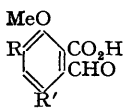
735. *Phthalaldehydes and Related Compounds. Part III.* Synthesis of Deoxygladiolic Acid and Experiments relating to the Structure of Dihydrogladiolic Acid.*

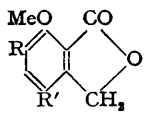
By J. J. Brown and G. T. Newbold.

Treatment of 4-hydroxymethyl-7-methoxy-6-methylphthalide with *N*-bromosuccinimide, followed by hydrolysis of the intermediate bromo-compound, gave deoxygladiolic acid (4-formyl-7-methoxy-6-methylphthalide). The preparation of 3-hydroxymethylopianic acid † from 3-formylopianic acid by catalytic hydrogenation of its monoacetate and subsequent hydrolysis is described. Comparison of the properties of 3-hydroxymethylopianic acid with those of dihydrogladiolic acid shows that the structure of the latter is 3-hydroxymethyl-6-methoxy-5-methylphthalaldehydic acid † rather than 2-hydroxymethyl-3-formyl-6-methoxy-5-methylbenzoic acid as proposed by Raistrick and Ross (*Biochem. J.*, 1952, 635).

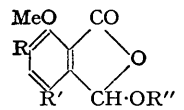
The elegant analytical work of Grove (*Biochem. J.*, 1952, 648) and Raistrick and Ross (*ibid*, p. 635) has established the structure of gladiolic acid, an antifungal metabolic product of *Penicillium gladioli* Machacek, as (I; R = Me, R′ = CHO) tautomeric with (III; R = Me, R′ = CHO, R″ = H) (see Grove, *J.*, 1952, 3345). We have put forward evidence (*J.*, 1952, 4878) in support by an examination of 3-formylopianic acid (I; R = OMe, R′ = CHO), obtained by treatment of 4-chloromethylmeconin (II; R = OMe, R′ = CH_2Cl) with *N*-bromosuccinimide and subsequent hydrolysis. Further synthetical progress was made by the preparation of *iso*gladiolic acid (II; R = Me, R′ = CO_2H) (Brown and Newbold, *J.*, 1953, 1285), the product of alkaline rearrangement of gladiolic acid (Grove, Raistrick, and Ross, *loc. cit.*), by permanganate oxidation of 4-hydroxymethyl-7-methoxy-6-methylphthalide (II; R = Me, R′ = CH_2·OH).



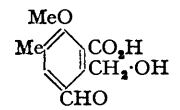
(I)



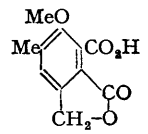
(II)



(III)



(IV)



(V)

The first part of this paper reports the synthesis of deoxygladiolic acid (II; R = Me, R′ = CHO). Our starting material was 4-chloromethyl-7-methoxy-6-methylphthalide (II; R = Me, R′ = CH_2Cl). Reaction of this compound with three mols. of *N*-bromosuccinimide and hydrolysis of the intermediate bromo-compound gave 4-formyl-7-methoxy-6-methylphthalide (II; R = Me, R′ = CHO), identical with deoxygladiolic acid obtained by Grove (*Biochem. J.*, 1952, 648) by reduction of gladiolic acid with iron powder and acetic acid. From the crystallisation mother-liquor of the phthalide there was obtained a trace of crude material which gave a positive ammonia test—a sensitive reaction for gladiolic acid (*loc. cit.*)—but no modification of the reaction conditions gave an isolatable quantity of this compound. Reaction of 4-hydroxymethyl-7-methoxy-6-methylphthalide (II; R = Me, R′ = CH_2·OH) with three mols. of *N*-bromosuccinimide, followed by hydrolysis, gave 7-methoxy-6-methylphthalide-4-carboxylic acid (II; R = Me, R′ = CO_2H) (*iso*-gladiolic acid); by use of one mol. of reagent deoxygladiolic acid (II; R = Me, R′ = CHO) was obtained in good yield. In the dimethoxy-series 4-hydroxymethylmeconin (II; R = OMe, R′ = CH_2·OH) gave 4-formylmeconin (II; R = OMe, R′ = CHO) with one mol. of *N*-bromosuccinimide, and meconin-4-carboxylic acid (II; R = OMe, R′ = CO_2H) with three mols. 4-Formylmeconin was also obtained by chromic acid oxidation of

* Part II, *J.*, 1953, 1285.

† These structures (I; R = OMe or Me, R′ = CH_2·OH), tautomeric with the lactol forms (III; R = OMe or Me, R′ = CH_2·OH, R″ = H), are used in this paper since we present no evidence which enables a decision to be made between them (see Duncanson, Grove, and Zealley, *J.*, 1953, 3637).

4-hydroxymethylmeconin. We have shown (*J.*, 1952, 4878) that 4-chloromethylmeconin on treatment with three mols. of *N*-bromosuccinimide gave 3-formylopianic acid (I; R = OMe, R′ = CHO) in good yield in contrast to the behaviour of 4-chloromethyl-7-methoxy-6-methylphthalide above. Clearly the methylene group in the phthalide ring in the latter compound is less reactive than that in 4-chloromethylmeconin. *N*-Bromosuccinimide is an electrophilic reagent and attack by it on the 3-methylene group will be facilitated by the presence of an electron-releasing group *para* to it, *i.e.*, in the 6-position. Since the methoxyl group is much more electron-releasing than the methyl group the lack of reactivity of the 3-methylene group in (II; R = Me, R′ = CH_2Cl) to attack by *N*-bromosuccinimide follows.

A further problem in the chemistry of the antifungal metabolic products of *Penicillium gladioli* Machacek was the structure of dihydrogladiolic acid which occurs with gladiolic acid (Raistrick and Ross, *loc. cit.*; Grove, *Biochem. J.*, 1952, 648). Dihydrogladiolic acid has been formulated as (IV) by Raistrick and Ross; such a structure appeared to us unlikely in view of the known instability of *o*-hydroxymethylbenzoic acids, which cyclise when their salts are acidified to give phthalides. Since Raistrick and Ross showed that periodate oxidation of dihydrogladiolic acid gave gladiolic acid in good yield the only other possible structure for the former compound, which must be gladiolic acid with one of the formyl groups reduced to hydroxymethyl, is (I; R = Me, R′ = CH_2·OH). Gladiolic acid not being available to us in quantity we decided to convert 3-formylopianic acid (I; R = OMe, R′ = CHO) into 3-hydroxymethylopianic acid (I; R = OMe, R′ = CH_2·OH) and compare the properties of the latter with those of dihydrogladiolic acid. While this work was being carried out we were informed by Mr. J. F. Grove that his group (Duncanson, Grove, and Zealley, *loc. cit.*) had synthesised the oxidation product of dihydrogladiolic acid described by Raistrick and Ross (*loc. cit.*) and had shown its structure to be (V), thus proving that dihydrogladiolic acid is (I; R = Me, R′ = CH_2·OH).

Treatment of 3-formylopianic acid with acetic anhydride–acetic acid as described by Grove (*loc. cit.*) for the formation of monoacetylgladiolic acid (III; R = Me, R′ = CHO, R″ = Ac) gave the analogous 3-acetoxy-4-formylmeconin (III; R = OMe, R′ = CHO, R″ = Ac), a neutral compound readily hydrolysed to 3-formylopianic acid by boiling dilute sulphuric acid. As in the case of gladiolic acid the action of acetic anhydride in the presence of mineral acid on 3-formylopianic acid gave a triacetate, 3-acetoxy-4-diacetoxymethylmeconin [III; R = OMe, R′ = $CH(OAc)_2$, R″ = Ac]. Hydrogenation of 3-acetoxy-4-formylmeconin in acetic acid in presence of platinum gave, in excellent yield, 3-acetoxy-4-hydroxymethylmeconin (III; R = OMe, R′ = CH_2·OH, R″ = Ac) which was characterized by the formation of its acetate (III; R = OMe, R′ = CH_2·OAc, R″ = Ac). Hydrolysis of the monoacetate (III; R = OMe, R′ = CH_2·OH, R″ = Ac) with dilute alkali at room temperature gave after acidification 3-hydroxymethylopianic acid (I; R = OMe, R′ = CH_2·OH). A similar series of changes were developed independently by Duncanson, Grove, and Zealley (*loc. cit.*) for the conversion of gladiolic acid into dihydrogladiolic acid. In common with dihydrogladiolic acid (Raistrick and Ross, *loc. cit.*) the compound (I; R = OMe, R′ = CH_2·OH) dissolved in sodium hydrogen carbonate solution with effervescence, titrated sharply as a monocarboxylic acid with sodium hydroxide, formed a 2 : 4-dinitrophenylhydrazone, and did not reduce Schiff's reagent, Fehling's solution, or ammoniacal silver nitrate. Oxidation of 3-hydroxymethylopianic acid with sodium metaperiodate in dilute sulphuric acid gave 3-formylopianic acid (I; R = OMe, R′ = CHO) in good yield. On acetylation the compound (I; R = OMe, R′ = CH_2·OH) gave 3-acetoxy-4-acetoxymethylmeconin (III; R = OMe, R′ = CH_2·OAc, R″ = Ac), *i.e.*, the diacetate of the lactol form (III; R = Me, R′ = CH_2·OH, R″ = H). On sublimation 3-hydroxymethylopianic acid gave 4-formylmeconin (II; R = OMe, R′ = CHO) in very low yield [compare the similar formation of deoxygladiolic acid (II; R = Me, R′ = CHO), " dihydrogladiolide," by Raistrick and Ross (*loc. cit.*)]. Raistrick and Ross also describe the formation of deoxygladiolic acid from the acetylation product of dihydrogladiolic acid by boiling mineral acid; this acetylation product described as " dihydrogladiolide diacetate," *i.e.*, [II; R = Me, R′ = $CH(OAc)_2$], must be (III; R = Me, R′ = CH_2·OAc, R″ = Ac) by analogy with the acetylation of 3-hydroxymethylopianic acid described above.

Though 3-formylmeconin was obtained by heating 3-hydroxymethylopianic acid with mineral acid the yield was very poor, much tar being formed, in contrast to the conversion of Raistrick and Ross's diacetate into deoxygladiolic acid. It is therefore evident that a molecular rearrangement takes place during the formation of the latter compound from dihydrogladiolic acid and during the analogous change in the dimethoxy-series.

Reduction by sodium borohydride is a simple method of preparing 4-hydroxymethylphthalides from the vicinal *o*-carboxyphthalaldehydes and derivatives. When 3-formylopianic acid (I; R = OMe, R′ = CHO) was dissolved in aqueous sodium hydrogen carbonate and treated with the reagent at room temperature, 4-hydroxymethylmeconin (II; R = OMe, R′ = CH_2·OH) was obtained in good yield. The same product was also readily formed from 3-acetoxy-4-formylmeconin (III; R = OMe, R′ = CHO, R″ = Ac), 3-acetoxy-4-hydroxymethylmeconin (III; R = OMe, R′ = CH_2·OH, R″ = Ac), and 3-hydroxymethylopianic acid (I; R = OMe, R′ = CH_2·OH) by the action of the same reagent, which with gladiolic acid (I; R = Me, R′ = CHO) gave 4-hydroxymethyl-7-methoxy-6-methylphthalide (II; R = Me, R′ = CH_2·OH), identical with the synthetic material of Brown and Newbold (*J.*, 1953, 1285).

Since ultra-violet absorption data are available for a number of corresponding compounds in the dimethoxy- and the methylmethoxy-series a comparison has been made in the Table, the position of the maximum nearest to the visible region being given for each compound. In each of the first twelve structures in the Table replacement of the methyl substituent by methoxyl causes a bathochromic shift in the position of maximal absorption in ethanol solution of 16 ± 3 mμ, supporting the chemical evidence of structural similarity between compounds of the two series. The position of maximal absorption in ethanol for dihydrogladiolic acid, in contrast with that for 3-hydroxymethylopianic acid, is dependent on concentration (Duncanson, Grove, and Zealley, *loc. cit.*), showing a large hypsochromic shift with dilution. Chloroform is a better solvent for the comparison of spectral absorption of the two compounds; values for 4-hydroxymethylmeconin (II; R = OMe, R′ = CH_2·OH) and 4-hydroxymethyl-7-methoxy-6-methylphthalide (II; R = Me, R′ = CH_2·OH) in this solvent are included in the Table to indicate that the change of solvent causes no fundamental change in absorption maximum for normal compounds.

(Solvent: ethanol unless otherwise indicated.)

Compound	$\lambda_{max.}$ (mμ) (R = OMe)	$\lambda_{max.}$ (mμ) (R = Me)	Δλ (mμ)
(I; R′ = CHO)	320 [a]	305 [c]	15
(II; R′ = H)	308 [a]	295 [b]	13
(II; R′ = CH_2Cl)	315 [a]	298 [b]	17
(II; R′ = CH_2·OH)	312 [a]	298 [b]	14
	310 [c] ($CHCl_3$)	299 [c] ($CHCl_3$)	11
(II; R′ = CH_2·OAc)	314 [d]	296 [c]	18
(II; R′ = CHO)	324 [c]	306 [c]	18
(II; R′ = CO_2H)	316 [a]	298 [c]	18
(III; R′ = CHO, R″ = Et)	323 [c]	305 [c]	18
(III; R′ = CHO, R″ = Ac)	320 [c]	306 [c]	14
[III; R′ = $CH(OAc)_2$, R″ = Ac]	312 [c]	297 [c]	15
(III; R′ = CH_2·OH, R″ = Ac)	314 [c]	299 [f]	15
(III; R′ = CH_2·OAc, R″ = Ac)	312 [c]	298 [f]	14
(I; R′ = CH_2·OH)	310 [c] ($3{\cdot}7 \times 10^{-4}$M)	296 [f] ($4{\cdot}9 \times 10^{-3}$M)	14
	308 [c] ($3{\cdot}4 \times 10^{-5}$M)	276 [f] ($2{\cdot}2 \times 10^{-4}$M)	
	311 [c] ($CHCl_3$)	299 [g] ($CHCl_3$)	12

[a] Brown and Newbold, *J.*, 1952, 4878. [b] *Idem*, *J.*, 1953, 1285. [c] Grove, *J.*, 1952, 3345. [d] This compound was prepared by Brown and Newbold (*J.*, 1952, 4878); it has light absorption in ethanol: Max. at 213 (ε = 28,200) and 314 mμ (ε = 4300). [e] This paper. [f] Grove (personal communication), $\varepsilon_{max.}$ values for (III; R = Me, R′ = CH_2·OH, R″ = Ac), 2500; for (III; R = Me, R′ = CH_2·OAc, R″ = Ac), 3000; and for (I; R = Me, R′ = CH_2·OH, 2050. [g] Duncanson, Grove, and Zealley, *loc. cit.*

Experimental

Ultra-violet absorption spectra were determined in ethanol solution unless otherwise stated. Brominations using *N*-bromosuccinimide were carried out with irradiation from a 60-w lamp adjacent to the flask.

4-Formylmeconin.—(*a*) A solution of 4-hydroxymethylmeconin (500 mg.) (Brown and New-

bold, *J.*, 1952, 4878) in dry carbon tetrachloride (25 c.c.) and dry benzene (25 c.c.) was refluxed with *N*-bromosuccinimide (430 mg., 1 mol.) for 15 min. The filtered mixture was evaporated under reduced pressure and the residual oil heated on the steam-bath with water (50 c.c.) for 1 hr. The cooled mixture was extracted with chloroform (50 c.c.), and the extract washed with sodium hydrogen carbonatesolution (2 × 25 c.c.) and water (2 × 25 c.c.), and dried (Na_2SO_4). Removal of the chloroform under reduced pressure gave a solid which crystallised from methanol, to give 4-*formylmeconin* (170 mg.) as blades, m. p. 195—196° (Found: C, 59·5; H, 4·8. $C_{11}H_{10}O_5$ requires C, 59·5; H, 4·5%). The compound sublimed at 150°/10^{-3} mm. and showed light absorption: Max. at 227 (ε = 20,000), 277 (ε = 4600), 324 (ε = 6000), and inflexion at 240 mμ (ε = 16,000). The 2 : 4-*dinitrophenylhydrazone*, prepared by the action of methanolic 2 : 4-dinitrophenylhydrazine sulphate and washed with methanol, formed needles gradually decomposing but not melting below 350° (Found: N, 13·5. $C_{17}H_{14}O_8N_4$ requires N, 13·9%).

(*b*) 4-Hydroxymethylmeconin (500 mg.), dissolved in glacial acetic acid (10 c.c.), was treated at 15° with chromic anhydride (500 mg.) in glacial acetic acid (10 c.c.) added during 2 min. with stirring. After 5 min. the solution was diluted with water (20 c.c.) and extracted with chloroform (3 × 15 c.c.). The combined chloroform extracts were washed with water (15 c.c.), followed by aqueous sodium hydrogen carbonate (3 × 15 c.c.; 10%) and water (15 c.c.), and dried (Na_2SO_4). Removal of the chloroform gave 4-formylmeconin (300 mg.), separating from methanol as blades, m. p. 196° (Found: C, 60·0; H, 4·2%).

4-*Formyl*-7-*methoxy*-6-*methylphthalide*.—(i) A solution of pure 4-chloromethyl-7-methoxy-6-methylphthalide (284 mg.) (*idem*, *J.*, 1953, 1285) in dry carbon tetrachloride (25 c.c.) was heated under reflux with *N*-bromosuccinimide (670 mg., 3 mols.) for 1½ hr. The filtered mixture was evaporated under reduced pressure, to give a yellow oil which was heated with water (25 c.c.) on the steam-bath for 1 hr. The hot solution was decanted from a little tar and on cooling deposited a solid which on crystallisation from methanol gave 4-*formyl*-7-*methoxy*-6-*methylphthalide* (80 mg.) as needles, m. p. 173—174° alone or mixed with a specimen of deoxygladiolic acid (Found: C, 64·0; H, 5·1. $C_{11}H_{10}O_4$ requires C, 64·1; H, 4·9%). Light absorption: Max. at 224 (ε = 23,300), 268 (ε = 8500), and 306 mμ (ε = 4550). The compound sublimed at 120°/10^{-3} mm.

(ii) 4-Hydroxymethyl-7-methoxy-6-methylphthalide (500 mg.) (*loc. cit.*), dissolved in a mixture of benzene and carbon tetrachloride (50 c.c.; 1 : 1), was heated under reflux with *N*-bromosuccinimide (430 mg., 1 mol.) for 15 min. The filtered mixture was evaporated under reduced pressure and the residual solid heated with water (50 c.c.) on the steam-bath for ½ hr., cooled, and extracted with chloroform (3 × 25 c.c.). The combined extracts were washed with water (25 c.c.), aqueous sodium hydrogen carbonate (25 c.c.; 10%), and water (25 c.c.), and dried (Na_2SO_4). Removal of the chloroform and crystallisation of the solid from benzene–light petroleum (b. p. 60—80°) gave 4-formyl-7-methoxy-6-methylphthalide (350 mg.) as needles, m. p. 172—173°, undepressed on mixing with preparation (i) (Found: C, 64·45; H, 5·0%).

Meconin-4-*carboxylic Acid*.—4-Hydroxymethylmeconin (500 mg.) was refluxed with *N*-bromosuccinimide (1·2 g., 3 mols.) in carbon tetrachloride (25 c.c.) and benzene (25 c.c.) for 20 min. The reaction mixture was hydrolysed and worked up as in (ii), to give a neutral fraction from which 4-formylmeconin (20 mg.) was obtained, separating from methanol as blades, m. p. 193° undepressed by the preparation above. The acidic fraction crystallised from aqueous ethanol (charcoal), to give meconin-4-carboxylic acid (150 mg.) as needles, m. p. and mixed m. p. 220—221° (*idem*, *J.*, 1952, 4878) (Found: C, 55·7; H, 4·4. Calc. for $C_{11}H_{10}O_6$: C, 55·5; H, 4·2%). Light absorption: Max. at 216 (ε = 28,700) and 318 mμ (ε = 6000).

7-*Methoxy*-6-*methylphthalide*-4-*carboxylic Acid*.—4-Hydroxymethyl-7-methoxy-6-methylphthalide (250 mg.) was treated with *N*-bromosuccinimide (3 mols.) as in the foregoing experiment. No crystalline material was obtained from the neutral fraction. The acidic fraction gave 7-methoxy-6-methylphthalide-4-carboxylic acid (150 mg.), separating from aqueous ethanol as needles, m. p. 232—233° alone or mixed with *iso*gladiolic acid (Found: C, 59·5; H, 4·8. Calc. for $C_{11}H_{10}O_5$: C, 59·5; H, 4·5%). Light absorption: Max. at 216 (ε = 34,000), 298 (ε = 4800), and inflexion at 248 mμ (ε = 8,500).

3-*Acetoxy*-4-*formylmeconin*.—3-Formylopianic acid (500 mg.) (*loc. cit.*) was heated with acetic anhydride (5 c.c.) and glacial acetic acid (5 c.c.) on the steam-bath for 1½ hr. The cooled solution was poured on ice (30 g.), and the mixture extracted with chloroform (3 × 30 c.c.). The chloroform extract was washed with water, sodium hydrogen carbonate solution, and water, and dried (Na_2SO_4). Removal of the chloroform under reduced pressure followed by crystallisation from ethanol gave 3-*acetoxy*-4-*formylmeconin* (400 mg.) as needles, m. p. 177° (Found:

C, 55·7; H, 4·5. $C_{13}H_{12}O_7$ requires C, 55·7; H, 4·3%). Light absorption: Max. at 235 (ε = 18,500), 280 (ε = 3700) and 320 mμ (ε = 4300). It is most important that the reaction mixture should be free from mineral acid since the presence of a trace of the latter causes formation of 3-acetoxy-4-diacetoxymethylmeconin.

3-*Acetoxy*-4-*diacetoxymethylmeconin*.—3-Formylopianic acid (100 mg.), suspended in acetic anhydride (2 c.c.), was treated with sulphuric acid (1 drop; *d* 1·84); dissolution took place rapidly. The solution was heated on the steam-bath for 5 min., cooled, and poured on ice. The precipitate was collected and crystallised from aqueous ethanol from which 3-*acetoxy*-4-*diacetoxymethylmeconin* (120 mg.) separated as needles, m. p. 120—121° (Found: C, 53·5; H, 5·0. $C_{17}H_{18}O_{10}$ requires C, 53·4; H, 4·75%). Light absorption: Max. at 219 (ε = 29,400) and 312 mμ (ε = 4000).

3-*Acetoxy*-4-*hydroxymethylmeconin*.—3-Acetoxy-4-formylmeconin (1·43 g.), partly dissolved in glacial acetic acid (150 c.c.), was added to a suspension of freshly reduced platinum (from Adams platinum oxide; 300 mg.) in glacial acetic acid (25 c.c.), and the mixture shaken with hydrogen at room temperature for 3 hr., by which time absorption (150 c.c.; calc., 135 c.c. for 1 mol.) had ceased. Removal of the catalyst and evaporation under reduced pressure gave an oil which rapidly solidified. Crystallisation from benzene–light petroleum (b. p. 60—80°) gave 3-*acetoxy*-4-*hydroxymethylmeconin* (1·1 g.) as needles, m. p. 136° (Found: C, 55·5; H, 5·2. $C_{13}H_{14}O_7$ requires C, 55·3; H, 5·0%). Light absorption: Max. at 218 (ε = 31,400) and 314 mμ (ε = 4200).

3-*Hydroxymethylopianic Acid*.—3-Acetoxy-4-hydroxymethylmeconin (1·08 g.) was treated with aqueous sodium hydroxide (60 c.c.; 0·1N) at room temperature; dissolution was rapid. After 2 min. the solution was acidified (Congo-red) with hydrochloric acid (*d* 1·16) and stored at 0° overnight. The solid which had separated was collected, washed with water, dried over phosphoric oxide *in vacuo*, and crystallised from ethyl acetate–light petroleum (b. p. 60—80°), to give 3-*hydroxymethylopianic acid* (500 mg.) as fine needles, m. p. 141° (Found: C, 55·2; H, 5·2%; equiv., 235. $C_{11}H_{12}O_6$ requires C, 55·0; H, 5·0%; equiv., 240). Light absorption: Max. at 216 (ε = 27,400) and 308 mμ (ε = 3500) in ethanol; 246 (ε = 3900) and 311 mμ (ε = 3150) in chloroform. The 2 : 4-*dinitrophenylhydrazone* separated from ethanol as red needles, which shrink at 215—220° and decompose gradually as the temperature is raised to 350° (Found: N, 13·5. $C_{17}H_{16}O_9N_4$ requires N, 13·3%). 3-Hydroxymethylopianic acid gave no colour with aqueous ammonia (*d* 0·88), and did not reduce Schiff's reagent, Fehling's solution, or ammoniacal silver nitrate.

4-*Formylmeconin from* 3-*Hydroxymethylopianic Acid*.—(*a*) The acid (140 mg.) was heated under reflux with sulphuric acid (5 c.c.; 2N) for 4½ hr. The red solution was decanted from tar and cooled, and the solid collected, washed with sodium hydrogen carbonate solution, and water, and crystallised from methanol. 4-Formylmeconin (10 mg.) separated as blades, m. p. 194—195° alone or mixed with an authentic specimen (Found: C, 59·4; H, 4·9. Calc. for $C_{11}H_{10}O_5$: C, 59·5; H, 4·5%).

(*b*) 3-Hydroxymethylopianic acid (100 mg.) was heated to 200° and the melt sublimed at 190°/10^{-3} mm. The small amount of sublimate was crystallised from methanol to give 4-formylmeconin (2 mg.) as blades, m. p. 192—193° alone or mixed with preparation (*a*).

3-*Acetoxy*-4-*acetoxymethylmeconin*.—(*a*) 3-Acetoxy-4-hydroxymethylmeconin (40 mg.) in dry pyridine (0·2 c.c.) and acetic anhydride (0·2 c.c.) was kept at room temperature overnight. The product was precipitated by addition of water (5 c.c.), separated, and crystallised from aqueous ethanol from which 3-*acetoxy*-4-*acetoxymethylmeconin* (38 mg.) formed needles, m. p. 124° (Found: C, 55·7; H, 5·3. $C_{15}H_{16}O_8$ requires C, 55·55; H, 5·0%). Light absorption: Max. at 218 (ε = 30,800) and 213 mμ (ε = 4000).

(*b*) 3-Hydroxymethylopianic acid (50 mg.) was acetylated as in (*a*), giving 3-acetoxy-4-acetoxymethylmeconin (50 mg.) which separated from aqueous ethanol as needles, m. p. 125° alone or mixed with preparation (*a*) (Found: C, 55·4; H, 5·3%).

3-*Ethoxy*-4-*formylmeconin*.—A solution of 3-formylopianic acid (500 mg.) in dry ethanol (5 c.c.), with sulphuric acid (5 drops; *d* 1·84) added, was heated under reflux for 30 min. The cooled solution was diluted with water and extracted with ether, and the ethereal extract washed with sodium hydrogen carbonate solution, and water, and dried (Na_2SO_4). Removal of the ether and crystallisation of the residue from benzene–light petroleum (b. p. 60—80°) gave 3-ethoxy-4-formylmeconin (200 mg.) as needles, m. p. 107—108° (Found: C, 58·6; H, 5·5. $C_{13}H_{14}O_6$ requires C, 58·6; H, 5·3%). Light absorption: Max. at 230 (ε = 16,800), 278 (ε = 3700), and 323 mμ (ε = 3900).

4-*Hydroxymethylmeconin*.—(*a*) A solution of 3-formylopianic acid (250 mg.) in sodium hydro-

gen carbonate solution (15 c.c.; 10%) was treated at room temperature with sodium borohydride (250 mg.) and stored overnight. The solution was acidified (Congo-red) with dilute hydrochloric acid and extracted with chloroform (3 × 20 c.c.). The combined extracts were washed with water (20 c.c.), dried (Na_2SO_4), and evaporated. Crystallisation of the residue from benzene gave 4-hydroxymethylmeconin (200 mg.) as needles, m. p. 129° alone or mixed with a specimen prepared by Brown and Newbold (*J.*, 1952, 4878) (Found: C, 59·0; H, 5·7. Calc. for $C_{11}H_{12}O_5$: C, 58·9; H, 5·4%). Light absorption in ethanol: Max. at 212 (ε = 28,600) and 312 mμ (ε = 4100); in chloroform: Max. at 244 (ε = 5750) and 310 mμ (ε = 4400).

(*b*) A solution of 3-acetoxy-4-formylmeconin (150 mg.) in ethanol (30 c.c.) was added to a solution of sodium borohydride (150 mg.) in water (10 c.c.) at room temperature and kept for 5 hr. Working up as in (*a*) gave 4-hydroxymethylmeconin (70 mg.) which separated from benzene as needles, m. p. 127° alone or mixed with preparation (*a*) (Found: C, 59·25; H, 5·55%).

(*c*) A suspension of 3-acetoxy-4-hydroxymethylmeconin (50 mg.) in water (10 c.c.) was shaken with sodium borohydride (250 mg.) with warming to 40°, until dissolution was complete (5 min.). The solution was stored overnight at room temperature and worked up as in (*a*), to give 4-hydroxymethylmeconin (37 mg.), separating from benzene as needles, m. p. 127—128° alone or mixed with preparation (*a*) or (*b*) (Found: C, 58·65; H, 5·5%). 4-Hydroxymethylmeconin was similarly obtained from sodium borohydride reduction of 3-hydroxymethylopianic acid, and had m. p. and mixed m. p. 128°. The *benzoyl* derivative, prepared by the action of benzoyl chloride–pyridine on 4-hydroxymethylmeconin at room temperature overnight followed by working up *via* ether, separated from ethanol as needles, m. p. 131—132° (Found: C, 66·1; H, 5·2. $C_{18}H_{16}O_6$ requires C, 65·85; H, 4·9%).

4-Hydroxymethyl-7-methoxy-6-methylphthalide.—Gladiolic acid (100 mg.), dissolved in sodium hydrogen carbonate solution (10 c.c.; 10%), was treated with sodium borohydride (200 mg.) added in one portion at room temperature, and the solution was stored overnight, then acidified (Congo-red) with 3N-hydrochloric acid and extracted with chloroform (3 × 15 c.c.). The combined chloroform extracts were washed once with water, dried (Na_2SO_4), and evaporated, and the solid crystallised from benzene, to give 4-hydroxymethyl-7-methoxy-6-methylphthalide (80 mg.) as needles, m. p. 119° alone or mixed with a specimen prepared by Brown and Newbold (*J.*, 1953, 1285) (Found: C, 63·8; H, 6·0. Calc. for $C_{11}H_{12}O_4$: C, 63·45; H, 5·8%). Light absorption in ethanol: Max. at 212 (ε = 28,000), 237 (ε = 6200) and 298 mμ (ε = 3000); in chloroform: Max. at 244 (ε = 2250) and 299 mμ (ε = 3200). The *acetate*, prepared by the action of acetic anhydride and pyridine at room temperature overnight, separated from aqueous ethanol as needles, m. p. 95° (Found: C, 62·5; H, 5·8. $C_{13}H_{14}O_5$ requires C, 62·4; H, 5·6%). The compound sublimed rapidly at 90°/10^{-3} mm., and showed light absorption: Max. at 212 (ε = 33,800), 296 (ε = 3500), and an inflexion at 234 mμ (ε = 8200).

3-Formylopianic Acid.—3-Hydroxymethylopianic acid (170 mg.) was heated under reflux with a solution of sodium metaperiodate (500 mg.) in N-sulphuric acid (5 c.c.) for 15 min. The cooled solution deposited a crystalline sodium salt. This was dissolved in aqueous sodium carbonate (10%) and acidified (Congo-red) with hydrochloric acid (5N). The precipitated solid was crystallised from water, to give 3-formylopianic acid (105 mg.) as needles, m. p. and mixed m. p. 175—176° (Found: C, 55·6; H, 4·4. Calc. for $C_{11}H_{10}O_6$: C, 55·5; H, 4·2%).

The authors thank Professor F. S. Spring, F.R.S., for his continued encouragement, Mr. J. F. Grove, whose co-operation has been most valuable, the Governors of The Royal Technical College for the award of the Nobel Scholarship (to J. J. B.), and Messrs. T. & H. Smith, Ltd., for gifts of chemicals. The microanalyses were by Mr. Wm. McCorkindale and the ultra-violet absorption spectra were measured by Miss Elizabeth Davidson. Mr. J. McDonald gave some experimental assistance.

THE ROYAL TECHNICAL COLLEGE, GLASGOW. [*Received, July 15th*, 1953.]