Phthalaldehydes and Related Compounds. Part VI. Further Studies on Vicinal Carboxyphthalaldehydes.*

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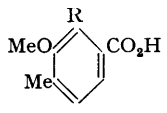
The syntheses of 3-formyl-4-methylopianic acid and 3-formyl-4-methoxyopianic acid by the action of *N*-bromosuccinimide on the corresponding substituted 5 : 6-dimethoxyphthalan-4-carboxylic acids, obtained respectively from 5-methylmeconin and 5 : 6 : 7-trimethoxyphthalide, are described. A more detailed examination of the 4-hydroxymethylphthalide–carboxyphthalan rearrangement (Brown and Newbold, *J.*, 1952, 4878) has been made and its mechanism is discussed.

THIS paper is a continuation of studies on the synthesis of vicinal carboxy-*o*-phthalaldehydes related to gladiolic acid (III; R = Me, R′ = H) tautomeric with (IV; R = Me, R′ = H, R″ = OH), the antifungal metabolic product of *Penicillium gladioli* Machacek (see Brown and Newbold, *J.*, 1954, 1076, for references). It was desirable to prepare such compounds in order to obtain more evidence concerning the relation between structure and fungistatic activity (see Grove, *Biochem. J.*, 1953, **54**, 664). The preparation of 3-formyl-4-methylopianic acid (III; R = OMe, R′ = Me), tautomeric with (IV; R = OMe, R′ = Me, R″ = OH), and 3-formyl-4-methoxyopianic acid (III; R = R′ = OMe), tautomeric with (IV; R = R′ = OMe, R″ = OH), was therefore undertaken.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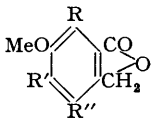
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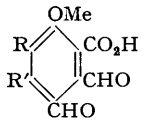
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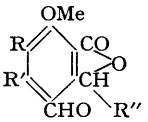
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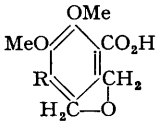
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The starting material for the synthesis of (III; R = OMe, R′ = Me) was 6-methoxy-5-methylphthalide (II; R = R″ = H, R′ = Me) which was readily obtained by the action of formaldehyde and hydrochloric acid on 3-methoxy-*p*-toluic acid (I; R = H) (Charlesworth, Rennie, Sinder, and Yan, *Canad. J. Res.*, 1945, **23**, *B*, 17). Nitration of (II; R = R″ = H, R′ = Me) gave 6-methoxy-5-methyl-7-nitrophthalide (II; R = NO_2, R′ = Me, R″ = H), the orientation of the nitro-group being apparent from subsequent reactions of the compound. The nitrophthalide was hydrogenated in the presence of nickel to the amine, and the amino-group was converted, *via* the iodo-group, into the methoxy-group, giving 5-methylmeconin (II; R = OMe, R′ = Me, R″ = H), m. p. 82·5°, using the method developed by McRae, Van Order, Griffiths, and Habgood (*Canad. J. Chem.*, 1951, **29**, 482; cf. Manske, McRae, and Moir, *ibid.*, p. 526) for the synthesis of 5 : 6 : 7-trimethoxyphthalide. If nitration of (II; R = R″ = H, R′ = Me) had taken place in the 4-position, the derived methoxy-compound would have been 4 : 6-dimethoxy-5-methylphthalide (II; R = H, R′ = Me, R″ = OMe); this compound, m. p. 158°, has been prepared from 3 : 5-dimethoxy-*p*-toluic acid (CO_2H = 1) independently by Asahina and Hayashi (*Ber.*, 1933, **66**, 1023) and Charlesworth and Robinson (*J.*, 1934, 1531). Thus nitration of 6-methoxy-5-methylphthalide is comparable with that of *m*-meconin (II; R = R″ = H, R′ = OMe) which gave the 7-nitro-derivative (II; R = NO_2, R′ = OMe, R″ = H) (Ray and Robinson, *J.*, 1925, 1621) and that of (I; R = H) which gave (I; R = NO_2) (Simonsen and Rau, *J.*, 1921, 1339); these reactions demonstrate the powerful directive influence into the vicinal position of the methoxy-group *meta*-substituted to the carboxyl group, an example of the general behaviour where a group of the $+E$ type is substituted in the *meta*-position to one of the $-I - M$ type (Ingold, " Structure and Mechanism in Organic Chemistry," Bell, London, 1953, pp. 267, 268).

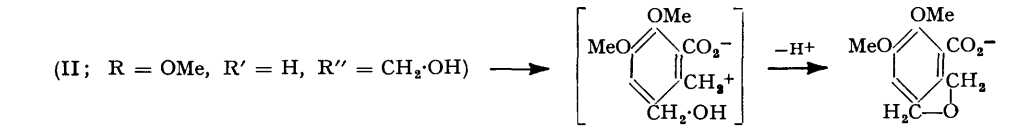
* Part V, *J.*, 1954, 1836.

Chloromethylation of 5-methylmeconin gave the 4-chloromethyl derivative (II; R = OMe, R′ = Me, R″ = CH_2Cl), m. p. 118—121°, different from the product, 7-chloromethyl-4 : 6-dimethoxy-5-methylphthalide (II; R = CH_2Cl, R′ = Me, R″ = OMe), m. p. 130—131°, obtained by the action of formaldehyde and hydrochloric acid on 3 : 5-dimethoxy-*p*-toluic acid (Charlesworth, Rennie, Sinder, and Yan, *loc. cit.*); this is further evidence of the correctness of our orientation in (II; R = NO_2, R′ = Me, R″ = H). The chloromethyl compound on reduction with zinc gave 4 : 5-dimethylmeconin (II; R = OMe, R′ = R″ = Me). In Part I of this series (Brown and Newbold, *J.*, 1952, 4878) heating 4-chloromethylmeconin (II; R = OMe, R′ = H, R″ = CH_2Cl) with aqueous sodium carbonate was shown to yield 4-hydroxymethylmeconin (II; R = OMe, R′ = H, R″ = CH_2·OH) which underwent a novel isomerisation, on being heated with aluminium *tert.*-butoxide in benzene, to give 5 : 6-dimethoxyphthalan-4-carboxylic acid (V; R = H), the reverse process being effected by the action of hot dilute mineral acid. On similar hydrolysis by carbonate 4-chloromethyl-5-methylmeconin gave 5 : 6-dimethoxy-7-methylphthalan-4-carboxylic acid (V; R = Me) as the major product with some 4-hydroxymethyl-5-methylmeconin (II; R = OMe, R′=Me, R″ = CH_2OH); the yield of the former product was increased by prolonging the reaction time and 5 : 6-dimethoxy-7-methylphthalan-4-carboxylic acid could be isomerised to 4-hydroxymethyl-5-methylmeconin by heating it with mineral acid. Attempts to convert 4-chloromethyl-5-methylmeconin into 3-formyl-4-methylopianic acid by the action of *N*-bromosuccinimide followed by hydrolysis, an effective method for the formation of 3-formylopianic acid (III; R = OMe, R′ = H), tautomeric with (IV; R = OMe, R′ = H, R″ = OH), were unsuccessful, no crystalline product being obtained. Attention was then turned to the alternative approach (*loc. cit.*), that of treating the carboxyphthalan with *N*-bromosuccinimide with subsequent hydrolysis of the intermediate; by this means 3-formyl-4-methylopianic acid (III; R = OMe, R′ = Me) was obtained from 5 : 6-dimethoxy-7-methylphthalan-4-carboxylic acid. 3-Formyl-4-methylopianic acid, when heated with aqueous sodium hydroxide, undergoes the characteristic isomerisation to the carboxyphthalide (cf. Grove, *Biochem. J.*, 1952, **50**, 648; Raistrick and Ross, *ibid.*, p. 635; Brown and Newbold, *loc. cit.*), giving 5-methylmeconin-4-carboxylic acid (II; R = OMe, R′ = Me, R″ = CO_2H); the same compound was obtained by oxidation of 5 : 6-dimethoxy-7-methylphthalan-4-carboxylic acid with chromium trioxide.

The preparation of 3-formyl-4-methoxyopianic acid (III; R = R′ = OMe) utilised 5 : 6 : 7-trimethoxyphthalide (II; R = R′ = OMe, R″ = H) (McRae *et al.*, *loc. cit.*) as starting material. Though no homogeneous product could be obtained by the action of formaldehyde and hydrochloric acid on this phthalide under the usual reflux conditions, the mild ones used by Wilson, Zirkle, Anderson, Stehle, and Ullyot (*J. Org. Chem.*, 1951, **16**, 792) for the conversion of *o*-veratric acid into meconin, gave 4-chloromethyl-5 : 6 : 7-trimethoxyphthalide (II; R = R′ = OMe, R″ = CH_2Cl) in excellent yield. Sodium carbonate hydrolysis of the chloromethyl derivative gave 4-hydroxymethyl-5 : 6 : 7-trimethoxyphthalide (II; R = R′ = OMe, R″ = CH_2·OH) and 5 : 6 : 7-trimethoxyphthalan-4-carboxylic acid (V; R = OMe), the proportion of the latter compound being increased by prolongation of the reaction time. The acid (V; R = OMe) was isomerised to 4-hydroxymethyl-5 : 6 : 7-trimethoxyphthalide by hot mineral acid while the reverse change could be partially achieved by means of sodium carbonate. The action of *N*-bromosuccinimide on the acid (V; R = OMe), followed by hydrolysis of the product, afforded 3-formyl-4-methoxyopianic acid (III; R = R′ = OMe) in good yield. Isomerisation of (III; R = R′ = OMe) by alkali gave 5 : 6 : 7-trimethoxyphthalide-4-carboxylic acid (II; R = R′ = OMe, R″ = CO_2H).

In order to gain information on the hydroxymethylphthalide–carboxyphthalan rearrangement the behaviour of 4-hydroxymethylmeconin with different bases was studied. The isomerisation of 4-hydroxymethylmeconin to 5 : 6-dimethoxyphthalan-4-carboxylic acid was achieved in 8% yield by heating with aqueous sodium hydroxide, in 31% yield by prolonged heating with sodium carbonate, in 39% yield by heating with sodium methoxide in benzene, in 60% yield by heating with aluminium *tert.*-butoxide in benzene (Brown and Newbold, *loc. cit.*), and in quantitative yield by using sodium methoxide in methanol. It is notable that in the last reaction no ester was formed and it is suggested that the course of

the rearrangement consists in the opening of the lactone ring of 4-hydroxymethylmeconin between the methylene group and the adjacent oxygen atom, giving a sodium salt bearing an intermediate carbonium ion which then forms the phthalan ring by interaction with the 4-hydroxymethyl group with loss of a proton :



A precedent is found in the reaction of phthalide with potassium cyanide, giving the salt of *o*-carboxyphenylacetonitrile (Wislicenus, *Annalen*, 1886, **233**, 102), which may involve an intermediate carbonium ion.

The dissociation constants of some of the acids described in this paper have been measured. 5 : 6-Dimethoxyphthalan-4-carboxylic acid has pK_a 3·5, its 7-methyl derivative pK_a 3·75, and its 7-methoxy-derivative pK_a 3·73 ; the 7-substituents thus increase electron-availability in the *para*-position, though their effects on acidic strength are in reverse order compared with the strengths of *p*-toluic acid and *p*-anisic acid (Dippy, *Chem. Reviews*, 1939, **25**, 151). The acidic strengths, pK_a, of 3-formyl-4-methylopianic acid and 3-formyl-4-methoxyopianic acid are respectively 3·5 and 3·8. Comparison with the pK_a of 3-formylopianic acid (4·3) indicates that the effect of substitution in the 5-position does not follow the normal effect of substitution on the strengths of benzoic acid derivatives and is no doubt complicated by interaction between the 5-substituent and the tautomeric phthalaldehydic acid system.

Experimental

Ultra-violet absorption spectra were determined in ethanol solution, unless otherwise stated, with a Unicam S.P.500 spectrophotometer. The pK_a values (classical) and equivalents were determined in water potentiometrically under nitrogen, according to the micro-method of Catch, Cook, and Kitchener (*J.*, 1945, 319), 0·05N-sodium hydroxide being used with an initial 0·10M-concentration of acid.

6-Methoxy-5-methyl-7-nitrophthalide (with W. Laird).—Finely divided 6-methoxy-5-methylphthalide (Charlesworth, Rennie, Sinder, and Yan, *loc. cit.*; 5 g.) was added during 5 min. to a stirred mixture of nitric acid (16 c.c.; *d* 1·5) and acetic anhydride (24 g.) at 0°. When all the phthalide had dissolved, the solution was poured on ice, and the solid separated, washed with water, and crystallised from ethanol, to give *6-methoxy-5-methyl-7-nitrophthalide* (4·5 g., 73%) as needles, m. p. 146° (Found : C, 54·2; H, 4·1. $C_{10}H_9O_5N$ requires C, 53·8; H, 4·1%). Light absorption : Max. at 2080 (ε 28,800) and 2890 (ε 2650) ; inflexion at 2410 Å (ε 6800).

7-Amino-6-methoxy-5-methylphthalide (with W. Laird).—A solution of 6-methoxy-5-methyl-7-nitrophthalide (2 g.) in ethyl acetate (200 c.c.) was shaken with hydrogen at room temperature and atmospheric pressure in the presence of freshly prepared Raney nickel (1·2 g.; W.6, *Org. Synth.*, **29**, 24). When absorption was complete (*ca.* 15 min.) the mixture was filtered, the filtrate evaporated to dryness under reduced pressure, and the residual solid crystallised from benzene–light petroleum (b. p. 60—80°) from which *7-amino-6-methoxy-5-methylphthalide* (1·7 g.) separated as needles, m. p. 109—110° (Found : C, 62·5; H, 5·65. $C_{10}H_{11}O_3N$ requires C, 62·2; H, 5·7%). Light absorption : Max. at 2340 (ε 34,700), 2500 (ε 7800), and 3280 Å (ε 5700).

7-Iodo-6-methoxy-5-methylphthalide.—The foregoing aminophthalide (4 g.) in sulphuric acid (3 c.c.; *d* 1·84) and water (20 c.c.) was diazotized at 0° with sodium nitrite (2 g.). After the addition of urea, a solution of potassium iodide (4 g.) in water (15 c.c.) was added and the mixture kept at room temperature for 3 hr. and then heated on the steam-bath for 10 min. After cooling, the solid was separated and crystallised from ethanol (charcoal), to give *7-iodo-6-methoxy-5-methylphthalide* (3·4 g.) as needles, m. p. 117—118° (Found : C, 39·3; H, 3·1. $C_{10}H_9O_3I$ requires C, 39·5; H, 3·0%). Light absorption : Max. at 2220 (ε 28,000), 2460 (ε 9000), and 3020 Å (ε 4700).

5-Methylmeconin.—The iodo-compound (3·2 g.) and copper bronze (100 mg.) were added to a solution of potassium methoxide from potassium (0·9 g.) and dry methanol (50 c.c.) and the mixture was refluxed for 24 hr. The filtered solution was diluted with water (25 c.c.), made

acid (Congo-red) with 5N-hydrochloric acid, and extracted with ether (3 × 50 c.c.). The combined ethereal extract was washed with water, dried (Na_2SO_4), and evaporated, and the residue crystallised from light petroleum (b. p. 40—60°), to yield *5-methylmeconin* (1·6 g.) as felted needles, m. p. 82·5° (Found : C, 63·1; H, 5·85. $C_{11}H_{12}O_4$ requires C, 63·45; H, 5·8%). Light absorption : Max at. 2130 (ε 29,600), 2460 (ε 8300), and 2960 Å (ε 3000).

4-Chloromethyl-5-methylmeconin.—5-Methylmeconin (400 mg.), hydrochloric acid (5 c.c.; *d* 1·16), and aqueous formaldehyde (3 c.c.; 40%) were heated under reflux for 30 min. The cooled mixture was diluted with water (10 c.c.) and extracted with chloroform (3 × 10 c.c.). The combined chloroform extracts were washed with aqueous sodium hydrogen carbonate, then water, dried (Na_2SO_4), and evaporated. Crystallisation of the residue from benzene–light petroleum (b. p. 60—80°) gave *4-chloromethyl-5-methylmeconin* (250 mg.) as needles, m. p. 118—121° (Found : C, 56·4; H, 5·3. $C_{12}H_{13}O_4Cl$ requires C, 56·15; H, 5·1%). Light absorption : Max. at 2190 (ε 40,100) and 3050 (ε 3800); inflexion at 2420—2480 Å (ε 9700).

4 : 5-*Dimethylmeconin.*—4-Chloromethyl-5-methylphthalide (200 mg.) in ethanol (5 c.c.; 95%) was heated under reflux with zinc dust (250 mg.) and treated with hydrochloric acid (2·5 c.c.; *d* 1·16) added in portions during 2 hr. The mixture was evaporated under reduced pressure; water was added and the product isolated by means of ether. Removal of the ether and crystallisation of the residue from hexane gave 4 : 5-*dimethylmeconin* (100 mg.) as prisms, m. p. 110° (Found : C, 65·2; H, 6·5. $C_{12}H_{14}O_4$ requires C, 64·85; H, 6·35%). Light absorption : Max. at 2160 (ε 28,800), 2480 (ε 11,000), and 3000 Å (ε 3900).

5 : 6-*Dimethoxy-7-methylphthalan-4-carboxylic Acid.*—4-Chloromethyl-5-methylmeconin (100 mg.) was heated under reflux with a solution of anhydrous sodium carbonate (400 mg.) in water (6 c.c.) for 1½ hr. The cooled solution was made acid to Congo-red with 3N-hydrochloric acid and extracted with chloroform (3 × 10 c.c.), The combined, dried (Na_2SO_4) extracts were evaporated and the residue was crystallised from aqueous ethanol, to give 5 : 6-*dimethoxy-7-methylphthalan-4-carboxylic acid* (75 mg.) as plates, m. p. 156—157° (Found : C, 60·7; H, 5·9%); equiv., 232. $C_{12}H_{14}O_5$ requires C, 60·5; H, 5·9%; equiv., 238). The compound sublimed unchanged at 120°/10^{-4} mm. and showed light absorption : Max. at 2120 (ε 29,000), 2420 (ε 7400), and 2960 Å (ε 2800). Under the same conditions save that heating was carried out for ½ hr., 4-chloromethyl-5-methylmeconin (400 mg.) gave 5 : 6-dimethoxy-7-methylphthalan-4-carboxylic acid (130 mg.) and 4-hydroxymethyl-5-methylmeconin (70 mg.), the separation being achieved by use of chloroform and aqueous sodium hydrogen carbonate.

4-Hydroxymethyl-5-methylmeconin.—The foregoing phthalan acid (100 mg.) was heated under reflux with 5N-hydrochloric acid (4 c.c.) for 1 hr. The cooled solution was extracted with chloroform (3 × 10 c.c.), the combined extracts were dried (Na_2SO_4) and evaporated, and the residue crystallised from benzene–light petroleum (b. p. 60—80°) to give *4-hydroxymethyl-5-methylmeconin* (60 mg.) as needles, m. p. 101—102° (Found : C, 60·6; H, 4·7. $C_{12}H_{14}O_5$ requires C, 60·5; H, 5·9%). Light absorption : Max. at 2140 (ε 41,000), 2470 (ε 9100), and 2990 Å (ε 3600).

3-Formyl-4-methylopianic Acid.—A solution of 5 : 6-dimethoxy-7-methylphthalan-4-carboxylic acid (200 mg.) in dry benzene (12 c.c.) and dry carbon tetrachloride (12 c.c.) was refluxed with *N*-bromosuccinimide (2·25 mols.) for 15 min. with irradiation from a 60-w lamp. The cold mixture was filtered, the filtrate evaporated under reduced pressure, and the remaining oil heated with water (10 c.c.) on the steam-bath while being stirred for 1½ hr. Isolation by use of chloroform gave an acid fraction which crystallised from benzene, to yield *3-formyl-4-methylopianic acid* (77 mg.) as needles, m. p. 145—146° (Found : C, 57·0; H, 5·0%; equiv., 247. $C_{12}H_{12}O_6$ requires C, 57·1; H, 4·8%; equiv., 252). Light absorption in water : Max. at 2070 (ε 29,600) and 2800 Å (ε 2000). 3-Formyl-4-methylopianic acid dissolves in concentrated sulphuric acid, giving a yellow-brown solution; on exposure to ammonia vapour the solid becomes brown and resinifies; it becomes pink on prolonged exposure to light.

5-Methylmeconin-4-carboxylic Acid.—(*a*) A solution of 5 : 6-dimethoxy-7-methylphthalan-4-carboxylic acid (200 mg.) in glacial acetic acid (5 c.c.) was treated with chromium trioxide (200 mg.) in glacial acetic acid (5 c.c.) during 1 min. with stirring. After 5 min. the mixture was diluted with water (10 c.c.) and extracted with chloroform (3 × 15 c.c.). The combined extracts were washed with sodium hydrogen carbonate (30 c.c.; 10%); acidification of this extract with 5N-hydrochloric acid and isolation with chloroform gave *5-methylmeconin-4-carboxylic acid* (100 mg.) which separated from aqueous ethanol as needles, m. p. 195—196·5° (Found : C, 57·3; H, 4·9. $C_{12}H_{12}O_6$ requires C, 57·1; H, 4·8%). Light absorption: Max. at 2200 (ε 31,200) and 3000 Å (ε 3200).

(*b*) 3-Formyl-4-methylopianic acid (25 mg.) in 3N-sodium hydroxide (10 c.c.) was refluxed for 30 min. The cooled mixture was extracted with chloroform; no neutral fraction was obtained

from the extract. Acidification of the alkaline solution (Congo-red) with 5N-hydrochloric acid gave 5-methylmeconin-4-carboxylic acid (12 mg.) which crystallised from aqueous ethanol as needles, m. p. and mixed m. p. 195—196·5°.

4-Chloromethyl-5 : 6 : 7-trimethoxyphthalide.—A suspension of 5 : 6 : 7-trimethoxyphthalide (McRae *et al.*, *loc. cit.*) (1·0 g.) in hydrochloric acid (2 c.c.; *d* 1·16) and aqueous formaldehyde (1 c.c.; 40%) was treated with gaseous hydrogen chloride at 0° until solution was complete (*ca.* 10 min.). After being kept overnight at room temperature the solution was diluted with water and the product isolated by means of chloroform. Crystallisation from light petroleum (b. p. 60—80°) gave *4-chloromethyl-5 : 6 : 7-trimethoxyphthalide* (1·1 g.) as needles, m. p. 82·5° (Found : C, 52·7; H, 4·9. $C_{12}H_{13}O_5Cl$ requires C, 52·85; H, 4·8%). Light absorption : Max. at 2240 (ε 39,200) and 2970 (ε 2900); inflexion at 2420—2520 Å (ε 8300).

Sodium Carbonate Treatment of 4-Chloromethyl-5 : 6 : 7-trimethoxyphthalide.—A solution of sodium carbonate (500 mg.) in water (10 c.c.) was refluxed for ½ hr. with 4-chloromethyl-5 : 6 : 7-trimethoxyphthalide (200 mg.). After acidification and extraction with chloroform (3 × 10 c.c.) the combined extracts were separated into acid and neutral fractions by using sodium hydrogen carbonate solution. The former fraction crystallised from benzene–light petroleum (b. p. 60—80°) to give *5 : 6 : 7-trimethoxyphthalan-4-carboxylic acid* (60 mg.) as prisms, m. p. 125—126° (Found : C, 57·0; H, 5·8%; equiv., 254. $C_{12}H_{14}O_6$ requires C, 56·7; H, 5·55%; equiv., 254). Light absorption : Max. at 2160 (ε 31,200), 2530 (ε 9800), and 2940 Å (ε 2700). The neutral fraction separated from the same solvents, to give *4-hydroxymethyl-5 : 6 : 7-trimethoxyphthalide* (80 mg.) as needles, m. p. 73° (Found : C, 56·3; H, 5·8. $C_{12}H_{14}O_6$ requires C, 56·7; H, 5·55%). Light absorption : Max. at 2180 (ε 36,400), 2520 (ε 9950), and 2960 Å (ε 3000).

When 4-chloromethyl-5 : 6 : 7-trimethoxyphthalide (500 mg.) was refluxed for 2 hr. with sodium carbonate (1·0 g.) in water (15 c.c.), and the products were isolated as above, 5 : 6 : 7-trimethoxyphthalan-4-carboxylic acid (340 mg.) and 4-hydroxymethyl-5 : 6 : 7-trimethoxyphthalide (110 mg.) were obtained. The latter compound (140 mg.), when refluxed for ½ hr. with sodium carbonate (500 mg.) in water (10 c.c.), gave the corresponding carboxyphthalan (60 mg.), the remainder being unchanged. 5 : 6 : 7-Trimethoxyphthalan-4-carboxylic acid (100 mg.) was refluxed with hydrochloric acid (40 c.c.; 3N) for 2 hr. and 4-hydroxymethyl-5 : 6 : 7-trimethoxyphthalide (55 mg.), m. p. and mixed m. p. 73°, isolated in the usual way.

3-Formyl-4-methoxyopianic Acid.—5 : 6 : 7-Trimethoxyphthalan-4-carboxylic acid (250 mg.) in benzene (12 c.c.) and carbon tetrachloride (12 c.c.) was refluxed for 20 min. with *N*-bromosuccinimide (2·2 mols.) with irradiation from a 60-w lamp. Further treatment as described for 3-formyl-4-methylopianic acid gave *3-formyl-4-methoxyopianic acid* (130 mg.) which separated from benzene as needles, m. p. 146° (Found : C, 53·55; H, 4·7%; equiv., 262. $C_{12}H_{12}O_7$ requires C, 53·7; H, 4·5%; equiv., 268). Light absorption in water : Max. at 2080 (ε 32,400); inflexion at 2700—2750 Å (ε 2100). The compound dissolves in concentrated sulphuric acid giving a yellow solution; on exposure to ammonia vapour the solid becomes brown and resinifies.

5-Methoxymeconin-4-carboxylic Acid.—3-Formyl-4-methoxyopianic acid (100 mg.) was refluxed in 3N-sodium hydroxide (30 c.c.) for 30 min. Isolation by means of chloroform gave *5-methoxymeconin-4-carboxylic acid* (70 mg.) which separated from benzene as needles, m. p. 176° (Found : C, 53·9; H, 4·6. $C_{12}H_{12}O_7$ requires C, 53·7; H, 4·5%). Light absorption : Max. at 2270 (ε 36,000) and 3000 (ε 3300); inflexion at 2530—2560 Å (ε 10,400).

5 : 6-Dimethoxyphthalan-4-carboxylic Acid (with D. H. Kenny).—(*a*) 4-Hydroxymethylmeconin (0·5 g.) was heated under reflux for 7¼ hr. with a solution of sodium methoxide in anhydrous methanol, from sodium (0·25 g.) and methanol (11 c.c.). The solution was diluted with water, made acid to Congo-red with dilute hydrochloric acid, and extracted with chloroform. The chloroform extracts were washed with aqueous sodium hydrogen carbonate, then water, dried (Na_2SO_4), and evaporated, giving no residue. Acidification of the alkaline washings and isolation of the product by use of chloroform gave 5 : 6-dimethoxyphthalan-4-carboxylic acid (0·5 g.), which separated from water as needles, m. p. 148—149° alone or mixed with Brown and Newbold's sample (*loc. cit.*).

(*b*) 4-Hydroxymethylmeconin (0·5 g.) in dry benzene (10 c.c.) was heated under reflux for 18 hr. with sodium methoxide (0·5 g.). Isolation in the usual way gave 4-hydroxymethylmeconin (264 mg.), m. p. and mixed m. p. 126—128° and 5 : 6-dimethoxyphthalan-4-carboxylic acid (194 mg., 39%), m. p. and mixed m. p. 148—149°.

(*c*) 4-Hydroxymethylmeconin (1·0 g.) was heated on the steam-bath for 7¼ hr. in 3N-sodium hydroxide (15 c.c.). Isolation gave unchanged material (840 mg.) and 5 : 6-dimethoxyphthalan-4-carboxylic acid (110 mg., 8%), m. p. and mixed m. p. 146—148°. Brown and Newbold (*loc.*

cit.) reported that 4-hydroxymethylmeconin was unchanged after 2 hours' boiling with 3N-sodium hydroxide.

(*d*) 4-Hydroxymethylmeconin (1·0 g.) was heated under reflux for 7½ hr. with a solution of anhydrous sodium carbonate (2·5 g.) in water (25 c.c.). Isolation gave starting material (700 mg.) and 5 : 6-dimethoxyphthalan-4-carboxylic acid (300 mg., 31%), m. p. and mixed m. p. 145—147°.

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