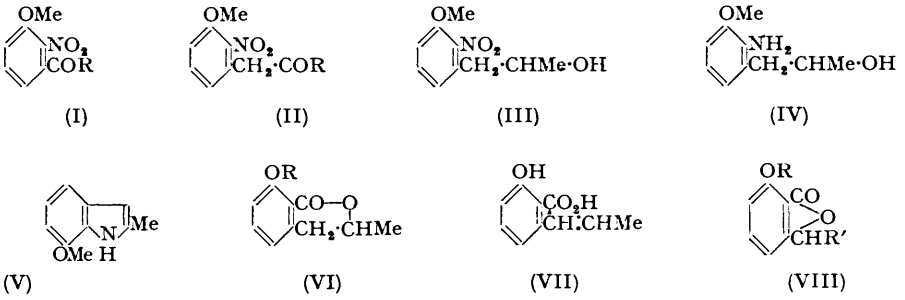
Lactones. Part II. The Structure of Mellein.*

By JOHN BLAIR and G. T. NEWBOLD.

[Reprint Order No. 6337.]

Mellein (ochracin) is shown to be (−)-3 : 4-dihydro-8-hydroxy-3-methyl-*iso*coumarin by the synthesis of its (±)-methyl ether (cf. *Chem. and Ind.*, 1955, 93). Two new syntheses of *iso*ochracin confirm its structure as 3-ethyl-7-hydroxyphthalide.

WHEN the fungus *Aspergillus melleus* Yukawa is grown on a medium containing sucrose (Nishikawa, *J. Agric. Chem. Soc. Japan*, 1933, **9**, 772) or maltose (Burton, *Nature*, 1950, **165**, 274) mellein is produced. Yabuta and Sumiki (*J. Agric. Chem. Soc. Japan*, 1934, **10**, 703) have shown that mellein is identical with ochracin, a metabolic product of *A. ochraceus* (*idem*, *ibid.*, 1933, **9**, 1264). Chemical studies on mellein (Nishikawa, *ibid.*, 1933, **9**, 1059; Yabuta and Sumiki, *locc. cit.*) indicate that mellein must have either structure (VI; R = H) or (VIII; R = H, R′ = Et). Tamura (*ibid.*, 1939, **15**, 685) has claimed a synthesis of the latter compound, 3-ethyl-7-hydroxyphthalide, which was identical with *iso*ochracin [formed by the action of hot sulphuric acid on melleic acid (VII) which is produced by mild alkali fusion of mellein (Yabuta and Sumiki, *loc. cit.*, 1934)]. Tamura's synthesis, further discussed below, was ambiguous in that the structural assignment of the product was entirely dependent on the degradative studies on mellein. Mellein has been given the phthalide structure or the related hydroxy-acid formulation in two recent reviews on mould products (Raistrick, *Proc. Roy. Soc.*, 1949, *A*, **199**, 141; Aghoramurthy and Seshadri, *J. Sci. Ind. Res., India*, 1954, **13**, *A*, 114); more recently Birch and Donovan (*Chem. and Ind.*, 1954, 1047) have favoured the structure (VI; R = H) on chemical and biogenetic grounds but cite no additional experimental support. We therefore considered it desirable to confirm that mellein has structure (VI; R = H) by a direct synthetical approach.



The starting material for this work was 3-methoxy-2-nitrobenzoic acid (I; R = OH) (Ewins, *J.*, 1912, **101**, 544) which was converted by the Arndt–Eistert procedure into 3-methoxy-2-nitrophenylacetic acid (II; R = OH), previously prepared from 3-methoxy-2-nitrotoluene by the oxalation method (Blaikie and Perkin, *J.*, 1924, **125**, 296). The acid chloride (II; R = Cl), obtained as described by Barger and Schlittler (*Helv. Chim. Acta*, 1932, **15**, 381), was transformed by the ethoxymagnesiomalonate method *via* the intermediate ethyl 3-methoxy-2-nitrophenylacetylmalonate into 3-methoxy-2-nitrophenylacetone (II; R = Me). This nitro-ketone on reduction with sodium borohydride gave a high yield of 1-(3-methoxy-2-nitrophenyl)propan-2-ol (III) which on hydrogenation over nickel afforded the amine (IV). If 3-methoxy-2-nitrophenylacetone is hydrogenated over nickel, 7-methoxy-2-methylindole (V) is formed in good yield. Diazotisation of the amine, conversion into the nitrile (which was not purified), and subsequent alkaline hydrolysis gave (±)-3 : 4-dihydro-8-methoxy-3-methyl*iso*coumarin (VI; R = Me), m. p. 66—67°. The compound gave an intermediate m. p. on admixture with (−)-mellein

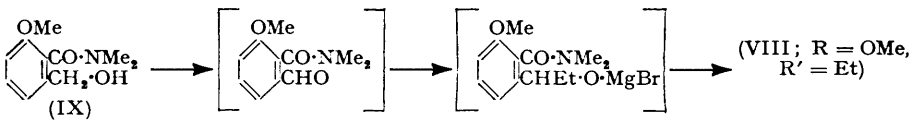
* Part I, *J.*, 1955, 708.

methyl ether, m. p. 88—89°, and the ultraviolet and infrared absorption spectra of both compounds (the latter in CCl_4) were identical. The carbonyl stretching frequencies of both compounds in solution (1741 cm.$^{-1}$) and in the solid state (1716 cm.$^{-1}$) when compared with those of 7-methoxyphthalide (Duncanson, Grove, and Zealley, *J.*, 1953, 1331) in the same solvent (1782 cm.$^{-1}$) and in the solid state (1748 cm.$^{-1}$) are consistent with the existence of a six-membered ring in (VI; R = Me). (—)-Mellein methyl ether is recovered after boiling with alkali, no appreciable racemization being detected.

Having established that mellein is (—)-3 : 4-dihydro-8-hydroxy-3-methyl*iso*coumarin (VI; R = H), we directed attention to *iso*ochracin which must be 3-ethyl-7-hydroxyphthalide (VIII; R = H, R′ = Et).

In Tamura's synthesis (*loc. cit.*) of 3-ethyl-7-hydroxyphthalide (VIII; R = H, R′ = Et) the first stage consisted in the condensation of 3-nitrophthalic anhydride with sodium propionate and propionic anhydride to give 3-ethylidene-7-nitrophthalide. We have been unable to repeat this work and this, together with recent experiences in the orientation of products of the Doebner reaction of 3-methoxy- (Kuhn and Dury, *Chem. Ber.*, 1951, **84**, 848; Hochstein and Pasternack, *J. Amer. Chem. Soc.*, 1952, **74**, 3905) and 3-nitro-phthalic anhydride (*loc. cit.*) in which the condensations went in the opposite direction from those described by Tamura, made it desirable to synthesise *iso*ochracin by an unambiguous method, and in fact two such methods have been developed. In the first, an obvious analogy with the use of 2-amino-3-methoxyacetophenone in the synthesis of 7-methoxy-3-methylphthalide (VIII; R = H, R′ = Me) by Kushner, Morton, Boothe, and Williams (*J. Amer. Chem. Soc.*, 1953, **75**, 1097) suggested the corresponding propiophenone as a starting material. Though in our hands attempts to nitrate *m*-methoxypropiophenone were unsuccessful, 3-methoxy-2-nitropropiophenone (I; R = Et) was obtained from 3-methoxy-2-nitrobenzoyl chloride by application of the ethoxymagnesiomalonate method to give ethyl 3-methoxy-2-nitrobenzoylmalonate (not isolated), which was *C*-methylated; the product on hydrolysis and decarboxylation gave the ketone (I; R = Et), a useful extension of Walker and Hauser's reaction. 3-Methoxy-2-nitropropiophenone was reduced by sodium borohydride to the corresponding nitro-alcohol which was hydrogenated to the amino-alcohol, and the latter, by successive diazotisation, treatment with nickel potassium cyanide, and alkaline hydrolysis, was converted into crude 3-ethyl-7-methoxyphthalide. All these compounds were uncrystallisable; the last was chromatographed but remained a viscous oil (cf. Tamura, *loc. cit.*). Demethylation of 3-ethyl-7-methoxyphthalide gave the phthalide (VIII; R = H, R′ = Et) which was identical with *iso*ochracin.

The second method for the synthesis of *iso*ochracin was based on the reaction of a phthalaldehydic acid with excess of an alkylmagnesium halide to give a 3-alkylphthalide (Simonis, Marben, and Mermod, *Ber.*, 1905, **38**, 398; Mermod and Simonis, *ibid.*, 1906, **39**, 897). The latter authors claim an 86% yield of 3-ethylmeconin (3-ethyl-6 : 7-dimethoxyphthalide) from opianic acid (5 : 6-dimethoxyphthalaldehydic acid); in our hands a very low yield was obtained in this reaction with high recovery of the acid. We attribute the failure of this reaction to the low solubility of opianic acid in ether; therefore,



the ether-soluble 6-formyl-2 : 3-dimethoxy-*NN*-dimethylbenzamide, the intermediate in the preparation of opianic acid by the method of Blair, Brown, and Newbold (*J.*, 1955, 708), was treated with an excess of the appropriate Grignard reagent; acid hydrolysis of the products gave 3-methyl- and 3-ethyl-meconin in good yields. Application of this method starting from 6-hydroxymethyl-2-methoxy-*NN*-dimethylbenzamide (IX) (Blair, Brown, and Newbold, *loc. cit.*) gave in good yield 3-ethyl-7-methoxyphthalide which on demethylation gave 3-ethyl-7-hydroxyphthalide (*iso*ochracin).

A comparison between the ultraviolet absorption spectrum above 2200 Å of mellein

with those of certain 7-hydroxyphthalides is given in the Table. The strong bathochromic shift of the maxima in mellein compared with the positions of those in the phthalides is noteworthy and might be of diagnostic use in deciding between isomeric 3 : 4-dihydro*iso*-coumarin and phthalide structures.

Compound	Solvent	$\lambda_{max.}$ (Å)	ε	$\lambda_{max.}$ (Å)	ε
Mellein [a]	EtOH	2460	6500	3140	4100
*iso*Ochracin [a]	EtOH	2340	7000	3000	4600
7-Hydroxy-3-methylphthalide [b]	MeOH	2320	7500	2980	4700
7-Hydroxyphthalide [c]	EtOH	2320	8700	2990	4600

[a] This paper; [b] Hochstein and Pasternack (*loc. cit.*); [c] Blair, Brown, and Newbold (*loc. cit.*).

Experimental

Ultraviolet spectra were determined in ethanol.

* 3-*Methoxy*-2-*nitrobenzoyl Chloride*.—3-Methoxy-2-nitrobenzoic acid (9·0 g.; Ewins, *loc. cit.*) was refluxed with redistilled thionyl chloride (60 c.c.) for 2 hr. Excess of reagent was removed under reduced pressure, benzene added to the residue, and this likewise removed, both operations conducted at bath-temperature $< 40°$. The solid residue was kept *in vacuo* overnight over sodium hydroxide, the crude product being used directly for the next stage. A specimen, crystallised from anhydrous ether, gave 3-*methoxy*-2-*nitrobenzoyl chloride* as needles, m. p. 85° (Found: C, 44·7; H, 2·55. $C_8H_6O_4NCl$ requires C, 44·6; H, 2·8%). The acid chloride decomposes on storage.

* *Diazomethyl* 3-*Methoxy*-2-*nitrophenyl Ketone*.—A solution of diazomethane in ether (250 c.c.) [from methylnitrosourea (33 g.)] was treated with a solution of 3-methoxy-2-nitrobenzoyl chloride (9·0 g.) in dioxan (30 c.c.) with agitation at 0°, and kept overnight at room temperature. Removal of the solvent under reduced pressure gave the diazo-ketone (9·0 g.). Crystallisation from dioxan gave *diazomethyl* 3-*methoxy*-2-*nitrophenyl ketone* as prisms, m. p. 144° (decomp.) (Found: C, 49·2; H, 3·45. $C_9H_7O_4N_3$ requires C, 48·9; H, 3·2%). Light absorption: Max. at 2160 (ε 24,000), 2480 (ε 18,400) and 2980 Å (ε 10,400).

* 3-*Methoxy*-2-*nitrophenylacetic Acid*.—A solution of the foregoing diazo-ketone (9·0 g.) in warm dioxan (75 c.c.) was added in portions during 20 min. to a stirred mixture of freshly prepared silver oxide (4·0 g.) in distilled water (150 c.c.) in which sodium thiosulphate (3·0 g.) and anhydrous sodium carbonate (5·0 g.) had been dissolved, the temperature being kept at 50—60°. After a further hour at 50—60° the temperature was raised to 90—95° for ½ hr. and then the mixture was filtered and the filtrate diluted with water (200 c.c.), acidified with dilute nitric acid, and extracted with chloroform (3 × 200 c.c.). The combined chloroform extracts were washed with water (50 c.c.) and dried (Na_2SO_4). Removal of the chloroform gave a tar which was extracted with boiling water (2 × 100 c.c.). Concentration of the combined extracts, followed by cooling, gave 3-*methoxy*-2-*nitrophenylacetic acid* (6·05 g.) which separated from water (charcoal) as needles, m. p. 136—137° (Found: C, 51·2; H, 4·2. Calc. for $C_9H_9O_5N$: C, 51·2; H, 4·3%). Light absorption: Max. at 2090 (ε 13,000), 2540—2600 (ε 2800), and 3000 Å (ε 1800). Blaikie and Perkin (*loc. cit.*) give m. p. 137—138°.

Ethyl 3-*Methoxy*-2-*nitrophenylacetylmalonate*.—3-Methoxy-2-nitrophenylacetic acid (4·22 g.) was converted into the acid chloride as described by Barger and Schlittler (*loc. cit.*) and a solution of the latter compound in ether (25 c.c.) added during 10 min. to refluxing ethereal ethyl ethoxymagnesiomalonate, prepared from ethyl malonate (3·52 g.) as prescribed in *Org. Synth.*, **30**, 70. A thick viscous oil was formed and heating was continued for ½ hr. until stirring became difficult. The cooled mixture was shaken with dilute sulphuric acid (2·5 g. in 20 c.c. of water) until the oily magnesium complex had dissolved. The ethereal phase was separated, washed with water, dried (Na_2SO_4), and evaporated, to give the crude product (6·0 g.) which solidified. A specimen, crystallized from aqueous ethanol, gave *ethyl* 3-*methoxy*-2-*nitrophenylacetylmalonate* as fine needles, m. p. 85—86° (Found: C, 54·4; H, 5·2. $C_{16}H_{19}O_8N$ requires C, 54·4; H, 5·4%). Light absorption: Max. at 2060 (ε 16,000) and 2500 Å (ε 7250).

3-*Methoxy*-2-*nitrophenylacetone*.—Crude ethyl 3-methoxy-2-nitrophenylacetylmalonate (5·7 g.) in acetic acid (12 c.c.), sulphuric acid (1·5 c.c.; *d* 1·84), and water (8 c.c.) was refluxed for 6 hr.; evolution of carbon dioxide was then no longer apparent. The cooled solution was made alkaline with 5N-sodium hydroxide and extracted with ether (3 × 50 c.c.). The combined ethereal extract was washed with water, dried (Na_2SO_4), and evaporated, to give an oil which rapidly solidified. Crystallisation from aqueous ethanol gave 3-*methoxy*-2-*nitrophenylacetone*

* Dr. J. J. Brown assisted in experiments marked thus.

(2·0 g.) as long needles, m. p. 61—62° (Found : C, 57·6; H, 5·15. $C_{10}H_{11}O_4N$ requires C, 57·4; H, 5·3%). Light absorption : Max. at 2060 (ε 15,800), 2650 (ε 1500), and 2900—3060 Å (ε 1200).

7-Methoxy-2-methylindole.—3-Methoxy-2-nitrophenylacetone (1·2 g.) in ethyl acetate (100 c.c.) was shaken at room temperature and atmospheric pressure in hydrogen in the presence of Raney nickel (1 g.; W6, *Org. Synth.*, **29**, 25). Absorption was rapid, and complete after ½ hr. The filtered solution was evaporated under reduced pressure and the residue crystallized from light petroleum (b. p. 40—60°), to give *7-methoxy-2-methylindole* (900 mg.) as long needles, m. p. 83—85° (Found : C, 74·6; H, 6·4. $C_{10}H_{11}ON$ requires C, 74·5; H, 6·8%). Light absorption : Max. at 2200 (ε 50,000) and 2650 Å (ε 9000). The *picrate* separated from aqueous methanol as fine red needles, m. p. 153° (Found : C, 48·85; H, 3·42. $C_{16}H_{14}O_8N_4$ requires C, 49·2; H, 3·6%). Light absorption : Max. at 2220 (ε 45,000), 2380—2420 (ε 13,400), and 3570 Å (ε 16,200). 7-Methoxy-2-methylindole dissolves in warm 5N-hydrochloric acid, being recovered on basification of the solution; in benzene solution, on treatment with aqueous-ethanolic *p*-dimethylaminobenzaldehyde hydrochloride, it gives a violet-red colour, indistinguishable from that given by 2-methylindole (Ehrlich's reaction).

1-(3-Methoxy-2-nitrophenyl)propan-2-ol.—A solution of 3-methoxy-2-nitrophenylacetone (1·0 g.) in ethanol (30 c.c.) and water (10 c.c.) was kept at room temperature for 2 hr. with sodium borohydride (750 mg.), then diluted with water (100 c.c.) and extracted with chloroform (3 × 50 c.c.). The dried (Na_2SO_4) extract was evaporated and the residue crystallized from benzene–light petroleum (b. p. 60—80°), to give the *alcohol* (900 mg.) as needles, m. p. 82—83° subliming at 70°/0·001 mm. (Found : C, 56·8; H, 6·4. $C_{10}H_{13}O_4N$ requires C, 56·9; H, 6·2%). Light absorption : Max. at 2140 (ε 11,600), 2720 (ε 1550), and inflexion at 2360—2460 Å (ε 1700).

1-(2-Amino-3-methoxyphenyl)propan-2-ol.—The foregoing alcohol (500 mg.) in ethyl acetate (50 c.c.) was shaken at room temperature and atmospheric pressure in hydrogen with the above Raney nickel catalyst (0·5 g.) until absorption was complete (5 min. with fresh catalyst). The filtered solution was evaporated under reduced pressure and the residue crystallized from light petroleum (b. p. 40—60°), to give the *amine* (400 mg.) as needles, m. p. 69° subliming at 60°/0·001 mm. (Found : C, 66·4; H, 8·6. $C_{10}H_{15}O_2N$ requires C, 66·3; H, 8·3%). Light absorption : Max. at 2120 (ε 21,000), 2380 (ε 6600), and 2860 Å (ε 2500).

3 : 4-Dihydro-8-methoxy-3-methylisocoumarin.—A solution of the foregoing amino-alcohol (300 mg.) in hydrochloric acid (0·43 c.c.; *d* 1·16) and water (9 c.c.) was diazotised with a solution of sodium nitrite (120 mg.) in water (1 c.c.) at 0°. After neutralization with sodium carbonate the diazonium solution was added to one of potassium cyanide (380 mg.), nickel chloride (300 mg.), and anhydrous sodium carbonate (100 mg.) in water (10 c.c.) at 15° with stirring, kept for 2 hr., and heated at 70° for 15 min. The cooled reaction solution was extracted with ether (3 × 20 c.c.), and the combined, dried (Na_2SO_4) extracts were evaporated, to give a gum which was treated with aqueous potassium hydroxide (20 c.c.; 10%) and refluxed for 3 hr. The solution was acidified (Congo-red) and extracted with chloroform (3 × 25 c.c.); evaporation of the dried (Na_2SO_4) extract gave a gum which slowly solidified. Crystallization from light petroleum (b. p. 40—60°) gave *3 : 4-dihydro-8-methoxy-3-methylisocoumarin* (60 mg.) as prisms, m. p. 66—67° (Found : C, 68·7; H, 6·6. $C_{11}H_{12}O_3$ requires C, 68·7; H, 6·3%). Light absorption : Max. at 2120 (ε 28,000), 2440 (ε 7400), and 3050 Å (ε 4700).

Mellein Methyl Ether.—Mellein (26 mg.), m. p. 56—57° (lit., m. p. 58°), having absorption max. at 2120 (ε 20,000), 2460 (ε 6500), and 3140 Å (ε 4100), was kept in excess of ethereal diazomethane at room temperature for 3 days. The solution was evaporated, the residual gum taken up in benzene (5 c.c.), the solution filtered through a column of Grade II alumina (3 × 1 cm.), and the column washed with benzene (200 c.c.). Evaporation of the combined eluates and crystallization of the solute from light petroleum (b. p. 60—80°) gave mellein methyl ether (18 mg.) as prisms, m. p. 88—89° (lit., 88—89°), $[\alpha]_D^{15}$ −245°, −250° (*c*, 1·1, 0·5 in $CHCl_3$). A mixture with the synthetic lactone had an intermediate m. p. Light absorption : Max. at 2130 (ε 27,000), 2430 (ε 7200), and 3050 Å (ε 4500).

Attempted racemization. Mellein methyl ether (11 mg.) was refluxed for 6 hr. with 3N-sodium hydroxide (5 c.c.). Acidification and isolation, by means of chloroform, followed by crystallization from light petroleum (b. p. 60—80°), gave starting material (8 mg.) as prisms, m. p. and mixed m. p. 86—88°, $[\alpha]_D^{15}$ −240° (*c*, 0·4 in $CHCl_3$).

3-Methylmeconin.—6-Hydroxymethyl-2 : 3-dimethoxy-*NN*-dimethylbenzamide (2·0 g.) was prepared and oxidised with chromic acid as described by Blair, Brown, and Newbold (*loc. cit.*) and the resulting crude aldehyde in ether (10 c.c.) treated at 15° with the Grignard reagent prepared from methyl iodide (1·42 g.) and magnesium (250 mg.) in ether (10 c.c.). The mixture was refluxed for 1 hr., cooled, treated with hydrochloric acid (100 c.c.; 3N), and refluxed for

1½ hr. The cooled mixture was extracted with ether (3 × 100 c.c.), and the combined extracts were washed with water, 10% aqueous sodium hydrogen carbonate, and water, and dried (Na_2SO_4). Evaporation of the ether and crystallization of the residue from benzene–light petroleum (b. p. 60—80°) gave 3-methylmeconin (60%) as prismatic needles, m. p. 101° (subliming at 100°/0·001 mm.) and not depressed on admixture with a specimen prepared in 5% yield by the method of Simonis, Marben, and Mermod (*loc. cit.*) (Found: C, 63·0; H, 6·0. Calc. for $C_{11}H_{12}O_4$: C, 63·45; H, 5·8%). Light absorption: Max. at 2150 (ε 29,000) and 3060 Å (ε 4300). By the same method, except that ethylmagnesium bromide was used, 3-ethylmeconin was prepared in 70% yield; it separated from aqueous ethanol as short prisms, m. p. 98° (Found: C, 65·1; H, 6·3. Calc. for $C_{12}H_{14}O_4$: C, 64·85; H, 6·35%). Light absorption: Max. at 2140 (ε 27,500) and 3080 Å (ε 4000). Mermod and Simonis (*loc. cit.*) give m. p. 98°.

3-*Methoxy*-2-*nitropropiophenone*.—By the technique described above for the preparation of ethyl 3-methoxy-2-nitrophenylacetylmalonate, 3-methoxy-2-nitrobenzoyl chloride (4·4 g.) was converted into crude ethyl 3-methoxy-2-nitrobenzoylmalonate (5·5 g.). This semi-solid was dissolved in ethanolic sodium ethoxide [from sodium (0·5 g.) and ethanol (10 c.c.)], methyl iodide (2 c c.) was added, and the solution refluxed for 3 hr. during which methyl iodide (2 c.c.) was added in four portions. The cooled solution was diluted with water and extracted with ether (3 × 15 c c.), and the combined ethereal extracts were washed with water and dried (Na_2SO_4). Removal of the ether gave a gum which was treated as described in the preparation of 3-methoxy-2-nitrophenylacetone, to give 3-methoxy-2-nitropropiophenone (1·1 g.) which separated from aqueous ethanol as small needles, m. p. 96° subliming at 80°/0·001 mm. (Found: C, 57·3; H, 5·1. $C_{10}H_{11}O_4N$ requires C, 57·4; H, 5·3%). Light absorption: Max. at 2120 (ε 22,000), 2340—2400 (ε 5800), and 3080 Å (ε 2500).

3-*Ethyl*-7-*hydroxyphthalide*.—(*a*) 6-Hydroxymethyl-2-methoxy-*NN*-dimethylbenzamide (290 mg.) was oxidized as described by Blair, Brown, and Newbold (*loc. cit.*) and the resulting crude aldehyde in ether (20 c.c.) treated with ethereal ethylmagnesium bromide prepared from ethyl bromide (0·54 g.) and magnesium (0·12 g.) in ether (6 c.c.). A precipitate was formed immediately and the mixture was refluxed for 10 min., cooled, and treated with 3N-hydrochloric acid (40 c.c.), the ether distilled off, and the aqueous solution refluxed for ½ hr. The cooled solution was extracted with chloroform (3 × 50 c.c.), and the combined extracts were washed with water (25 c.c.), dried (Na_2SO_4), and evaporated to give a viscous oil, which did not crystallize even after filtration in benzene solution through Grade II alumina. The gum was refluxed with aqueous hydrobromic acid (20 c.c.; *d* 1·46) in a stream of coal-gas for 1 hr. The cooled solution was diluted with water (20 c.c.) and extracted with chloroform (4 × 50 c.c.), and the combined extracts were dried (Na_2SO_4) and evaporated to a brown resin. The latter was extracted with boiling light petroleum (b. p. 60—80°) (4 × 50 c.c.), and the combined extracts were concentrated to *ca.* 2 c.c. and kept at 0°. The resulting solid recrystallized from light petroleum (b. p. 40—60°), to give 3-ethyl-7-hydroxyphthalide (75 mg.) as needles, m. p. 78° subliming at 75°/0·001 mm. (Found: C, 67·2; H, 6·1. Calc. for $C_{10}H_{10}O_3$: C, 67·4; H, 5·7%). The compound was undepressed in m. p. on admixture with a specimen of *iso*ochracin, m. p. 78° (lit., 78—79°), prepared from mellein according to Yabuta and Sumiki's method (*J. Agric. Chem. Soc. Japan*, **1934**, **10**, 703). It gives a violet colour with ferric chloride in aqueous ethanol. Light absorption: Max. at 2140 (ε 18,400), 2340 (ε 7000), and 3000 Å (ε 4600).

(*b*) By the method described above for the preparation of 1-(3-methoxy-2-nitrophenyl)-propan-2-ol, 3-methoxy-2-nitropropiophenone (700 mg.) was reduced to the corresponding alcohol, a viscous oil, which was hydrogenated as given for its analogue. The product, a viscous oil, was converted into the oily 3-ethyl-7-methoxyphthalide by the method described above for the formation of 3 : 4-dihydro-8-methoxy-3-methyl*iso*coumarin. The crude methoxy-phthalide was demethylated with boiling aqueous hydrobromic acid as in (*a*), to give 3-ethyl-7-hydroxy-phthalide (20 mg.) which separated from light petroleum (b. p. 40—60°) as needles, m. p. 77—78° alone or mixed with preparation (*a*).

We are indebted to Dr. H. S. Burton for the generous gift of a sample of mellein, to Mr. J. F. Grove and Dr. L. A. Duncanson for the infrared data, to Dr. J. J. Brown for assistance, and to Messrs. T. and H. Smith, Ltd., for gifts of chemicals.

THE ROYAL TECHNICAL COLLEGE, GLASGOW. [*Received, April 15th*, 1955.]