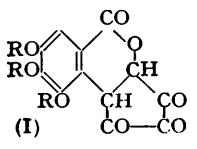
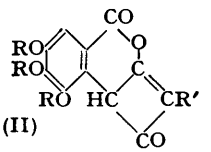
290. *Galloflavin. Part I.*

By R. D. Haworth and (Miss) J. M. McLachlan.

The preparation of galloflavin by aeration of alkaline solutions of gallic acid has been improved, the earlier degradative work of Herzig and his collaborators has been largely confirmed and extended, and new formulæ (IX; R = H) and (VII; R = H, R′ = CO_2H) have been proposed for galloflavin and *iso*galloflavin respectively. Two syntheses of 3-acetyl-4 : 5 : 6-trimethoxyphthalide (IV; R = Me), a degradation product of galloflavin, are described.

The yellow mordant dye, galloflavin, was first prepared by Bohn and Graebe (*Ber.*, 1897, **30**, 2327) by aeration of a solution of gallic acid in aqueous-alcoholic potassium hydroxide at 0°. The molecular formula, $C_{13}H_6O_9$, was proposed and crystalline tetra-acetyl and tetrachloroacetyl derivatives were described. Herzig and Tscherne (*Monatsh.*, 1904, **25**, 603) methylated galloflavin with diazomethane and later Herzig and Ruzicka (*ibid.*, 1910, **31**, 799) suggested that galloflavin was $C_{12}H_6O_8$ containing three phenolic hydroxyl groups and a lactone group. Methylation yielded a tetramethylgalloflavin, $C_{16}H_{14}O_8$, which on alkaline hydrolysis gave trimethyl*iso*galloflavin, $C_{15}H_{12}O_8$, containing a carboxyl group, esterified with methanolic hydrogen chloride to tetramethyl*iso*galloflavin, $C_{16}H_{14}O_8$. Methylation of tri- and tetra-methyl*iso*galloflavin first with methyl sulphate in alkaline solution, and then with diazomethane ruptured a lactone ring and gave a hexamethyl derivative, $C_{18}H_{20}O_9$, yielding, on hydrolysis, a dicarboxylic acid, $C_{16}H_{16}O_9$. On the basis of this experimental work, Herzig and Ruzicka suggested the presence of a carboxyl, a lactone, and three hydroxyl groups in *iso*galloflavin. They also showed that trimethyl*iso*-galloflavin and the dicarboxylic acid, $C_{16}H_{16}O_9$, were decarboxylated by heat and the products were more fully investigated later by Herzig and Waschler (*ibid.*, 1914, **35**, 77). This extension was made possible as these workers devised an improved preparation (28% yield) of *iso*galloflavin by the action of cold 10% potassium hydroxide on galloflavin. Methylation with diazomethane to tetramethyl*iso*galloflavin and subsequent alkaline hydrolysis gave trimethyl*iso*galloflavin, which was decarboxylated, and the product, $C_{14}H_{12}O_6$, subjected to regulated degradation with alkali. Heating with 5% aqueous-alcoholic potassium hydroxide gave a ketonic compound, $C_{13}H_{14}O_6$, which yielded 4 : 5 : 6-trimethoxyphthalide after treatment with 10% potassium hydroxide. In 1920, Herzig


(I)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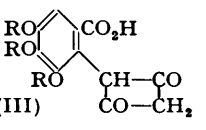
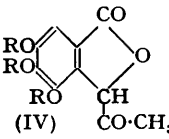

(III)

(*Annalen*, **421**, 247) interpreted these experimental findings on the basis of structures (I; R = H) and (II; R = H, R′ = CO_2H) for galloflavin and *iso*galloflavin, respectively, and the latter was derived from the former by a benzilic acid-type rearrangement. The ready decarboxylation of trimethyl*iso*galloflavin (II; R = Me, R′ = CO_2H) is understandable on the basis of the β-keto-acid structure and the subsequent conversion by alkaline hydrolysis into 4 : 5 : 6-trimethoxyphthalide was assumed to involve (*a*) hydrolysis of the lactone ring to a diketo*cyclo*butane derivative (III; R = Me), (*b*) fission of the latter to give (IV; R = Me) and formic acid, and (*c*) hydrolysis of (IV; R = Me) to 4 : 5 : 6-trimethoxyphthalide and acetic acid. The schemes relating to stage (*b*) are extremely improbable and unsatisfactory and in addition there are obvious stereochemical objections to structures such as (II).

As no research on the constitution of galloflavin has been reported since 1920, and in view of our interest in the oxidation of pyrogallol and other phenols, it was decided to reinvestigate the problem. The preparation and purification of galloflavin have been improved by the methods described in the Experimental section and the molecular formula,

$C_{12}H_6O_8$, confirmed. Galloflavin and its tetramethyl ether did not react with 2 : 4-dinitrophenylhydrazine or *o*-phenylenediamine, and the lack of ketonic activity is inconsistent with structure (I; R = Me). That a *cyclo*pentenedione system does in fact form ketonic derivatives is shown by the work of Koelsch and Geissmann (*J. Org. Chem.*, 1938, **3**, 480, 489) who prepared an oxime from 3 : 4-diphenyl*cyclo*pentene-1 : 2-dione and a quinoxaline from 3 : 4 : 5-triphenyl*cyclo*pentene-1 : 2-dione. Tetramethylgalloflavin contained no active hydrogen atoms, it was recovered from attempted reduction with hydrogen in presence of palladium–charcoal or platinic oxide catalysts, but oxidation with potassium permanganate in acetone solution gave 3 : 4 : 5-trimethoxyphthalic acid, thus



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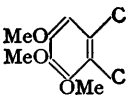

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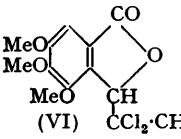


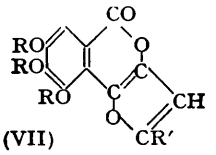
(VI)

establishing the presence of the grouping (V). An improved preparation of *iso*galloflavin is reported in the Experimental section and new analytical data suggest that *iso*galloflavin separates as a monohydrate, but the triacetyl, and tri- and tetra-methyl derivatives were readily obtained in solvent-free states. The decarboxylation and alkaline degradation of trimethyl*iso*galloflavin, reported by Herzig and his colleagues, has been repeated and confirmed, and the constitution of the phthalide precursor (IV; R = Me) has been established synthetically. 4 : 5 : 6-Trimethoxyphthalide-3-carboxylic acid, prepared as described by Bargellini and Molina (*Atti R. Accad. Lincei*, 1912, **21**, ii, 146), was converted by thionyl chloride into the corresponding chloride, which reacted with dimethylcadmium to yield an oil, from which a small yield of ketonic material was extracted with Girard-T reagent. The ketone was recovered as an impure oil, which gave a 2 : 4-dinitrophenylhydrazone identical with the derivative prepared from the phthalide precursor (IV; R = Me). In a second attempted synthesis the 4 : 5 : 6-trimethoxyphthalide-3-carboxylic acid chloride was converted into the corresponding amide, which was dehydrated with phosphoric oxide in boiling toluene to yield 3-cyano-4 : 5 : 6-trimethoxyphthalide, but no ketonic material was obtained by reaction of this nitrile with methylmagnesium iodide. A satisfactory synthesis of (IV; R = Me) was, however, effected by condensing αα-dichloropropaldehyde (Moelants, *Bull. Soc. chim. Belg.*, 1943, **52**, 53) with methyl trimethylgallate in presence of 98% sulphuric acid; 3-1′ : 1′-dichloroethyl-4 : 5 : 6-trimethoxyphthalide (VI), obtained in 75% yields, was converted by careful treatment with 2N-sodium hydroxide into 3-acetyl-4 : 5 : 6-trimethoxyphthalide (IV; R = Me) identical with the phthalide precursor, and this was converted into 3-1′ : 1′-dichloroethyl-4 : 5 : 6-trimethoxyphthalide (VI) by treatment with phosphorus pentachloride in toluene.

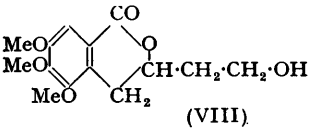
The positive identification of this degradation product (IV; R = Me) encouraged further investigation on the structure of *iso*galloflavin, and our experiments support Herzig's view that it contained three phenolic hydroxyl groups, a lactone group, and a carboxyl group so situated that it could be readily eliminated on heating. But as the triacetyl and tri- and tetra-methyl derivatives of *iso*galloflavin gave no ketonic reactions with 2 : 4-dinitrophenylhydrazine or *o*-phenylenediamine, and as the tri- and tetra-methyl derivatives were recovered from attempted Clemmensen reduction, it was unlikely that the eighth oxygen atom was ketonic. There are very few references in the literature to *cyclo*butenones but Dixit (*J. Univ. Bombay*, 1935, **4**, 153) claims to have prepared 2-carboxy-3-*p*-hydroxyphenyl*cyclo*but-2-enone, which gave a semicarbazone and a phenylhydrazone, and, unlike *iso*galloflavin, was unstable to moisture and dilute alkali. Further, as tetramethyl*iso*galloflavin evolved no methane in the Zerewitinoff test, hydroxyl groups must be excluded. When trimethyl*iso*galloflavin was decarboxylated, the product, $C_{14}H_{12}O_6$, was non-ketonic and much less stable towards acids and alkalis; it was resinified by acids and degraded by alkali to the acetylphthalide derivative (IV; R = Me), described previously. In addition, the product, $C_{14}H_{12}O_6$, was easily reduced in presence of palladium–charcoal to a mixture, which was separated by chromatography into tetra-

hydro- and hexahydro-derivatives melting at 83° and 84—85° respectively, and the former was converted into the hexahydro-derivative by further reduction. Both these reduction products were lactones, neither reacted with ketonic reagents, and the tetrahydro-derivative gave no methane with methylmagnesium iodide, but the hexahydro-derivative contained an active hydrogen atom and also yielded a crystalline 3 : 5-dinitrobenzoate. These results are inconsistent with both the *iso*galloflavin formula (II; R = H, R′ = CO_2H) and the structure (II; R = Me, R′ = H) for the decarboxylation product which should lead to a tetrahydro-derivative with secondary alcoholic properties, and the formation of the hexahydro-derivative would involve a rupture of the *cyclo*butane ring under exceptionally mild conditions.

Although it was abundantly clear that Herzig's formulæ were untenable, more satisfactory structures for galloflavin and its derivatives must still remain conjectural. In spite of this, however, we feel justified in proposing structures (VII; R = H, R′ = CO_2H), (VII; R = Me, R′ = CO_2Me), (VII; R = Me, R′ = CO_2H), and (VII; R = Me,

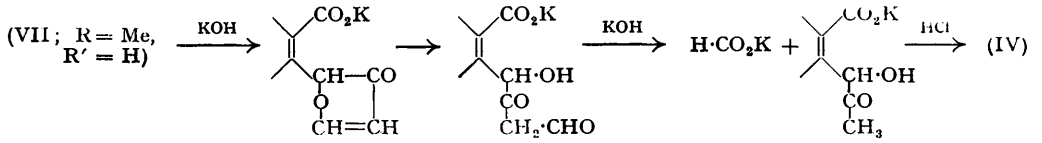


(VII)

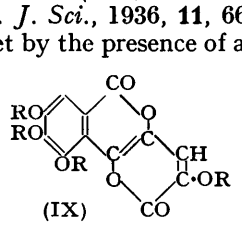


(VIII)

R′ = H) for *iso*galloflavin, tetramethyl*iso*galloflavin, trimethyl*iso*galloflavin, and the decarboxylation product, $C_{14}H_{12}O_6$, respectively, and a brief statement in support of these structures is advanced. The non-ketonic properties are explained, the tetrahydro-derivative mentioned above is interpreted as a tetrahydrofuran derivative, and its conversion into the hexahydro-derivative (VIII) containing an alcoholic group, corresponds to the usual hydrogenolysis of a benzyl ether. The furan-2-carboxylic acid structure (VII; R = H, R′ = CO_2H) for *iso*galloflavin and its derivatives is preferred to an analogous 3-carboxylic acid structure because it is consistent with (*a*) the ready decarboxylation of trimethyl*iso*galloflavin, (*b*) the influence of the 2-carboxyl group in stabilising the nucleus towards acids (as already indicated, trimethyl*iso*galloflavin is stable whereas the decarboxylation product is unstable to acids), and (*c*) the alkaline degradation of trimethyl-*iso*galloflavin, which is interpreted by the following scheme :



Although the furan ring is usually stable towards alkalis, the introduction of a 3-hydroxyl group causes instability (cf. Kohler, Westheimer, and Tischler, *J. Amer. Chem. Soc.*, 1936, **58**, 264) and the ring rupture employed in the scheme above corresponds exactly with ester or lactone hydrolysis. The mechanism accounts for the absorption of two equivalents of alkali, and the production of formic acid, and the increased stability of trimethyl*iso*-galloflavin (VII; R = Me, R′ = CO_2H) finds an analogy in the work of Hoehn (*Iowa State Coll. J. Sci.*, 1936, **11**, 66), who showed that the normal instability of 3-hydroxyfuran is offset by the presence of a 2-carboxyl group.



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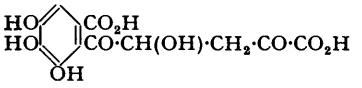

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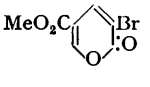


(XI)

On the basis of formula (VII; R = H, R′ = CO_2H) for *iso*galloflavin, the α-pyrone structure (IX; R = H) may be deduced for galloflavin. This is consistent with the

properties of the dye and the conversion into *iso*galloflavin *via* the hypothetical γ-diketonic intermediate product (X) is rational and analogous with the formation of furan-2 : 4-dicarboxylic acid by the action of alkali on (XI) (Feist, *Ber.*, 1901, **34**, 1992). Further work on these topics is in progress and a preliminary attempt to approach structure (VIII) from 4 : 5 : 6-trimethoxyindan-1-one, described in the Experimental section, indicates one of the synthetical routes which we are continuing to investigate.

Experimental

Galloflavin (IX; R = H).—Potassium hydroxide (67 c.c. of 28%) was added to gallic acid (25 g.) in water (500 c.c.) and ethyl alcohol (435 c.c.), and the solution was aerated at 0° for 5 hours. The precipitated yellow-green potassium salt was redissolved in water, then decomposed with 2N-hydrochloric acid in a nitrogen atmosphere, and the galloflavin (10 g.) collected, washed, and dried. A specimen was sublimed at 0·005 mm. (bath-temp., 220°); aggregates of small, stout, pale yellow prisms (Found : C, 51·5; H, 2·0. Calc. for $C_{12}H_6O_8$: C, 51·8; H, 2·2%) were obtained which decomposed at 290°. The alkaline filtrate from the potassium salt gave an additional small yield on further aeration.

Tetramethylgalloflavin (IX; R = Me).—An ethereal solution of diazomethane, prepared from nitrosomethylurea (10 g.), was added to a suspension of galloflavin (10 g.) in ether (50 c.c.). After 12 hours, tetramethylgalloflavin was collected; it crystallised from glacial acetic acid or amyl acetate in pale yellow needles (10 g.), m. p. 236—237° [Found : C, 57·2; H, 4·3; OMe, 36·6. Calc. for $C_{12}H_2O_4(OMe)_4$: C, 57·5; H, 4·2; OMe, 37·1%].

Oxidation of Tetramethylgalloflavin.—Potassium permanganate (75 c.c. of 2%) was added gradually with shaking to a suspension of tetramethylgalloflavin (0·5 g.) in acetone (12·5 c.c.). After a further 2 hours' shaking, the mixture was set aside overnight and then treated with a slight excess of sulphur dioxide. The solution was made strongly alkaline, evaporated to a small bulk, acidified with concentrated hydrochloric acid, and continuously extracted with ether for 6 hours. The dried extract was evaporated, and the residue sublimed at 0·3 mm. (bath-temp., 140—160°). The sublimate was triturated with chloroform and the insoluble crystals were collected and identified as oxalic acid. The chloroform filtrate was evaporated and the pale yellow residue, after two crystallisations from ether, gave colourless needles, m. p. 143—144°, which gave no depression with a synthetic specimen of 3 : 4 : 5-trimethoxyphthalic anhydride, m. p. 144—145°.

iso*Galloflavin* (VII; R = H, R′ = CO_2H).—A solution of galloflavin (10 g.) in 10% potassium hydroxide (175 c.c.) rapidly became dark, and after 45 minutes at room temperature concentrated hydrochloric acid was added carefully until the precipitate first formed just redissolved. Warming on the water-bath precipitated crude *iso*galloflavin as a dark solid which was collected and repeatedly extracted with hot methyl alcohol. The pale residue (4·8 g.) was insoluble in the usual organic solvents but, after treatment with boiling water, a *monohydrate* was obtained which crystallised from hot methyl alcohol in colourless needles, decomposing at 275—280° (Found, on material dried at 130°/0·5 mm. : C, 48·6; H, 2·6. $C_{12}H_6O_8,H_2O$ requires C, 48·7; H, 2·7%).

Triacetyl*iso*galloflavin (III; R = Ac, R′ = CO_2H), prepared by the action of acetic anhydride and sodium acetate on the monohydrate, crystallised from methyl alcohol in colourless silky needles, m. p. 223° (decomp.)[Found : C, 53·7; H, 3·1. Calc. for $C_{12}H_3O_5(OAc)_3$: C, 53·5; H, 3·0%], which did not react with 2 : 4-dinitrophenylhydrazine.

Tetramethyl*iso*galloflavin (VII; R = Me, R′ = CO_2Me), prepared by the action of diazomethane on an ethereal suspension of the monohydrate, separated from ethyl alcohol in colourless needles, m. p. 233—234° (Found : C, 57·5; H, 4·2. Calc. for $C_{16}H_{14}O_8$: C, 57·5; H, 4·2%), which did not react with 2 : 4-dinitrophenylhydrazine or with hydrogen in presence of a palladium–carbon catalyst, and gave a negative Zerewitinoff test.

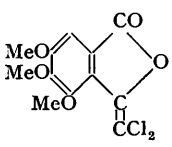
Trimethyl*iso*galloflavin (VII; R = Me, R′ = CO_2H), prepared by hydrolysis of tetramethyl*iso*galloflavin with potassium hydroxide as described by Herzig and Waschler (*loc. cit.*), separated from ethyl alcohol in colourless needles, m. p. 259—260° (Herzig and Waschler give m. p. 255—258°) (Found : C, 56·4; H, 3·9. Calc. for $C_{15}H_{12}O_8$: C, 56·3; H, 3·8%).

*Decarboxylation of Trimethyl*iso*galloflavin* (VII; R = Me, R′ = CO_2H).—Trimethyl*iso*galloflavin (1 g.) and copper powder (0·1 g.) were heated at 280° for 10 minutes. Distillation at 15 mm. (bath-temp., 280°) gave a yellow oil, which solidified on cooling; the product (VII; R = Me, R′ = H) crystallised from methyl alcohol in colourless needles (0·8 g.), m. p. 130—132° (Herzig, *Monatsh.*, 1910, **31**, 799, gives m. p. 130—134°) (Found : C, 61·5; H, 4·5. Calc.

for $C_{14}H_{12}O_6$: C, 60·9; H, 4·3%), which gave a negative Zerewitinoff test and failed to react with 2 : 4-dinitrophenylhydrazine.

Catalytic Reduction of $C_{14}H_{12}O_6$ (VII; R = Me, R′ = H).—A solution of the decarboxylation product (VII; R = Me, R′ = H) (0·47 g.) in ethyl alcohol was shaken with 25% palladium–charcoal (0·04 g.) in hydrogen for 6 hours at room temperature; 55·c.c. of hydrogen were absorbed. The mixture was then heated to 50° and the shaking continued for a further 12 hours, an additional 54 c.c. of hydrogen being taken up. After removal of the catalyst, concentration of the solution gave a small quantity (0·02 g.) of unchanged (VII; R = Me, R′ = H) and distillation of the residual oil (0·46 g.) at 0·007 mm. gave two fractions (*a*) and (*b*) with b. p. 215° and 230° (bath-temp.), respectively. Fraction (*a*) crystallised from ether in colourless prisms (0·04 g.), m. p. 83° (Found: C, 60·0; H, 5·7. $C_{14}H_{16}O_6$ requires C, 60·0; H, 5·7%). This *tetrahydrofuran* derivative, which gave a negative Zerewitinoff test and failed to react with 3 : 5-dinitrobenzoyl chloride and ketonic reagents, was insoluble in cold, but soluble in hot sodium hydroxide solution; it was recovered by acidification of the hot alkaline solution. A solution of fraction (*b*) (0·29 g.) in benzene (20 c.c.) was adsorbed on a column of alumina (12 g.) and eluted successively with benzene (75 c.c.), benzene–ether (9 : 1) (40 c.c.), benzene–ether (1 : 1) (100 c.c.), ether (50 c.c.), ether–acetone (9 : 1) (60 c.c.), and ether–acetone (1 : 1) (60 c.c.). The first five eluates were discarded but the sixth gave the *hexahydro*-derivative (VIII) (0·2 g.), which separated from ether in large colourless plates, m. p. 84—85° (Found: C, 59·6; H, 6·6; active hydrogen, 0·98. $C_{14}H_{18}O_6$ requires C, 59·6; H, 6·4%) depressed to 75—78° when mixed with a sample of the tetrahydrofuran derivative, m. p. 83°, described above. The hexahydro-derivative (VIII) had no ketonic properties, it was insoluble in cold but soluble in hot sodium hydroxide solution, and it was recovered by acidifying the solution and warming gently. The 3 : 5-*dinitrobenzoate*, prepared by reaction with 3 : 5-dinitrobenzoyl chloride and pyridine for 10 days at room temperature, separated from benzene in stout colourless prisms, m. p. 147·5—148·5° (Found: C, 53·3; H, 4·3; N, 6·0. $C_{21}H_{20}O_{11}N_2$ requires C, 52·9; H, 4·2; N, 5·9%). This hexahydro-derivative was also prepared from the tetrahydrofuran derivative (50 mg.) by reduction in presence of 10% palladium–charcoal (50 mg.) in ethyl alcohol at room temperature for 12 hours.

3-*Acetyl*-4 : 5 : 6-*trimethoxyphthalide* (IV; R = Me).—Prepared as described by Herzig and Tscherne (*loc. cit.*), this crystallised from methyl alcohol in colourless needles, m. p. 75—76° (Herzig and Tscherne, *loc. cit.*, give m. p. 74—77°) (Found: C, 58·9; H, 5·5. Calc. for $C_{13}H_{14}O_9$: C, 58·6; H, 5·3%), gave a 2 : 4-*dinitrophenylhydrazone*, m. p. 203—204° (Found: C, 51·3; H, 4·3; N, 12·4. $C_{19}H_{18}O_9N_4$ requires C, 51·1; H, 4·0; N, 12·5%), and, on hydrolysis with warm 10% alcoholic potassium hydroxide (20 parts) for 20 minutes, yielded 4 : 5 : 6-trimethoxyphthalide, m. p. 134—135°, identical with a synthetic specimen prepared from trimethylgallic acid, formaldehyde, and concentrated hydrochloric acid. The ketone (IV; R = Me) (0·1 g.), phosphorus pentachloride (0·2 g.), and benzene (25 c.c.) were refluxed for 12 hours. After being washed first with water and then with sodium hydrogen carbonate solution, the benzene solution was dried and the solvent removed; 3-1′ : 1′-dichloroethyl-4 : 5 : 6-trimethoxyphthalide (VI), m. p. 110—112°, was obtained, identical with the synthetic product described below (p. 1588).



3-*Dichloromethylene*-4 : 5 : 6-*trimethoxyphthalide* (inset).—This *phthalide* was obtained during the preparation of 4 : 5 : 6-trimethoxyphthalide-3-carboxylic acid, by boiling 3-trichloromethyl-4 : 5 : 6-trimethoxyphthalide (1 g.) (Bargellini and Molina, *loc. cit.*) with 12% sodium hydroxide solution (8 c.c.) for 2 hours. The mixture was cooled, and the solid crystallised from ethyl alcohol; colourless needles, m. p. 145—146° (Found: C, 46·9; H, 3·8; Cl, 22·9. $C_{12}H_{10}O_5Cl_2$ requires C, 47·2; H, 3·4; Cl, 23·2%), were obtained which gave 4 : 5 : 6-trimethoxyphthalide-3-carboxylic acid on further refluxing with sodium hydroxide solution.

4 : 5 : 6-*Trimethoxyphthalide*-3-*carboxyamide*.—4 : 5 : 6-Trimethoxyphthalide-3-carboxylic acid (1·2 g.) was heated with thionyl chloride (10 c.c.), and after 2 hours excess of thionyl chloride was removed under reduced pressure and the last traces by evaporation with benzene. Addition of excess of aqueous ammonia to the residual acid chloride precipitated the *amide*, crystallising from alcohol in colourless needles (0·51 g.), m. p. 203—205° (Found: N, 5·3. $C_{12}H_{13}O_6N$ requires N, 5·2%).

3-*Cyano*-4 : 5 : 6-*trimethoxyphthalide*.—A solution of 4 : 5 : 6-trimethoxyphthalide-3-carboxyamide (1·8 g.) in toluene (40 c.c.) was refluxed for 12 hours with phosphoric oxide (1·8 g.). The mixture was decomposed with ice-water, and extracted several times with ether. The combined ether and toluene extracts were washed successively with water, sodium hydrogen carbonate

solution, and water, solvents were removed under reduced pressure, and the residual *nitrile* crystallised from ethyl alcohol; colourless needles (1 g.), m. p. 136—138° (Found: C, 57·8; H, 4·9; N, 5·7. $C_{12}H_{11}O_5N$ requires C, 57·8; H, 4·5; N, 5·6%), were obtained.

Synthesis of 3-*Acetyl*-4 : 5 : 6-*trimethoxyphthalide* (IV; R = Me).—(*a*) Cadmium chloride (5 g., dried at 120°) was added to the Grignard reagent prepared from magnesium (1·3 g.), methyl iodide (9 g.), and ether (200 c.c.). The mixture was stirred for 1 hour under nitrogen until a negative test was given with Michler's ketone. A toluene solution (50 c.c.) of the crude acid chloride obtained, as described above, by the action of thionyl chloride on 4 : 5 : 6-trimethoxyphthalide-3-carboxylic acid (3 g.) was now added, and after 3 hours at room temperature the mixture was decomposed with dilute hydrochloric acid at 0°. The product, isolated with ether as a dark viscous oil (1·4 g.), was taken up in alcohol (20 c.c.), refluxed for 1 hour with Girard-T reagent (1·5 g.) and glacial acetic acid (2 c.c.), and poured into an ice-cold sodium acetate solution. Non-ketonic material was removed with ether, and the aqueous layer was hydrolysed with cold hydrochloric acid and again extracted with ether. The washed and dried extract yielded an oil containing 3-acetyl-4 : 5 : 6-trimethoxyphthalide, which was isolated as the 2 : 4-*dinitrophenylhydrazone*, separating from alcohol in yellow needles, m. p. 202—203° (Found: C, 51·6; H, 4·3; N, 12·3. $C_{19}H_{18}O_9N_4$ requires C, 51·1; H, 4·0; N, 12·5%), undepressed on admixture with the 2 : 4-dinitrophenylhydrazone, m. p. 202—203°, from the ketone, $C_{13}H_{14}O_8$, prepared from galloflavin.

(*b*) αα-Dichloropropaldehyde (3 g.), prepared as described by Moelant (*loc. cit.*), methyl 3 4 : 5-trimethoxybenzoate (4 g.), and concentrated sulphuric acid (25 c.c.) were shaken for a few minutes and kept at room temperature for 40 hours. The mixture was decomposed with ice, and the sticky brown product crystallised from methyl alcohol, colourless prisms (3·6 g.), m. p. 110—112° (Found: C, 48·4; H, 4·2; Cl, 22·5. $C_{13}H_{14}O_5Cl_2$ requires C, 48·6; H, 4·4; Cl, 22·1%), being obtained. This 3-1′ : 1′-*dichloroethyl*-4 : 5 : 6-*trimethoxyphthalide* (VI) (0·2 g.) was boiled with 8% sodium hydroxide (3 c.c.) for a few minutes, the solution was acidified, heated on the water-bath for 30 minutes, and cooled, and 3-acetyl-4 : 5 : 6-trimethoxyphthalide (0·13 g.) was isolated with ether. Crystallisation from methyl alcohol yielded colourless needles, m. p. 74—75° (Found: C, 58·9; H, 5·5%), undepressed by admixture with the ketone, $C_{13}H_{14}O_8$, obtained from galloflavin. The 2 : 4-dinitrophenylhydrazone separated from ethyl alcohol in bright yellow needles, m. p. 202—203° (Found: C, 51·3; H, 4·3; N, 12·5%).

4 : 5 : 6-*Trimethoxyindan*-1-*one*.—A mixture of phosphoric oxide (4 g.) and β-(2 : 3 : 4-trimethoxyphenyl)propionic acid (1 g.) in benzene (20 c.c.) was refluxed for 1½ hours and then decomposed with ice. The product (0·7 g.) isolated with ether had m. p. 75—82°, and was redissolved in ether, adsorbed on alumina (40 g.), and eluted with ether (90 c.c.), ether (30 c.c.), and ether–acetone (9 : 1) (60 c.c.). The first eluate yielded 4 : 5 : 6-*trimethoxyindan*-1-*one* (0·35 g.) which separated from light petroleum (b. p. 40—60°) in colourless needles, m. p. 80—81° (Found: C, 65·0; H, 6·2. $C_{12}H_{14}O_4$ requires C, 64·9; H, 6·3%). 2-*Benzylidene*-4 : 5 : 6-*trimethoxyindan*-1-*one* crystallised from alcohol in slender pale yellow needles, m. p. 159—160° (Found: C, 73·8; H, 5·8. $C_{19}H_{18}O_4$ requires C, 73·5; H, 5·8%). The last eluate yielded pale yellow needles, m. p. 165—166° (Found: C, 67·7; H, 5·8. $C_{24}H_{26}O_7$ requires C, 67·6; H, 6·1%), from methanol; this is probably the *anhydrobisindanone* derivative.

Ethyl 1-*Keto*-4 : 5 : 6-*trimethoxyindane*-2-*glyoxylate*.—A solution of 4 : 5 : 6-trimethoxyindanone (4 g.) and ethyl oxalate (2·63 g.) in alcohol (21 c.c.) was added to a solution of sodium (0·414 g.) in cold alcohol (2 c.c.). An orange sodium salt rapidly separated, and after 24 hours the mixture was decomposed with dilute sulphuric acid. *Ethyl* 1-*keto*-4 : 5 : 6-*trimethoxyindane*-2-*glyoxylate* was obtained as slender yellow needles (4 g.), m. p. 145—146° (Found: C, 59·2; H, 5·6. $C_{16}H_{18}O_7$ requires C, 59·2; H, 5·6%), by crystallisation from alcohol, but attempts to decarbonylate the ester were unsuccessful.

2-*Bromo*-4 : 5 : 6-*trimethoxyindan*-1-*one*.—Bromine (0·434 g.) in chloroform (6·5 c.c.) was added to a solution of the indanone (0·5 g.) in chloroform (5 c.c.) at 0°. After 1 hour the chloroform solution was washed with sodium hydrogen carbonate solution and dried, and the solvent removed. The residual *indanone* crystallised from methyl alcohol in colourless needles (0·65 g.), m. p. 92° (Found: C, 47·5; H, 4·2; Br, 26·9. $C_{12}H_{13}O_4Br$ requires C, 47·8; H, 4·3; Br, 26·6%).

2-*Cyano*-4 : 5 : 6-*trimethoxyindanone*, obtained in 75% yield by warming 2-bromoindan-1-one with potassium cyanide (2 parts) in alcohol (30 vols.) for 25 minutes, separated from methyl alcohol in colourless needles, m. p. 111—112° (Found: 62·9; H, 5·2; N, 5·6. $C_{13}H_{13}O_4N$ requires C, 63·1; H, 5·3; N, 5·7%).

2-*Cyano*-2-2′-*hydroxyethyl*-4 : 5 : 6-*trimethoxyindan*-1-*one*.—A solution of 2-cyano-4 : 5 : 6-

trimethoxyindan-1-one (0·335 g.), ethylene oxide (0·1 g.), and piperidine (1 drop) in alcohol (15 c.c.) was left for 4 weeks at room temperature. The solvent was removed under reduced pressure and the residue was taken up in ether, washed successively with water, dilute hydrochloric acid, sodium hydroxide and water, and dried, and the ether removed. The residue (0·2 g.) separated from alcohol in colourless needles, m. p. 149—150° (Found : C, 61·7; H, 6·2; N, 4·8. $C_{15}H_{17}O_5N$ requires C, 61·9; H, 5·8; N, 4·8%). Inferior yields of the *cyano*-compound were obtained when the piperidine catalyst was replaced by sodium ethoxide.

Our thanks are due to the Research Fund Committee of the University for the award of a Henry Ellison Fellowship, and to Imperial Chemical Industries Limited for a grant towards the expenses of this investigation.

THE UNIVERSITY, SHEFFIELD, 10. [*Received, January 14th*, 1952.]