. The aqueous phase was acidified (Congo-red), and extracted with chloroform (3 × 100 c.c.), and the combined extracts were washed with sodium hydrogen carbonate solution (2 × 100 c.c.; 10%), then with water (100 c.c.), and dried (Na_2SO_4). Removal of the chloroform and crystallisation from ethanol gave meconin (47 g.) as needles, m. p. 101—103°. Light absorption in ethanol: Max. at 213 (ε = 25,000) and 308 mμ (ε = 3800).

4-*Chloromethylmeconin.*—Meconin (12·0 g.) was heated under reflux for 45 minutes with hydrochloric acid (50 c.c.; *d*, 1·19) and formaldehyde solution (30 c.c.; 40%). The mixture was diluted with water (50 c.c.) and extracted with chloroform (3 × 50 c.c.). The combined chloroform extracts were washed with water (50 c.c.), sodium hydrogen carbonate solution (50 c.c.; 10%), and water (50 c.c.) and dried (Na_2SO_4). Evaporation and crystallisation from ethanol gave 4-chloromethylmeconin (6·0 g.) as needles, m. p. 104—106°, undepressed by a specimen, m. p. 104—106°, prepared from *o*-veratric acid after Manske and Ledingham (*loc. cit.*) who give m. p. 106° (Found: C, 54·8; H, 4·9. Calc. for $C_{11}H_{11}O_4Cl$: C, 54·4; H, 4·6%). Light absorption in ethanol: Max. at 215 (ε = 28,000) and 315 mμ (ε = 4850).

4-*Hydroxymethylmeconin.*—4-Chloromethylmeconin (1·0 g.) was heated under reflux with a solution of anhydrous sodium carbonate (1·0 g.) in water (10 c.c.) for 30 minutes. The solution

was acidified (Congo-red) and extracted with chloroform (3 × 15 c.c.), and the combined extracts were washed with water and dried (Na_2SO_4). Removal of the chloroform gave 4-*hydroxymethylmeconin* which crystallised from benzene as needles (750 mg.), m. p. 130—132° (Found: C, 59·2; H, 5·6. $C_{11}H_{12}O_5$ requires C, 58·9; H, 5·4%). The compound sublimes rapidly at 125°/10^{-3} mm. and in ethanol has absorption max. at 214 (ε = 29,400) and 312 mμ (ε = 4550). 4-Hydroxymethylmeconin was quantitatively recovered after 2 hours in boiling 3N-sodium hydroxide. The *acetate* prepared by using acetic anhydride–pyridine at room temperature overnight separated from water as needles, m. p. 112—113° (Found: C, 59·0; H, 5·45. $C_{13}H_{14}O_6$ requires C, 58·6; H, 5·3%).

5 : 6-*Dimethoxyphthalan*-4-*carboxylic Acid*.—4-Hydroxymethylmeconin (2·5 g.) in dry benzene (50 c.c.) was heated under reflux for 18 hours with aluminium *tert*.-butoxide (2·5 g.). The filtered mixture was extracted with 0·5N-sodium hydroxide solution (3 × 30 c.c.), the combined extracts were acidified (Congo-red), and the precipitate was extracted with chloroform (3 × 20 c.c.). After being washed with water (25 c.c.) the chloroform extract was evaporated and the solid residue crystallised from water, to give 5 : 6-*dimethoxyphthalan*-4-*carboxylic acid* (1·5 g.) as fine needles, m. p. 148—150° (Found: C, 59·2; H, 5·5; *C*-Me, 0·0%; equiv., 230. $C_{11}H_{12}O_5$ requires C, 58·9; H, 5·4; *C*-Me, 6·7%; equiv., 224). Light absorption in ethanol: Max. at 213 (ε = 21,000) and 306 mμ (ε = 3300). The compound dissolves in cold saturated sodium hydrogen carbonate solution with effervescence. It was unaffected when heated on the steam-bath with 15% aqueous sodium hydroxide for 2 hours but in boiling 5N-hydrochloric acid was converted in good yield into 4-hydroxymethylmeconin, m. p. and mixed m. p. 130—131° (Found: C, 58·8; H, 5·7%). The *methyl* ester, formed by ethereal diazomethane, separated from aqueous ethanol as needles, m. p. 90°, which sublimed readily at 85°/10^{-3} mm. (Found: C, 60·7; H, 6·2. $C_{12}H_{14}O_5$ requires C, 60·5; H, 5·9%). Light absorption in ethanol: Max. at 214 (ε = 23,000) and 310 mμ (ε = 4300).

4-*Methylmeconin*.—Granulated zinc (5·0 g.) was shaken for 5 minutes with mercuric chloride (0·5 g.) in hydrochloric acid (0·25 c.c.; *d*, 1·19) and water (5 c.c.), and the solution decanted off and rejected. Water (4 c.c.), hydrochloric acid (5 c.c.; *d*, 1·19), and 5 : 6-dimethoxyphthalan-4-carboxylic acid (180 mg.) were added and the mixture was heated under reflux for 5 hours. The solution was decanted from zinc and extracted with chloroform (3 × 20 c.c.). The extract was dried (Na_2SO_4) and evaporated under reduced pressure. The residual 4-methylmeconin crystallised from aqueous ethanol as needles (150 mg.) (Found: C, 63·7; H, 6·0; *C*-Me, 7·1. Calc. for $C_{11}H_{12}O_4$: C, 63·45; H, 5·8; *C*-Me, 7·2%), m. p. 125—127° undepressed when mixed with a specimen, m. p. 125—127° (lit., m. p. 127°) prepared after Manske and Ledingham (*loc. cit.*). Light absorption in ethanol: Max. at 214 (ε = 18,900) and 310 mμ (ε = 3300).

3-*Formylopianic Acid*.—(*a*) A solution of 4-chloromethylmeconin (2·0 g.) in carbon tetrachloride (100 c.c.) was heated under reflux with *N*-bromosuccinimide (4·4 g.) for 1 hour with irradiation from a 60-w. lamp placed close to the flask. Solvent was removed under reduced pressure from the filtered mixture and the residual oil heated with water (250 c.c.) on the steam-bath for 1 hour with stirring. After being kept overnight at room temperature the solid (1·3 g.; m. p. 163—165°) which separated was collected and crystallised twice from water (charcoal), to give 3-*formylopianic acid* as needles, m. p. 176° (Found: C, 55·2; H, 4·5%; equiv., 236. $C_{11}H_{10}O_6$ requires C, 55·5; H, 4·2%; equiv., 238). Light absorption in ethanol: Max. at 212 (ε = 18,300), 273 (ε = 4200) and 320 mμ (ε = 3800).

(*b*) To a solution of 5 : 6-dimethoxyphthalan-4-carboxylic acid (2·0 g.) in benzene (150 c.c.) and carbon tetrachloride (150 c.c.) was added *N*-bromosuccinimide (3·18 g.; 2 mols.) and the mixture heated under reflux with irradiation as above for 10 minutes. The mixture was then treated as in (*a*), to give 3-formylopianic acid (1·0 g.) as needles, m. p. 175—176° (from water; charcoal) alone or mixed with preparation (*a*) (Found: C, 55·6; H, 4·3%). The compound dissolves in cold saturated aqueous sodium hydrogen carbonate with effervescence and gives a green-brown colour with aqueous ammonia (*d*, 0·88). It does not reduce Fehling's solution or Schiff's reagent but reduces hot ammoniacal silver nitrate; it gives a greenish-yellow solution in cold or warm sulphuric acid (*d*, 1·84), and a solution in technical benzene (but not pure benzene) gives a red-colour at the interface with sulphuric acid (*d*, 1·84). 3-Formylopianic acid is soluble in ethanol but sparingly so in ether, chloroform, or benzene. The 2 : 4-*dinitrophenylhydrazone* separated from 2-methoxyethanol as orange needles, m. p. 254—255° (decomp.) (Found: N, 12·9. $C_{17}H_{14}O_9N_4$ requires N, 13·4%).

Meconin-4-*carboxylic Acid*.—(*a*) 3-Formylopianic acid (500 mg.) in 3N-sodium hydroxide solution (25 c.c.) was refluxed for 30 minutes. The solution was acidified (Congo-red) and the precipitate crystallised from aqueous ethanol, to give *meconin*-4-*carboxylic acid* as needles, m. p.

219—221° (decomp.) (Found: C, 55·7; H, 4·4%; equiv., 232. $C_{11}H_{10}O_6$ requires C, 55·5; H, 4·2%; equiv., 238). The compound dissolved in sodium hydrogen carbonate solution with effervescence.

(*b*) A solution of 4-hydroxymethylmeconin (500 mg.) in acetone (20 c.c.) at 60° was treated during 5 minutes, with shaking, with potassium permanganate (1·0 g.) and magnesium sulphate (1·0 g.) in water (20 c.c.), added in portions. The solution was rapidly heated to boiling and filtered. The filtrate was cleared by sulphur dioxide, concentrated, and extracted with chloroform (3 × 25 c.c.). The combined extracts were washed with saturated sodium hydrogen carbonate solution (3 × 20 c.c.) and the combined washings acidified (Congo-red). Meconin-4-carboxylic acid (250 mg.), isolated *via* chloroform, separated from aqueous ethanol as needles, m. p. 220—222° (decomp.) alone or mixed with preparation (*a*) (Found: C, 55·6; H, 4·3%).

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