659. *Hydroxy-carbonyl Compounds. Part XIV. The Syntheses of Some* isoCoumarins.

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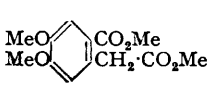
In exploratory experiments on the synthesis of *iso*coumarins 7-methoxy-, 6 : 7-dimethoxy-5-hydroxy-7-methyl-, and 5-methoxy-7-methyl-*iso*coumarin, together with 6-methoxy*iso*coumarin-4-carboxylic acid and methyl 5 : 7-dimethoxy*iso*coumarin-4-carboxylate, have been synthesised by the method of Dieckmann and Meiser.

The orientations of certain orcinol carboxylic acids described by Jerdan have been revised.

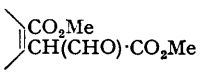
AN evaluation of the possible routes to the synthesis of *iso*coumarins of type (IV) with particular reference to the parent compound has been made by Johnson *et al.* (*J. Org. Chem.*, 1948, **13**, 477) whose findings are in agreement with the results obtained in this laboratory (unpublished work, 1938—1940). For the synthesis of *iso*coumarins devoid of alkyl groups in the 3- and 4-positions the method of Dieckmann and Meiser (*Ber.*, 1908, **41**, 3253), *viz.*, condensation of ethyl formate with a homophthalic ester followed by cyclisation and subsequent elimination of the carbomethoxy-group in the 4-position of the resulting product, appeared to be the most feasible, and the present communication deals with further exploratory work on the synthesis of methoxy*iso*coumarins by this method. These studies were undertaken primarily because, by comparison with known unsaturated lactones, *iso*coumarins may be expected to exhibit interesting physiological properties which, as far as we are aware, have not been examined systematically

(cf. Veldestra and Harigna, *Enzymologia*, 1944, **11**, 373; Lauger *et al.*, *Helv. Chim. Acta*, 1944, **27**, 892; Oxford, *Annual Rev. Biochem.*, 1945, **14**, 749; Haynes, *Quart. Reviews*, 1948, **2**, 46).

In the Dieckmann–Meiser route to *iso*coumarins of type (IV) two main problems arise : (*a*) the preparation of the required intermediate homophthalic acids for which a variety of procedures are available (cf. Johnson *et al.*, *loc. cit.*), and (*b*) the elimination of the ester group of the alkyl *iso*coumarin-4-carboxylate by hydrolysis and decarboxylation. Thus the interaction of methyl 2-carbomethoxy-4 : 5-dimethoxyphenylacetate (I) with methyl formate and sodium methoxide gave the α-formyl derivative (II) which was readily cyclised by warm hydrochloric acid to methyl



(I.)



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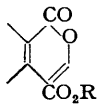

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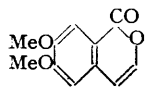
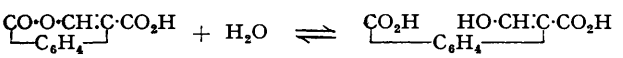


(IV.)

6 : 7-dimethoxy*iso*coumarin-4-carboxylate (III; R = Me), forming (IV) on hydrolysis and decarboxylation. In some instances much loss of material occurred in the elimination of the carbomethoxy- or carbethoxy-group for the hydrolysis of which an alkaline reagent is precluded; *e.g.*, whilst methyl 6 : 7-dimethoxy*iso*coumarin-4-carboxylate (III; R = Me) was readily hydrolysed with a warm mixture of concentrated hydrochloric and acetic acid giving (III; R = H), methyl 5-methoxy-7-methyl- and methyl 6 : 8-dimethoxy-*iso*coumarin-4-carboxylate required a warm mixture of concentrated hydriodic acid and acetic acid which simultaneously effected demethylation, giving rise to the corresponding hydroxy*iso*coumarin-4-carboxylic acids. It seems likely that the poor yields of methoxy*iso*coumarin-4-carboxylic acids arising from the prolonged action of a warm hydrochloric acid–acetic acid mixture on their esters is caused, in part at least, by the tendency for the following equilibrium to obtain :

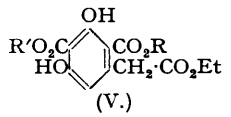


in which the latter component of the system, even if present only in small amount, could clearly give rise to polymerising side reactions. In a re-investigation of possible hydrolytic procedures it was discovered, after most of the experimental work had been completed, that a warm mixture of boron trifluoride and acetic acid gave satisfactory results. Thus with this reagent methyl *iso*coumarin-4-carboxylate (Dieckmann and Meiser, *loc. cit.*) and methyl 6 : 7-dimethoxy*iso*coumarin-4-carboxylate were smoothly converted into the corresponding 4-carboxylic acids, whilst in the case of methyl 5-methoxy-7-methyl*iso*coumarin-4-carboxylate the hydrolysis was accompanied by decarboxylation giving 5-methoxy-7-methyl*iso*coumarin.

In the synthesis of ethyl 6 : 8-dimethoxy*iso*coumarin-4-carboxylate, ethyl 2-carbethoxy-3 : 5-dimethoxyphenylacetate (VII; R = OEt, R′ = Et) was prepared from the acid (V; R = Et, R′ = H) by way of the ester (VI; R = Et) and, on condensation with ethyl formate, gave the formyl derivative (VIII) which was cyclised with warm hydrochloric acid. Treatment of the resulting ethyl 6 : 8-dimethoxy*iso*coumarin-4-carboxylate with a warm mixture of hydriodic acid and acetic acid gave 6 : 8-dihydroxy*iso*coumarin-4-carboxylic acid.

The acid (V; R = Et, R′ = H) was described by Jerdan (*J.*, 1899, **75**, 808) in his extensive memoir on the synthesis of orcinol-carboxylic acids, but the structure (V; R = H, R′ = Et) there attributed to the compound was shown to be untenable by Asahina and Nogami (*Proc. Imp. Acad., Tokyo*, 1940, **16**, 119) whose results could only be explained on the assumption that it had the structure (V; R = Et, R′ = H). In view of the earlier erroneous formulation it seemed desirable that the revised formula should be verified. The orientation of the tribasic acid obtained as its triethyl ester (V; R = R′ = Et) by the intramolecular condensation of ethyl acetonedicarboxylate with sodium (Jerdan, *loc. cit.*; cf. Pechmann *et al.*, *Ber.*, 1886, **19**, 1446; 1898, **31**, 2014) was confirmed by Dootson (*J.*, 1900, **77**, 1196). By fusion of this ester with alkali Jerdan (*loc. cit.*) prepared a dibasic acid (A) which he believed to be (VI; R = H). When ethyl acetonedicarboxylate was heated with magnesium and a little ethyl chloroacetate Jerdan (*loc. cit.* obtained the diethyl ester (B) of a tribasic acid to which he allocated formula (V; R = H, R′ = Et). On esterification, (B) gave rise to the triethyl ester (V; R and R′ = Et) and on being heated with alkali it yielded the dibasic acid (A). As a result of their failure to synthesise 6 : 8-dimethoxy-3-methyl*iso*coumarin when Jerdan's dibasic acid (A) was employed as the starting material Asahina and Nogami (*loc. cit.*) inferred that, in the intermediate which they prepared from (A) and expected to have the structure (VII; R = Me, R′ = H), the carboxyl

group was not in the *ortho*-position to the acetonyl residue. Consequently they concluded that (A) was 4-carboxy-3 : 5-hydroxyphenylacetic acid (IX; R = R′ = H). In agreement with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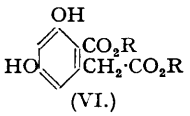
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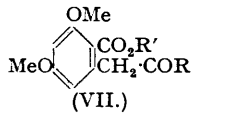
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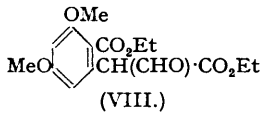
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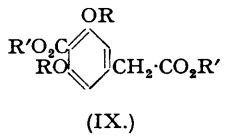
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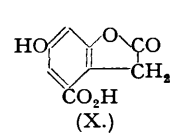
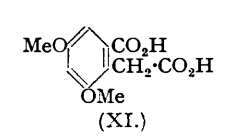

(X.)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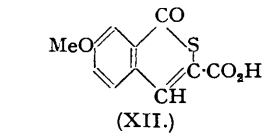
(XII.)

the latter structure for (A) it has now been shown that the α-formyl derivative obtained from the methyl ester of the *O*-dimethyl ether of (A) does not undergo cyclisation to *iso*coumarin, whilst on oxidation the dimethyl ether of (A) yielded 2 : 6-dimethoxyterephthalic acid. On the other hand, cyclisation of the α-formyl derivative of (V; R = R′ = Et) furnished ethyl 6 : 8-dimethoxy*iso*coumarin-3 : 7-dicarboxylate. In consequence it is clear that the following compounds considered by Jerdan (*loc. cit.*) to be (*a*) 4-carbethoxy-2-carboxy-3 : 5-dihydroxyphenylacetic acid, (*b*) ethyl 2-carboxy-3 : 5-dihydroxyphenylacetate, (*c*) ethyl 2-carbethoxy-3 : 5-dihydroxyphenylacetate, and (*d*) 2-carbethoxy-3 : 5-dihydroxyphenylacetic acid are, respectively, (1) 2-carbethoxy-4-carboxy-3 : 5-dihydroxyphenylacetic acid, (2) ethyl 4-carboxy-3 : 5-dihydroxyphenylacetate, (3) ethyl 4-carbethoxy-3 : 5-dihydroxyphenylacetate, and (4) 4-carbethoxy-3 : 5-dihydroxyphenylacetic acid (cf. Asahina and Nogami, *loc. cit.*).

In exploratory experiments on the preparation of 2-carboxy-4 : 6-dimethoxyphenylacetic acid (XI) required for the synthesis of methyl 5 : 7-dimethoxy*iso*coumarin-4-carboxylate, methyl 6-formyl-3 : 5-dimethoxybenzoate was condensed with rhodanine, giving 5-(6-carbomethoxy-2 : 4-dimethoxybenzylidene)rhodanine which on hydrolysis with aqueous sodium hydroxide gave rise to 5 : 7-dimethoxy*iso*thiocoumarin-3-carboxylic acid (XII). The formation of the latter acid is analogous to the conversion of *o*-carbethoxybenzylideneoxazolones into *iso*carbostyril-3-carboxylic acids (Bain *et al.*, *J.*, 1914, **105**, 2392). 2-Carboxy-4 : 6-dimethoxyphenylacetic acid was ultimately prepared by the methylation of 6-hydroxycoumaran-2-one-4-carboxylic acid (X) formed by the action of boiling hydriodic acid on 4 : 6-dimethoxyphthalide-3-carboxylic acid.

Experimental.

2-Carboxy-4-methoxyphenylacetic Acid.—An intimate mixture of 6-methoxyphthalide (Fritsch, *Annalen*, 1897, **296**, 355) (10 g.) and powdered potassium cyanide was kept at 185—195° with stirring for 45 minutes, cooled, and dissolved in a little water. Acidification of the filtered solution, at below 0°, with dilute hydrochloric acid furnished a dark brown precipitate which on crystallisation from methanol (charcoal) gave 2-carboxy-4-methoxybenzyl cyanide in light yellow prisms (6—7 g.), m. p. 135° (Found : C, 62·7; H, 4·9. Calc. for $C_{10}H_9O_3N$: C, 62·8; H, 4·7%) (cf. Chakravarti and Swaminathan, *J. Indian Chem. Soc.*, 1934, **11**, 101, who give m. p. 140° for the cyanide prepared by an alternative route). This cyanide (30 g.) was boiled with 20% potassium hydroxide solution (250 ml.) until the evolution of ammonia had ceased, and the hydrolysate was cooled, filtered, and acidified with concentrated hydrochloric acid, giving 2-carboxy-4-methoxyphenylacetic acid, which was isolated with ether and crystallised from methanol, forming leaflets (22—24 g.), m. p. 184°, readily soluble in acetic acid or ethyl acetate and moderately soluble in alcohol or chloroform (Found : C, 57·3; H, 5·0. Calc. for $C_{10}H_{10}O_5$: C, 57·1; H, 4·8%). Prepared by the methanol–sulphuric acid or diazomethane method, the methyl ester of this acid had m. p. 58° (cf. Ungnade *et al.*, *J. Org. Chem.*, 1945, **10**, 533, who give m. p. 53—54°).

*7-Methoxy*iso*coumarin.*—On the addition of sodium methoxide (from 0·2 g. of sodium) to a solution of methyl 2-carbomethoxy-4-methoxyphenylacetate (1·0 g.) in methyl formate (3 ml.) a vigorous reaction ensued. Next day the excess of methyl formate was removed in a vacuum, the residue was acidified with cold dilute hydrochloric acid, and the product isolated with ether. On being kept at below 0° a solution of this oil in a little methanol deposited *methyl α-(2-carbomethoxy-4-methoxyphenyl)-α-formylacetate* in colourless prisms (0·5 g.), m. p. 94° [Found : C, 59·0; H, 5·1; OMe, 35·7. $C_{10}H_5O_3(OMe)_3$ requires C, 58·7; H, 5·3; OMe, 34·6%], soluble in the usual organic solvents except light petroleum and readily reacting with alcoholic 2 : 4-dinitrophenylhydrazine hydrochloride. Cyclisation of this aldehyde-ester by warming it with a drop of hydrochloric acid yielded methyl 7-methoxy*iso*coumarin-4-carboxylate, m. p. 124°, which was identical with a specimen prepared by cyclisation of the crude formyl ester (cf. Ungnade *et al.*, *loc. cit.*) (Found : C, 61·4; H, 4·4. Calc. for $C_{12}H_{10}O_5$: C, 61·5; H, 4·3%); on hydrolysis the ester, m. p. 124°, gave 7-methoxy*iso*coumarin-4-carboxylic acid, m. p. 255°. An intimate mixture of this acid (1·6 g.) and copper-bronze (0·4 g.) was kept at 280—290° until the vigorous evolution of carbon dioxide had ceased, and the product was distilled in a vacuum, giving *7-methoxy*iso*coumarin*, b. p. 175°/12 mm., which separated from benzene–light petroleum (b. p. 60—80°) or chloroform in colourless prismatic

needles, m. p. 108—109° (Found : C, 68·2; H, 4·7; OMe, 17·3. $C_9H_8O_2$·OMe requires C, 68·2; H, 4·6; OMe, 17·6%).

6-*Methoxy*iso*coumarin*-4-*carboxylic Acid*.—Esterification of 2-carboxy-6-methoxybenzylacetic acid (Chakravarti and Swaminathan, *loc. cit.*) (3 g.) with a slight excess of ethereal diazomethane gave the *dimethyl* ester which formed elongated prisms (3 g.) from benzene–light petroleum (b. p. 60—80°) [Found : C, 60·1; H, 5·7; OMe, 37·0. $C_9H_5O_2(OMe)_3$ requires C, 60·5; H, 5·9; OMe, 39·1%]. Interaction of this ester (2 g.) with methyl formate (10 ml.) and sodium methoxide (1 g.) in absolute ether (10 ml.) during 24 hours gave an oily formyl derivative which, on being warmed with a drop of hydrochloric acid on the water-bath for 20 minutes, yielded *methyl* 6-*methoxy*iso*coumarin*-4-*carboxylate*. This compound separated from methanol in small rectangular prisms (1·5 g.), m. p. 128·5°, readily soluble in ether, acetone, or chloroform [Found : C, 61·1; H, 4·6; OMe, 26·0. $C_{10}H_4O_3(OMe)_3$ requires C, 61·5; H, 4·3; OMe, 26·5%]. When a mixture of this ester (0·2 g.), acetic acid (5 ml.), and concentrated hydrochloric acid (2 ml.) was refluxed for 7 hours, cooled, and diluted with a little water 6-*methoxy*iso*coumarin*-4-*carboxylic acid* separated and, on recrystallisation from dilute acetic acid, formed colourless rectangular plates, m. p. 256° (decomp.), readily soluble in alcohol, acetone, or ethyl acetate, and sparingly soluble in benzene (Found : C, 59·7; H, 4·0; OMe, 13·3. $C_{10}H_5O_4$·OMe requires C, 60·0; H, 3·6; OMe, 14·1%). The same acid, m. p. 256° (decomp.), was obtained when the hydrolysis of the ester (0·5 g.) was effected with a warm mixture of acetic acid (8·5 ml.) and concentrated hydriodic acid (1·3 ml.).

6 : 7-*Dimethoxy*iso*coumarin* (IV).—Toluene-*p*-sulphonyl chloride (9·1 g.) was added in small portions to a boiling solution of 5 : 6-dimethoxy-2-oximinoindan-1-one (Perkin and Robinson, *J.*, 1907, **91**, 1081) (6·4 g.) in 10% aqueous sodium hydroxide (65 ml.), and the mixture heated for 1 hour, treated with a little charcoal, filtered, cooled, and acidified with hydrochloric acid, giving 2-*carboxy*-4 : 5-*dimethoxyphenylacetonitrile*, which formed colourless prismatic needles (4·6 g.), m. p. 183·5°, from methanol (Found : C, 60·0; H, 5·2; N, 6·1. $C_{11}H_{11}O_4N$ requires C, 59·7; H, 5·0; N, 6·3%). Obtained from this nitrile, 2-carboxy-4 : 5-dimethoxyphenylacetic acid (Perkin and Robinson, *loc. cit.*) (20 g.) was almost quantitatively esterified with boiling methanol (600 ml.) and concentrated sulphuric acid (20 ml.) during 15 hours. On isolation in the usual manner the resulting *methyl* ester (I) crystallised from benzene in slender colourless needles, m. p. 92°, soluble in the usual organic solvents except light petroleum (Found : C, 58·4; H, 6·2. $C_{13}H_{16}O_6$ requires C, 58·2; H, 6·0%). A mixture of this compound (6·6 g.), methyl formate (40 ml.), and sodium methoxide (from 1·2 g. of sodium) in ether (30 ml.) was kept at room temperature for 24 hours and then heated under reflux with more methyl formate (10 ml.) for 4 hours. The residue left on evaporation of the reaction mixture was dissolved in water, the solution was acidified with 2N-hydrochloric acid and extracted several times with ether, and the combined extracts were washed with aqueous sodium hydrogen carbonate and then water, dried, and evaporated, leaving the oily formyl derivative (II) of methyl 2-carbomethoxy-4 : 5-dimethoxyphenylacetate which, on being warmed with a little concentrated hydrochloric acid on the steam-bath, was converted into *methyl* 6 : 7-*dimethoxy*iso*coumarin*-4-*carboxylate* (III; R = Me) (5—5·4 g.). Recrystallised from methanol, this compound formed colourless prismatic needles, m. p. 175°, soluble in warm alcohol, benzene, or ethyl acetate and insoluble in light petroleum [Found : C, 5·91; H, 4·6; OMe, 32·0. $C_{10}H_3O_3(OMe)_3$ requires C, 59·1; H, 4·6; OMe, 35·2%]. When methyl formate was replaced by ethyl formate in the foregoing condensation the product was *ethyl* 6 : 7-*dimethoxy*iso*coumarin*-4-*carboxylate* which formed needles, m. p. 156°, from alcohol (Found : C, 60·4; H, 5·2. $C_{14}H_{14}O_6$ requires C, 60·4; H, 5·0%), identical with a specimen obtained by the esterification of 6 : 7-dimethoxy*iso*coumarin-4-carboxylic acid.

A mixture of methyl 6 : 7-dimethoxy*iso*coumarin-4-carboxylate (6 g.), acetic acid (40 ml.), concentrated hydrochloric acid (120 ml.), and water (60 ml.) was heated under reflux for 4 hours and cooled, giving 6 : 7-*dimethoxy*iso*coumarin*-4-*carboxylic acid* (III; R = H) which formed slender needles (5·1 g.), m. p. 313° (decomp.), from acetic acid, insoluble in benzene and soluble in ether, alcohol, or ethyl acetate [Found : C, 57·5; H, 3·6; OMe, 23·3. $C_{10}H_4O_4(OMe)_2$ requires C, 57·6; H, 4·0; OMe, 24·8%]. When this acid (2 g.) was heated with copper-bronze (0·1 g.) to 325—335° a vigorous evolution of carbon dioxide ensued and on distillation in a vacuum the residue then gave 6 : 7-*dimethoxy*iso*coumarin* (IV) which separated from benzene–light petroleum (b. p. 60—80°) in clusters of colourless prisms (1·3 g.), m. p. 122°, soluble in alcohol, chloroform, or acetone [Found : C, 64·2; H, 5·0; OMe, 30·6. $C_9H_4O_2(OMe)_2$ requires C, 64·1; H, 4·9; OMe, 30·1%]. This decarboxylation was effected less satisfactorily by heating the acid (1 g.) with copper-bronze (0·5 g.) and glycerol (15 ml.) at 200—210° for 45 minutes; the *iso*coumarin (0·1 g.) was isolated with ether in a continuous-extraction apparatus from the diluted (water) reaction mixture and on purification had m. p. 121°.

5-*Hydroxy*-7-*methyl*iso*coumarin*.—Interaction of methyl 2-carbomethoxy-6-methoxy-4-methylphenylacetate (Berner, *J.*, 1946, 1052) (7 g.) with methyl formate (35 ml.), and sodium methoxide (3·5 g.) in ether (60 ml.) during 36 hours gave the α-formyl derivative as an oil which on treatment with a little hydrochloric acid on the steam-bath was converted into *methyl* 5-*methoxy*-7-*methyl*iso*coumarin*-4-*carboxylate*, forming prismatic needles (5·2 g.), m. p. 160°, from dilute acetic acid or methanol [Found : C, 62·5; H, 5·0; OMe, 24·9. $C_{11}H_8O_3(OMe)_2$ requires C, 62·9; H, 4·9; OMe, 25·0%]. A mixture of the latter ester (2·7 g.) and hydriodic acid (10 ml.; *d* 1·7) was kept at 60—65° for 8 hours and next day the product was collected, washed with a little aqueous sodium thiosulphate and then water, and crystallised from warm water, giving 5-*hydroxy*-7-*methyl*iso*coumarin*-4-*carboxylic acid* in microscopic prisms (0·6 g.), m. p. 265—267° (decomp.), soluble in alcohol, chloroform, or ethyl acetate (Found : C, 60·0; H, 3·6. $C_{11}H_8O_5$ requires C, 60·0; H, 3·6%). The same compound, m. p. 265—267° (decomp.), was obtained when the ester (0·5 g.) was heated under reflux with hydriodic acid (1·3 ml.; *d* 1·7) and acetic acid (5·5 ml.) for 6 hours, followed by the removal of the acetic acid in a vacuum.

Decarboxylation of 5-hydroxy-7-methyl*iso*coumarin-4-carboxylic acid (0·5 g.) with copper-bronze (0·1 g.) at 230—240° gave 5-*hydroxy*-7-*methyl*iso*coumarin* which was sublimed in a vacuum and then crystallised from benzene–light petroleum (b. p. 60—80°), forming colourless microscopic prisms, m. p.

163—164° (Found : C, 67·9; H, 4·9. $C_{10}H_8O_3$ requires C, 68·2; H, 4·6%) (0·6 g. from 2·5 g. of acid). This compound, which has a negative ferric reaction in alcohol, is readily soluble in dilute aqueous sodium hydroxide and in the usual organic solvents except light petroleum.

A mixture of methyl 5-methoxy-7-methyl*iso*coumarin-4-carboxylate (0·5 g.), acetic acid (15 ml.), and boron trifluoride (1 g.) was gently warmed under reflux for 4 hours and then evaporated in a vacuum. Crystallised from dilute methanol, the residue gave *5-methoxy-7-methylisocoumarin* in long colourless needles (0·15 g.), m. p. 108°, insoluble in cold dilute aqueous sodium hydroxide and readily soluble in alcohol or benzene (Found : C, 69·6; H, 5·3; OMe, 16·4. $C_{10}H_7O_2{\cdot}OMe$ requires C, 69·5; H, 5·3; OMe, 16·3%).

4-Carboxy-3 : 5-dimethoxyphenylacetic Acid (IX; R = R′ = H).—Esterification of 4-carboxy-3 : 5-dihydroxyphenylacetic acid (Jerdan, *loc. cit.*) with ethereal diazomethane gave the methyl ester (IX; R = H, R′ = Me), forming large prisms, m. p. 78°, from benzene (Found : C, 54·8; H, 5·2. Calc. for $C_{11}H_{12}O_6$: C, 55·0; H, 5·0%) (cf. Asahina and Nogami, *loc. cit.*). When a mixture of the ester (9 g.) with methyl iodide (8 ml., added in 2 portions), potassium carbonate (20 g.), and acetone was heated under reflux until a test sample failed to give a ferric reaction in alcohol, methyl 4-carbomethoxy-3 : 5-dimethoxyphenylacetate (IX; R = R′ = Me) was obtained in almost theoretical yield and formed colourless prisms, m. p. 82°, from a little benzene [Found : C, 58·5; H, 6·2; OMe, 45·6. Calc. for $C_9H_4O_2(OMe)_4$: C, 58·2; H, 6·0; OMe, 46·3%] (cf. Asahina and Nogami, *loc. cit.*, who give m. p. 72—73°). Prepared by the hydrolysis of this ester (1 g.) with 25% aqueous-alcoholic sodium hydroxide (10 ml.) on the steam-bath for 4 hours *4-carboxy-3 : 5-dimethoxyphenylacetic acid* (IX; R = Me, R′ = H) separated from acetic acid or dilute methanol in colourless prisms, m. p. 183° (decomp.) [Found : C, 54·8; H, 5·0; OMe, 23·7. $C_9H_6O_4(OMe)_2$ requires C, 55·0; H, 5·0; OMe, 25·8%].

Interaction of methyl 4-carbomethoxy-3 : 5-dimethoxyphenylacetate (6·6 g.), methyl formate (20 ml.), and sodium methoxide (from 1·15 g. of sodium) in ether at room temperature for 36 hours, followed by the isolation of the product in the usual manner, gave *methyl α-(4-carbomethoxy-3 : 5-dimethoxyphenyl)-α-formylacetate* which crystallised from ethyl acetate in colourless, irregular prisms (4·1 g.), m. p. 112·5° (Found : C, 56·8; H, 5·7. $C_{14}H_{16}O_7$ requires C, 56·7; H, 5·4%). This product, which was soluble in benzene or acetone and insoluble in light petroleum, gave the usual reactions of an aldehyde but did not cyclise to form an *iso*coumarin. When the compound (2·5 g.) was dissolved in 5% aqueous sodium hydroxide by gentle warming and the solution kept at room temperature for 36 hours and acidified, 4-carboxy-3 : 5-dimethoxyphenylacetic acid (IX; R = Me, R′ = H) was formed. Isolated with ether, the acid (2·4 g.) had m. p. 183° (decomp.) and was identified by comparison with an authentic specimen and by conversion into the dimethyl ester, m. p. and mixed m. p. 82°.

3% Aqueous potassium permanganate (30 ml.) was slowly added to a solution of 4-carboxy-3 : 5-dimethoxyphenylacetic acid (1 g.) in 5% aqueous sodium hydroxide (20 ml.) and next day the solution was filtered, acidified with sulphuric acid, saturated with ammonium sulphate, and extracted several times with ether. Evaporation of the dried extracts left 2 : 6-dimethoxyterephthalic acid which on repeated crystallisation from dilute methanol formed colourless prisms, m. p. 292° (decomp.), identical with an authentic specimen (Brunner, *Monatsh.*, 1928, **50**, 216, gave m. p. 284°) [Found : C, 53·1; H, 4·7; OMe, 28·3. Calc. for $C_8H_4O_4(OMe)_2$: C, 53·1; H, 4·4; OMe, 27·4%].

Ethyl 6 : 8-*Dimethoxy*iso*coumarin*-4 : 7-*dicarboxylate*.—Methylation of ethyl 2 : 4-dicarbethoxy-3 : 5-dihydroxyphenylacetate (Jerdan, *loc. cit.*) (4 g.) with methyl iodide (3 ml.) and potassium carbonate (5 g.) in boiling acetone (25 ml.) during 8 hours gave *ethyl 2 : 4-dicarbethoxy-3 : 5-dimethoxyphenylacetate* which separated from benzene–light petroleum (b. p. 60—80°) in colourless prisms (4 g.), m. p. 53—54°, readily soluble in alcohol, benzene, or acetone and having a negative ferric reaction (Found : C, 58·4; H, 6·4. $C_{18}H_{24}O_8$ requires C, 58·7; H, 6·5%). Sodium ethoxide (from 0·6 g. of sodium) was added to a solution of this ester (7 g.) in a mixture of ethyl formate (6 ml.) and ether (20 ml.), and the resulting reddish reaction mixture kept for 24 hours and evaporated in a vacuum. After the addition of dilute hydrochloric acid to the residue the formyl derivative was isolated with ether and cyclised with a little warm concentrated hydrochloric acid, giving *ethyl* 6 : 8-*dimethoxy*iso*coumarin*-4 : 7-*dicarboxylate* which formed slender colourless needles (5·1 g.), m. p. 135·5°, from alcohol–acetic acid (Found : C, 58·1; H, 5·3. $C_{17}H_{18}O_8$ requires C, 58·3; H, 5·1%). The colourless alcoholic solution of this compound, which exhibits a greenish-blue fluorescence, becomes red on exposure to light. Attempts to hydrolyse the carbethoxy-groups of this compound with warm acetic acid or formic acid–hydrochloric acid resulted in the production of dark intractable products. When a mixture of the compound (0·2 g.) and hydriodic acid (2 ml.; *d* 1·7) was kept at 65—70° for 2 hours, cooled, diluted with water, and extracted with ether, a phenolic substance was obtained which separated from alcohol in tiny needles, m. p. 112—113°, insoluble in aqueous sodium hydrogen carbonate and giving an intense blue-violet ferric reaction in alcohol (Found : C, 56·7; H, 4·6. Calc. for $C_{16}H_{16}O_8$: C, 57·1; H, 4·8%).

When ethyl 6 : 8-dimethoxy*iso*coumarin-4 : 7-dicarboxylate (2·5 g.) was heated with hydriodic acid (14 ml.; *d* 1·7) and acetic anhydride (9 ml.) on the steam-bath for 8 hours an acidic substance was obtained which crystallised from dilute methanol in tiny needles (1·1 g.), m. p. 238—239° (decomp.), giving a port-wine ferric reaction in alcohol (Found : C, 54·5; H, 3·7. Calc. for $C_{14}H_{12}O_8$: C, 54·5; H, 3·9%). This compound may be 7-carbethoxy-6-hydroxy-8-methoxy*iso*coumarin-4-carboxylic acid.

Ethyl 6 : 8-*Dimethoxy*iso*coumarin*-4-*carboxylate*.—The decarboxylation of ethyl 2-carbethoxy-4-carboxy-3 : 5-dihydroxyphenylacetate (V; R = Et, R′ = H) according to the method of Nogami (*J. Pharm. Soc.*, 1941, **61**, 56) (heating with quinoline and copper-bronze) was unsatisfactory. On being heated with glycerol (100 ml.) at 150° for about 15 minutes the acid (2 g.) gave ethyl 2-carbethoxy-3 : 5-dihydroxyphenylacetate (0·9 g.), m. p. 108°, which on methylation by the methyl iodide–potassium carbonate method furnished ethyl 2-carbethoxy-3 : 5-dimethoxyphenylacetate (cf. Nogami, *loc. cit.*). When sodium ethoxide (1 g.) was added to a mixture of this ester (1 g.), ethyl formate (5 ml.), and ether

(10 ml.) a vigorous reaction ensued with the separation of a solid which subsequently redissolved in the course of 24 hours. After the removal of the ether and unchanged ethyl formate in a vacuum the residue was treated with warm hydrochloric acid, and the resulting *ethyl* 6 : 8-*dimethoxy*iso*coumarin*-4-*carboxylate* was isolated with ether and crystallised from alcohol or acetic acid, forming colourless prismatic needles (0·5 g.), m. p. 148°, readily soluble in chloroform or acetone and sparingly soluble in benzene (Found : C, 60·3; H, 5·3. $C_{14}H_{14}O_6$ requires C, 60·4; H, 5·0%). Attempts to hydrolyse the carbethoxy-group with warm hydrochloric acid–acetic acid were unsuccessful but when the compound (0·1 g.) was heated with a mixture of hydriodic acid (2 ml.; *d* 1·7) and acetic anhydride (1 ml.) on the steam-bath for 5 hours simultaneous hydrolysis and demethylation took place, resulting in the formation of a small amount of an acidic substance which separated from dilute methanol in microscopic needles, m. p. 182°, and exhibited a blue-violet ferric reaction.

6-*Hydroxycoumaran*-2-*one*-4-*carboxylic Acid* (X).—When 4 : 6-dimethoxyphthalide-3-carboxylic acid (Graves and Adams, *J. Amer. Chem. Soc.*, 1923, **45**, 2451) (3·6 g.) was boiled with hydriodic acid (16 ml.; *d* 1·7) and red phosphorus (1 g.) for 5 hours the cooled mixture deposited 6-*hydroxycoumaran*-2-*one*-4-*carboxylic acid* (X) mixed with red phosphorus. On isolation with the aid of dilute aqueous sodium hydroxide the acid separated from dilute methanol in tiny prisms (2·7 g.), m. p. 306° (decomp.), readily soluble in alcohol or acetone and having a negative ferric reaction (Found : C, 55·5; H, 3·2. $C_9H_6O_5$ requires C, 55·7; H, 3·1%).

Methyl 5 : 7-*Dimethoxy*iso*coumarin*-4-*carboxylate*.—The foregoing coumaranone-4-carboxylic acid (2·7 g.) was methylated with an excess of methyl sulphate and 20% aqueous sodium hydroxide and the alkaline reaction mixture then heated under reflux for 2 hours. Acidification of the cooled solution with concentrated hydrochloric acid gave 2-*carboxy*-4 : 6-*dimethoxyphenylacetic acid* (XI) which formed needles, m. p. 202° (decomp.), from water, readily soluble in alcohol, acetone, or chloroform and sparingly soluble in benzene [Found : C, 54·8; H, 5·3; OMe, 24·7. $C_9H_6O_4(OMe)_2$ requires C, 55·0; H, 5·0; OMe, 25·8%]. Oxidation of this acid with chromic oxide in acetic acid gave rise to 3 : 5-dimethoxyphthalic acid, m. p. 158°, identical with an authentic specimen (Fritsch, *Annalen*, 1897, **296**, 357). Prepared quantitatively with ethereal diazomethane, *methyl* 2-*carbomethoxy*-4 : 6-*dimethoxyphenylacetate* separated from benzene–light petroleum (b. p. 60—80°) in rhombic prisms, m. p. 58·5° (Found : C, 58·1; H, 5·8. $C_{13}H_{16}O_6$ requires C, 58·2; H, 6·0%). When sodium ethoxide (from 0·8 g. of sodium) was added to a mixture of this ester (4·2 g.) and methyl formate (3 ml.) in ether (15 ml.) a vigorous reaction ensued and the solid initially produced subsequently dissolved in the course of 24 hours. After having been heated under reflux for ½ hour the solution was evaporated in a vacuum, the residue was treated with dilute hydrochloric acid, and the product was isolated with ether. Crystallised from warm methanol, the resulting *methyl* 5 : 7-*dimethoxy*iso*coumarin*-2-*carboxylate* formed colourless needles (0·7 g.), m. p. 161°, readily soluble in the usual solvents except benzene or light petroleum (Found : C, 59·3; H, 4·6. $C_{13}H_{12}O_6$ requires C, 59·1; H, 4·6%).

5 : 7-*Dimethoxy*iso*thiocoumarin*-3-*carboxylic Acid*.—Methylation of methyl 2-formyl-α-resorcylate (Birkinshaw and Bracken, *J.*, 1942, 368) (5 g.) with methyl iodide (4 ml.) and potassium carbonate (6 g.) in boiling acetone (40 ml.) for 10 hours gave *methyl* 2-*formyl*-3 : 5-*dimethoxybenzoate*, forming slender prisms, (3·5 g.), m. p. 106°, from benzene–light petroleum, identical with a specimen prepared with diazomethane [Found : C, 58·8; H, 5·1; OMe, 40·8. $C_8H_3O_2(OMe)_3$ requires C, 58·9; H, 5·4; OMe, 41·5%]. The 2 : 4-*dinitrophenylhydrazone* separated from dilute methanol in orange prisms, m. p. 245° (Found : N, 13·6. $C_{17}H_{16}O_8N_4$ requires N, 13·9%).

A mixture of methyl 2-formyl-3 : 5-dimethoxybenzoate (4·5 g.), rhodanine (Julian and Sturgis, *J. Amer. Chem. Soc.*, 1935, **57**, 1126) (3 g.), acetic acid (35 ml.), and sodium acetate (5 g.) was heated on the steam-bath for 40 minutes and then treated with water (100 ml.). Crystallised from acetone, the precipitate gave 6-*carbomethoxy*-2 : 4-*dimethoxybenzylidenerhodanine* in yellow needles (3·5 g.), m. p. 217·5° (Found : N, 4·0. $C_{14}H_{13}O_5NS_2$ requires N, 4·1%). This compound (2·7 g.) was heated with 15% aqueous sodium hydroxide (12·5 ml.) on the steam-bath for 1 hour and the mixture acidified at below 0° with 15% hydrochloric acid, giving a viscous yellow product which slowly solidified and then on crystallisation from methanol gave 5 : 7-*dimethoxy*iso*thiocoumarin*-3-*carboxylic acid* in slender pale yellow needles (1·1 g.), m. p. 264°, readily soluble in aqueous sodium hydrogen carbonate, alcohol, or acetone (Found : C, 54·5; H, 3·6; S, 11·5. $C_{12}H_{10}O_5S$ requires C, 54·1; H, 3·8; S, 12·0%).

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