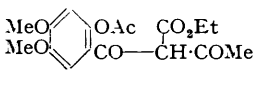
# 183. *The Chemistry of Fungi. Part X. The Synthesis of 4-Hydroxy-3-acetylcoumarins.*

By G. G. Badcock, F. M. Dean, Alexander Robertson, and W. B. Whalley.

Methods for the synthesis of 4-hydroxy-3-acetylcoumarins have been re-investigated and the novel synthetical procedures described in Part II (*loc. cit.*) have been further developed. It has been found that 4-hydroxycoumarins unsubstituted in the 3-position can be acetylated readily with acetic anhydride and boron trifluoride in acetic acid to give 4-hydroxy-3-acetylcoumarins, thus affording an unequivocal route to these interesting compounds. By this reaction the synthetic compound (Part II, *J.*, 1949, 562), m. p. 250°, has now been shown conclusively to be 4-hydroxy-6 : 7-dimethoxy-3-acetylcoumarin. The hydrolysis product, m. p. 208°, from *O*-dimethylcitromycinone (Part III, *J.*, 1949, 848) has been found to have formula (XIV) and arises by the hydration of the parent compound (XV) which it regenerates on treatment with concentrated sulphuric acid.

In the course of degradative experiments on *O*-dimethylcitromycinone (Part III, *J.*, 1949, 848) there was isolated a faintly acidic substance, m. p. 208°, which was regarded as 4-hydroxy-6 : 7-dimethoxy-3-acetylcoumarin (III) because it appeared to have the empirical formula $C_{11}H_6O_4(OMe)_2$, readily formed a 2 : 4-dinitrophenylhydrazone, and gave the requisite products on hydrolytic decomposition with alkalis. Unexpectedly, when the method of Anschütz (*Annalen*, 1906, **346**, 286) and the two novel procedures, *viz.*, the carbonyl chloride and the ethyl carbonate methods described in Part II (*J.*, 1949, 562), were applied to the synthesis of the coumarin (III) a product *P*, m. p. 250°, was invariably obtained which appeared not to react with 2 : 4-dinitrophenylhydrazine and was clearly not identical with the natural degradation product, m. p. 208°. From an examination of its properties and hydrolytic products, and in view of its apparent isomerism with the degradation product, m. p. 208°, the substance *P* was considered to be 6 : 7-dimethoxy-2-methylchromone-3-carboxylic acid (X; R = H). At the same time it was noted that the production of small amounts of 4-hydroxy-6 : 7-dimethoxycoumarin (IV) by the hydrolysis of *P* with alkalis was more in keeping with the 4-hydroxy-3-acetylcoumarin structure (III), but a plausible mechanism advanced for the derivation

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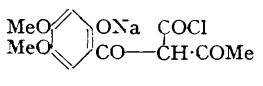


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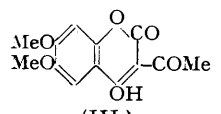


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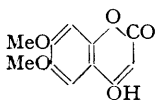


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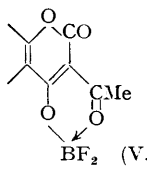


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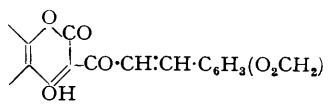


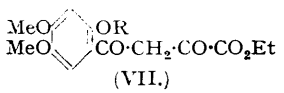

(VI.)

of 4-hydroxy-6 : 7-dimethoxycoumarin from (X; R = H) seemed to reconcile the apparent anomaly. Because of the possible ambiguity regarding the nature of the products obtained by the methods hitherto employed for the synthesis of 4-hydroxy-3-acetylcoumarins and since the substance, m. p. 208°, was regarded as an important hydrolytic product in the degradation series derived from *O*-dimethylcitromycinone, it seemed desirable to re-investigate the synthetical procedures and to examine the properties of 4-hydroxy-3-acetylcoumarins in some detail.

In our hands the procedure for the synthesis of 4-hydroxy-3-acetylcoumarins described by Anschütz (*loc. cit.*) gave somewhat uncertain results and a modified technique is now described whereby consistent yields of the required coumarins have been obtained. Of the novel alternative methods proposed in Part II (*loc. cit.*) the *o*-hydroxybenzoylacetone–ethyl carbonate method in the case of 2-*hydroxy*- and 2-*hydroxy*-5-*methyl-benzoylacetone* failed to yield the expected 4-hydroxy-3-acetylcoumarins, but with 2-hydroxy-4 : 5-dimethoxybenzoylacetone the results described in Part II (*loc. cit.*) were confirmed and a small yield of 4-hydroxy-3-acetyl-6 : 7-dimethoxycoumarin was invariably obtained. On the other hand, the carbonyl chloride method, *viz.*, the interaction of this reagent with the disodio-derivatives of *o*-hydroxybenzoylacetones, gave comparatively satisfactory yields of the requisite coumarins which were identical with the products obtained by the modified Anschütz method. It was recognised, however,

that in the latter procedure the initial reaction product, of type (I), might well undergo cyclisation to give a chromone of type (X; R = Et or R = H) in place of the expected coumarin of type (III), and that the carbonyl chloride method was open to the same objection, *e.g.*, the intermediate of type (II), if formed, could cyclise in two ways.

In a search for a more rational and general synthetical route to 4-hydroxy-3-acetylcoumarins it was ultimately discovered that 4-hydroxycoumarins, of type (IV), can be conveniently *C*-acetylated in the 3-position by means of acetic anhydride and boron trifluoride. From the initial reaction products water precipitated boron chelate complexes of type (V) which, on hydrolytic decomposition under the appropriate conditions (see Experimental section), furnished compounds of type (III). Accordingly, from 4-hydroxy-, 4-hydroxy-6-methyl-, 4-hydroxy-6-methoxy-, 4-hydroxy-7-methoxy-, and 4-hydroxy-6 : 7-dimethoxy-coumarin the corresponding 4-hydroxy-3-acetylcoumarins were prepared by this method and, except in the case of 4-*hydroxy*-6-*methoxy*-3-*acetylcoumarin* where a comparison was not possible, the products were identical with those from the modified Anschütz and the carbonyl chloride procedures, a result which clearly eliminates the possibility of the compounds prepared by the latter methods being 2-methylchromone-3-carboxylic acids of type (X; R = H). Consequently the compound *P*, formulated in Part II (*loc. cit.*) as 6 : 7-dimethoxy-2-methylchromone-3-carboxylic acid is 4-hydroxy-6 : 7-dimethoxy-3-acetylcoumarin, and its piperonylidene derivative is 4-*hydroxy*-6 : 7-*dimethoxy*-3-(3 : 4-*methylenedioxycinnamoyl*)*coumarin* (VI) and not the 2-styryl derivative



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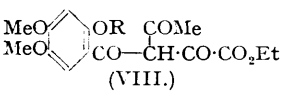

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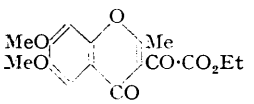

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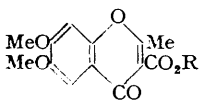
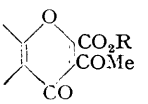


(X.)



(XI.)

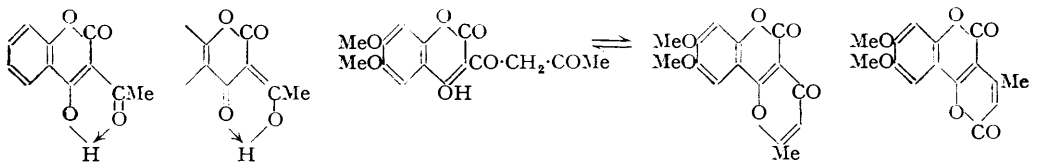
of the isomeric chromone. This conclusion has been substantiated by a synthesis of 6 : 7-*dimethoxy*-2-*methylchromone*-3-*carboxylic acid* (X; R = H). Condensation of 2-hydroxy-4 : 5-dimethoxyacetophenone with ethyl oxalate by means of sodium gave rise to *ethyl* 2-*hydroxy*-4 : 5-*dimethoxybenzoylpyruvate* (VII; R = H), the nature of which was clarified by cyclisation with alcoholic hydrochloric acid to *ethyl* 6 : 7-*dimethoxychromone*-2-*carboxylate*. Hydrolysis of the chromone and decarboxylation of the resulting *acid* gave 6 : 7-dimethoxychromone. Vigorous acetylation of (VII; R = H) furnished a small amount of *ethyl* 4 : 5-*dimethoxy*-2-*methylchromone*-3-*glyoxylate* accompanied by considerable amounts of ethyl 6 : 7-dimethoxychromone-2-carboxylate. The same glyoxylate (IX) was also formed by the foregoing method when (VII; R = H) was replaced by the *acetate* (VII, R = Ac), and more conveniently when (VII, R = H) was cyclised with acetic anhydride and boron trifluoride at 0°, a reaction which clearly proceeds by way of the intermediate (VIII; R = H). On treatment with warm concentrated sulphuric acid the glyoxylate (IX) was hydrolysed with the simultaneous evolution of carbon monoxide, giving rise to 6 : 7-dimethoxy-2-methylchromone-3-carboxylic acid (X; R = H) which had the expected properties of a carboxylic acid and was readily differentiated from the isomeric 4-hydroxy-3-acetylcoumarin (III).

In the conversion of (VII; R = H or Ac) into (IX) by vigorous acetylation, a reaction which presumably proceeds by way of (VIII), cyclisation of this intermediate could lead, by an alternative route, to *ethyl* 6 : 7-*dimethoxy*-3-*acetylchromone*-2-*carboxylate* (XI; R = Et). Although with (VII; R = H) as the starting material ethyl 6 : 7-dimethoxy-3-acetylchromone-2-carboxylate (XI; R = Et) could not be isolated, the acetate (VII; R = Ac) gave a small amount of (XI; R = Et) which accompanied the main reaction product (IX). This compound (XI; R = Et) is readily distinguished from the isomeric ethyl 4 : 5-dimethoxy-2-methylchromone-3-glyoxylate by the fact that unlike the latter it does not evolve carbon monoxide on being heated with sulphuric acid and on hydrolysis with concentrated acid gave 6 : 7-*dimethoxy*-3-*acetylchromone*-2-*carboxylic acid* (XI; R = H).

The 4-hydroxy-3-acetylcoumarins described in the present work melt without decomposition and are readily soluble in dilute aqueous sodium hydroxide. Unlike the parent 4-hydroxycoumarins, however, they dissolve but slowly in aqueous sodium hydrogen carbonate and apparently cannot be readily methylated or acetylated under the usual conditions, although it may be noted that Anschütz (*loc. cit.*) claims to have prepared a methyl ether of 4-hydroxy-

3-acetyl-7-methylcoumarin. With 2 : 4-dinitrophenylhydrazine sulphate solution 4-hydroxy-, 4-hydroxy-6-methyl-, and 4-hydroxy-7-methoxy-3-acetyl-coumarin reacted readily under the usual conditions, yielding the corresponding 2 : 4-dinitrophenylhydrazones, but 4-hydroxy-6-methoxy-3-acetylcoumarin reacted extremely slowly, whilst, as indicated in Part II (*loc. cit.*), 4-hydroxy-6 : 7-dimethoxy-3-acetylcoumarin did not form a dinitrophenylhydrazone. Treatment of the 4-hydroxy-3-acetylcoumarins with warm 80% sulphuric acid caused extrusion of the *C*-acetyl group and gave rise to the corresponding 4-hydroxycoumarins.

The properties of 4-hydroxy-3-acetylcoumarins are in keeping with the view that the molecule contains a hydrogen-bonded system involving a comparatively stable 6-atom ring of which the two formulæ (XII) and (XIII) represent the unperturbed forms of the resonating system. Substituents in the benzenoid ring appear to affect materially the stability of the chelate system.



(XII.) (XIII.) (XIV.) (XV.) (XVI.)

When it became clear that the hydrolytic product, m. p. 208°, from *O*-dimethylcitromycinone could not be 4-hydroxy-6 : 7-dimethoxy-3-acetylcoumarin (III), a re-examination of the compound was undertaken. The analytical results do not materially differ from the theoretical values required for (III) or for a *C*-acetyl derivative of this coumarin. On this account, combined with the fact that unlike (III) it readily formed a 2 : 4-dinitrophenylhydrazone, we concluded that the compound, m. p. 208°, was 4-*hydroxy*-6 : 7-*dimethoxy*-3-*acetoacetylcoumarin* (XIV) which was confirmed when it was found that cyclisation with warm sulphuric acid regenerated *O*-dimethylcitromycinone, identical with the product obtained by the oxidation of *O*-dimethylcitromycin. Since, in the conversion of (XIV) into *O*-dimethylcitromycinone, it is reasonably certain that the readily enolisable 4-carbonyl group (the 4-hydroxyl group of the coumarin system) was involved in the cyclisation and not the more stable carbonyl group of the lactone system, *O*-dimethylcitromycinone has the angular structure (XV) and not the linear formula proposed in Part III (*loc. cit.*). Mr. G. W. K. Cavill of this Department (private communication), who has examined the decomposition of *O*-dimethylcitromycinol (Part III, *loc. cit.*), has independently concluded that *O*-dimethylcitromycin as well as the primary oxidation products have angular structures corresponding to (XV), possibilities which were envisaged but not supported in Part III. Detailed experimental evidence in support of this revised structure for *O*-dimethylcitromycin and its derivatives will be discussed in a subsequent communication.

During numerous exploratory experiments on the synthesis of the diketone (XIV) and hence of *O*-dimethylcitromycinone (XV) it was found that 4-hydroxy-6 : 7-dimethoxy-3-acetylcoumarin could not be *C*-acetylated to give (XIV) [or its cyclisation product (XV)] by boron trifluoride–acetic anhydride, the Claisen reaction, or the Kostanecki vigorous-acetylation process. The alternative route of forming the γ-pyrone ring in (XV) by the condensation of acetoacetic acid or its ester with 4-hydroxy-6 : 7-dimethoxycoumarin was attempted but, as expected, with the usual condensing agents (concentrated sulphuric acid, phosphoric oxide, or phosphorus oxychloride) this reaction gave only 6 : 7-*dimethoxy*-4′-*methyl*-α-*pyrono*(5′ : 6′ : 3 : 4)*coumarin* (XVI) isomeric with *O*-dimethylcitromycinone. The failure of (XVI) to dissolve in concentrated hydrochloric acid or to form salts, and its behaviour with dilute aqueous sodium hydroxide, is in keeping with the α-pyrono-coumarin structure and readily serves to distinguish the compound from *O*-dimethylcitromycinone.

## Experimental.

4-*Hydroxy*-3-*acetylcoumarin*.—(*a*) Ethyl acetoacetate (3·8 ml.), dissolved in ether (20 ml.), was added to ethereal sodium ethoxide (from 0·7 g. of sodium, 5 ml. of alcohol, and 20 ml. of ether), followed by a solution of *o*-acetoxybenzoyl chloride (from 5 g. of acid) in ether (10 ml.), and the mixture warmed under reflux for 1 hour. More sodium ethoxide (from 0·7 g. of sodium) in a mixture of alcohol and ether (10 ml.) was added to the reaction mixture which became yellow and then deposited a yellow precipitate. The reaction was completed by warming the mixture for a further 3 hours and on isolation the solid was washed with ether, dried, and dissolved in water (150 ml.). Acidification of this solution with concentrated hydochloric acid gave 4-hydroxy-3-acetylcoumarin (2·9 g.) which formed needles, m. p. 138·5°, from alcohol (cf. Anschütz, *Annalen*, 1909, **367**, 194, who gives m. p. 134°).

(*b*) After the initial reaction between *o*-hydroxyacetophenone (5 g.), pulverised sodium (4 g.), and ethyl acetate (30 ml.) had somewhat subsided the mixture was heated on the water-bath for ½ hour, cooled, and treated with crushed ice (25 g.). The sodio-derivative of salicyloylacetone, which separated, was collected, washed with a little ice-water and then ether, and decomposed with dilute acetic acid, giving the diketone (3·2 g.) which formed square colourless prisms from alcohol, or plates, m. p. 95°, from light petroleum, and had a reddish-brown ferric reaction in alcohol (Found : C, 67·2; H, 5·6. Calc. for $C_{10}H_{10}O_3$ : C, 67·4; H, 5·7%) (Wittig, Bangert, and Richter, *Annalen*, 1926, **446**, 155, record m. p. 90·5—91·5°). Cyclisation of this ketone with sulphuric acid gave an almost theoretical yield of 2-methylchromone, m. p. 71° (Block and Kostanecki, *Ber.*, 1900, **33**, 1999, give m. p. 70—71°).

The foregoing diketone (5 g.) was added to a solution of sodium ethoxide (from 1·6 g. of sodium) in alcohol (50 ml.), the greater part of the solvent was distilled in a vacuum, and the disodio-derivative was precipitated from the cooled residue by means of ether (200 ml.), washed and dried (yield, 6·4 g. of a lemon-yellow powder). A slow stream of carbonyl chloride was led into a suspension of this derivative (5 g.) in toluene (75 ml.) cooled with ice–salt. The liquid became scarlet and next day the mixture was filtered, the sodium chloride was washed with a little toluene, and the combined filtrate and washings were concentrated by evaporation of most of the toluene in a vacuum. On being kept the residue deposited 4-hydroxy-3-acetylcoumarin which was washed with ether and obtained as a yellow crystalline powder (0·7 g.). Purified from alcohol, the compound had m. p. and mixed m. p. 138·5°. The 2 : 4-*dinitrophenylhydrazone*, which is very sparingly soluble in the usual organic solvents, separated from nitrobenzene in orange plates, m. p. 271° (decomp.) (Found : N, 14·9. $C_{17}H_{12}O_7N_4$ requires N, 14·6%).

(*c*) When boron trifluoride (from 22 g. of potassium fluoroborate) was slowly led into a mixture of acetic acid (5 ml.), acetic anhydride (2 g.), and 4-hydroxycoumarin (Boyd and Robertson, *J.*, 1948, 174) (1 g.) kept at room temperature, the solid quickly dissolved and next day the pale yellow viscous liquid was poured into water (100 ml.). After having been collected, thoroughly washed with water, and dried, the resulting fawn-coloured crystalline precipitate (1·2 g.) was decomposed with boiling 95% alcohol (50 ml.), and on cooling the mixture deposited 4-hydroxy-3-acetylcoumarin in long needles, m. p. and mixed m. p. 138°, identical with specimens prepared by methods (*a*) and (*b*). This coumarin dissolves slowly in aqueous sodium hydrogen carbonate and gives a yellow colour with alcoholic ferric chloride which becomes orange when the mixture is warmed. The 2 : 4-dinitrophenylhydrazone formed orange leaflets, m. p. and mixed m. p. 271° (decomp.), from nitrobenzene.

A mixture of 4-hydroxy-3-acetylcoumarin (0·2 g.), alcoholic sodium ethoxide (from 0·03 g. of sodium and 10 ml. of alcohol), and piperonal (0·15 g.) was warmed on the steam-bath for 30 minutes and the cooled orange reaction mixture poured into 2N-hydrochloric acid (20 ml.). Crystallisation of the resulting precipitate from acetic acid gave the *piperonylidene* derivative in orange needles (0·18 g.), m. p. 252° after sintering at 248° (Found : C, 67·6; H, 3·8. $C_{19}H_{12}O_6$ requires C, 67·9; H, 3·6%).

4-*Hydroxy*-3-*acetyl*-6-*methylcoumarin*.—(*a*) Prepared by the modification of Anschütz and Sieber's method (*Annalen*, 1909, **367**, 250) employed for the preparation of 4-hydroxy-3-acetylcoumarin, 4-hydroxy-3-acetyl-6-methylcoumarin had m. p. 147·5°, and gave a yellow ferric reaction in alcohol; yield, 1·7 g. from 5 g. of 2-acetoxy-5-methylbenzoyl chloride (Found : C, 66·0; H, 4·6. Calc. for $C_{12}H_{10}O_4$ : C, 66·0; H, 4·6%).

(*b*) Interaction of the disodio-derivative of 2-hydroxy-5-methylbenzoylacetone (Baker, *J.*, 1933, 1381) (5 g.) with excess of carbonyl chloride in toluene (75 ml.) gave rise to 4-hydroxy-3-acetyl-6-methylcoumarin (0·7 g.), m. p. and mixed m. p. 147·5°. The 2 : 4-*dinitrophenylhydrazone* formed clusters of orange needles from nitrobenzene or orange prisms, m. p. 265° (decomp.), from acetic acid (Found : N, 14·5. $C_{18}H_{14}O_7N_4$ requires N, 14·1%).

(*c*) The boron complex, m. p. 228° (decomp.), formed by the interaction of 4-hydroxy-6-methylcoumarin (Boyd and Robertson, *loc. cit.*) (1 g.), acetic acid (3 ml.), acetic anhydride (2 g.), and excess of boron trifluoride, was dissolved in boiling alcohol. On cooling, the solution deposited 4-hydroxy-3-acetyl-6-methylcoumarin as a mixture of rods and diamond-shaped prisms (0·9 g.), m. p. 148° after slight sintering at 140°, unchanged on further purification (Found : C, 66·1; H, 4·6%). The 2 : 4-dinitrophenylhydrazone had m. p. 264° (decomp.). Prepared by the method employed in the case of 4-hydroxy-3-acetylcoumarin, the *piperonylidene* derivative from 4-hydroxy-6-methyl-3-acetylcoumarin (0·2 g.) formed small orange needles (0·19 g.), m. p. 260—261°, from acetic acid and gave a violet colour with concentrated sulphuric acid (Found : C, 68·4; H, 4·1. $C_{20}H_{14}O_6$ requires C, 68·6; H, 4·0%).

4-*Hydroxy*-7-*methoxy*-3-*acetylcoumarin*.—(*a*) This *coumarin* (2·6 g.) was prepared from 2-hydroxy-4-methoxybenzoyl chloride (from 6·5 g. of acid) by the modified Anschütz method and on crystallisation from alcohol and then ethyl acetate–light petroleum (b. p. 80—100°) was obtained in yellowish-cream-coloured needles, m. p. 187·5°, giving a golden-yellow ferric reaction in alcohol which became red on warming (Found : C, 61·5; H, 4·7. $C_{12}H_{10}O_5$ requires C, 61·5; H, 4·3%).

(*b*) Interaction of the disodio-derivative of 2-hydroxy-4-methoxybenzoylacetone (Kostanecki and Lloyd, *Ber.*, 1901, **34**, 2942) (2·5 g.) with excess of carbonyl chloride in toluene (40 ml.) during 24 hours furnished 4-hydroxy-7-methoxy-3-acetylcoumarin (1·1 g.), m. p. 187·5°, after purification from alcohol. The 2 : 4-*dinitrophenylhydrazone* formed small red needles, m. p. 255°, from nitrobenzene (Found : N, 13·8. $C_{18}H_{14}O_8N_4$ requires N, 13·5%). When subjected to the standard method for the preparation of a piperonylidene derivative, almost all the 4-hydroxy-7-methoxy-3-acetylcoumarin was recovered unchanged.

(*c*) 4-*Acetoxy*-7-*methoxycoumarin* was prepared by the acetylation of 4-hydroxy-7-methoxycoumarin (Boyd and Robertson, *loc. cit.*) (4 g.) with hot acetic anhydride (40 ml.) during 1 hour and on isolation crystallised from alcohol in flat needles (4 g.), m. p. 133—134°, insoluble in aqueous sodium hydrogen carbonate (Found : C, 61·7; H, 4·5. $C_{12}H_{10}O_5$ requires C, 61·5; H, 4·3%). Interaction of the acetate (1 g.) with acetic acid (3 ml.), acetic anhydride (2 g.), and excess of boron trifluoride was accompanied by deacetylation and gave 4-hydroxy-7-methoxy-3-acetylcoumarin, m. p. 189, identical with specimens prepared by methods (*a*) and (*b*) (Found : C, 61·1; H, 4·4%). The 2 : 4-dinitrophenylhydrazone had m. p. 262° (decomp.) after sintering at 255°.

4-*Hydroxy*-6-*methoxycoumarin*.—When the vigorous reaction (initiated by gentle warming) between

2-hydroxy-5-methoxyacetophenone (Kostanecki and Lampe, *Ber.*, 1904, **37**, 774) (1·4 g.), ethyl carbonate (20 ml.), and pulverised sodium (0·4 g.) had somewhat subsided, the mixture was heated on the steam-bath for 1 hour, cooled, treated with a little methanol, and diluted with much ether. On isolation the solid was washed with ether and decomposed with excess of dilute hydrochloric acid, giving *4-hydroxy-6-methoxycoumarin* which formed colourless needles (1·6 g.), m. p. 170° (decomp.), from dilute alcohol, soluble in aqueous sodium hydrogen carbonate (Found : C, 62·5; H, 4·2. $C_{10}H_8O_4$ requires C, 62·5; H, 4·2%).

*4-Hydroxy-6-methoxy-3-acetylcoumarin.*—Interaction of the foregoing coumarin (0·7 g.), acetic acid (6 ml.), acetic anhydride (1·4 g.), and excess of boron trifluoride in the usual manner gave a solid (0·8 g.), m. p. ~180°, which on being dissolved in boiling alcohol yielded *4-hydroxy-6-methoxy-3-acetylcoumarin.* This compound separated from the cooled solution in long silky needles, changing to small prisms when left in contact with the solvent and, on recrystallisation from acetic acid, formed elongated rectangular prisms, m. p. 153°, slowly soluble in aqueous sodium hydrogen carbonate and giving an orange-yellow ferric reaction in alcohol (Found : C, 61·2; H, 4·5. $C_{12}H_{10}O_5$ requires C, 61·5; H, 4·3%). Prepared under the usual conditions, the 2 : 4-*dinitrophenylhydrazone* was very slowly formed and after being extracted with boiling alcohol the crude product crystallised from nitrobenzene in orange rectangular plates, m. p. 246—247° (Found : C, 52·5; H, 3·6. $C_{18}H_{14}O_8N_4$ requires C, 52·2; H, 3·4%).

*4-Hydroxy-6 : 7-dimethoxy-3-acetylcoumarin* (III).—(*a*) The interaction of 2-acetoxy-4 : 5-dimethoxybenzoyl chloride [from 5 g. of 2-acetoxy-4 : 5-dimethoxybenzoic acid (Head and Robertson, *J.*, 1931, 2432)], and ethyl sodioacetoacetate (from 3 ml. of ester and 0·52 g. of sodium) in ether (20 ml.), followed by treatment of the mixture with warm alcoholic sodium ethoxide (from 0·52 g. of sodium and 15 ml. of alcohol) in ether (50 ml.) on the water-bath for 3 hours, gave *4-hydroxy-6 : 7-dimethoxy-3-acetylcoumarin* which separated from alcohol in lemon-yellow needles, m. p. 250° (Found : C, 59·7; H, 4·6. $C_{13}H_{12}O_6$ requires C, 59·1; H, 4·6%).

(*b*) The foregoing coumarin was formed by the action of excess of carbonyl chloride on the disodio-derivative of 2-hydroxy-4 : 5-dimethoxybenzoylacetone (Part II, *loc. cit.*) in toluene cooled in an ice–salt bath during 24 hours. The product formed pale yellow needles (1·5 g.), m. p. and mixed m. p. 250°.

(*c*) Obtained by the interaction of 4-hydroxy-6 : 7-dimethoxycoumarin (1 g.), acetic anhydride (2 g.), and excess of boron trifluoride in acetic acid (5 ml.), the viscous reaction mixture was treated with water (50 ml.), and the bright yellow precipitate (1·1 g.) isolated, washed, and dried. On being cooled a solution of the product in hot acetic acid deposited the unchanged boron complex in yellow needles, m. p. 280°, insoluble in cold 2N-aqueous sodium hydroxide and giving a green flame test. When this compound was boiled with 50% aqueous sodium acetate or with sodium acetate in acetic acid, a colourless solution was slowly formed which, on being cooled, deposited 4-hydroxy-6 : 7-dimethoxy-3-acetylcoumarin in cream-coloured needles (0·8 g.), m. p. and mixed m. p. 250°. This compound, which gave a golden-yellow colour with ferric chloride in aclohol and slowly dissolved in aqueous sodium hydrogen carbonate, did not appear to form a 2 : 4-dinitrophenylhydrazone.

*Ethyl 2-Hydroxy-4 : 5-dimethoxybenzoylpyruvate* (VII; R = H).—When a well agitated mixture of 2-hydroxy-4 : 5-dimethoxyacetophenone (Part II, *loc. cit.*) (5 g.), ethyl oxalate (15 ml.), and pulverised sodium (0·8 g.), containing one drop of alcohol, was heated on the steam-bath, a vigorous reaction ensued and the reaction mixture set to a stiff paste. After the addition of sufficient methanol to destroy unchanged sodium, followed by an excess of ether, the sodio-derivative was collected, washed with ether, mixed with acetic acid (10 ml.), and then treated with a considerable volume of water. Thus precipitated, *ethyl 2-hydroxy-4 : 5-dimethoxybenzoylpyruvate* was collected and crystallised from aqueous alcohol, forming small yellow needles (4·9 g.), m. p. 157°, which give an olive-green, amber-tinged ferric reaction in alcohol (Found : C, 56·9; H, 5·6. $C_{14}H_{16}O_7$ requires C, 56·7; H, 5·4%).

A solution of this ester (3 g.) in pyridine (7 ml.) and acetic anhydride (10 ml.) was kept at room temperature for 18 hours and then mixed with an excess of dilute hydrochloric acid, giving a viscous precipitate which slowly solidified. Crystallised from alcohol this gave *ethyl 2-acetoxy-4 : 5-dimethoxy benzoylpyruvate* (VII; R = Ac) in pale lemon-yellow, feathery needles (2 g.), m. p. 133°, exhibiting a reddish-brown ferric reaction in alcohol (Found : C, 56·9; H, 5·4. $C_{16}H_{18}O_8$ requires C, 56·8; H, 5·3%).

A solution of ethyl 2-hydroxy-4 : 5-dimethoxybenzoylpyruvate (1 g.) in the minimum quantity of warm acetic acid was treated with a drop of concentrated hydrochloric acid, heated on the steam-bath for 15 minutes, and then poured on ice, giving a precipitate of *ethyl 6 : 7-dimethoxychromone-2-carboxylate* which, on crystallisation from alcohol or ethyl acetate–light petroleum (b. p. 60—80°), formed tiny, cream-coloured needles (0·88 g.), m. p. 182° (Found : C, 60·2; H, 5·2. $C_{14}H_{14}O_6$ requires C, 60·2; H, 5·1%). When a solution of this chromone-ester (5 g.) in hot alcohol (50 ml.) was mixed with concentrated hydrochloric acid (25 ml.) and then heated under reflux for 3 hours *6 : 7-dimethoxychromone-2-carboxylic acid* gradually separated. On isolation from the cooled mixture, this compound was purified by crystallisation from hot nitrobenzene and obtained in tiny, pale cream-coloured needles (3·5 g.), m. p. 303° (decomp.), readily soluble in cold aqueous sodium hydrogen carbonate and insoluble in the usual organic solvents (Found : C, 57·8; H, 4·2. $C_{12}H_{10}O_6$ requires C, 57·6; H, 4·0%). On being heated above its melting point this acid (1 g.) readily evolved carbon dioxide, leaving a residue of 6 : 7-dimethoxychromone which was purified by sublimation in a high vacuum at 180° and obtained in small irregular, almost colourless prisms (0·6 g.), m. p. 163°, from light petroleum (b. p. 60—80°), identical with an authentic specimen (Part II, *loc. cit.*).

*Ethyl 2-Methyl-6 : 7-dimethoxychromone-3-glyoxylate* (IX).—(*a*) A mixture of ethyl 2-hydroxy-4 : 5-dimethoxybenzoylpyruvate (6 g.), sodium acetate (6 g.), and acetic anhydride (30 ml.) was heated on the steam-bath for 15 minutes, treated with water (100 ml.), and then warmed until a clear solution was obtained. On being kept at 0° the reaction mixture slowly deposited ethyl 6 : 7-dimethoxychromone-2-carboxylate (3·2 g.) and, after the separation of the latter, the liquor on the addition of water (200 ml. and then 300 ml.) deposited more ethyl 6 : 7-dimethoxychromone-2-carboxylate (0·5 g.), followed by *ethyl 6 : 7-dimethoxy-2-methylchromone-3-glyoxylate* (IX) (*ca.* 0·5 g.). Although the glyoxylate separated in this manner in two experiments, in a number of cases it failed to do so and was isolated from the

diluted liquor by extraction with ethyl acetate. Repeated crystallisation of the crude glyoxylate from alcohol, benzene–light petroleum (b. p. 60—80°), and finally ethyl acetate gave the compound in almost colourless tiny needles, m. p. 182°, which on admixture with ethyl 6 : 7-dimethoxychromone-2-carboxylate had m. p. ~160° (Found : C, 59·8; H, 4·9. $C_{16}H_{16}O_7$ requires C, 60·0; H, 5·0%). The *semicarbazone* separated from water in small colourless prisms, m. p. 240° (decomp.) (Found : N, 10·7. $C_{17}H_{19}O_7N_3$ requires N, 11·1%).

(*b*) A mixture of ethyl 2-hydroxy-4 : 5-dimethoxybenzoylpyruvate (3 g.), acetic anhydride (11 ml.), and acetic acid (5 ml.) was saturated at 0° with boron trifluoride, and 24 hours later the orange-red complex was collected, washed with acetic acid, and warmed with acetic acid (17 ml.), water (7 ml.), and sodium acetate (7 g.). The resulting homogeneous solution was then diluted with water (250 ml.), and next day the gummy semi-crystalline product was collected and purified by crystallisation as in method (*a*), giving a small yield of ethyl 6 : 7-dimethoxy-2-methylchromone-3-glyoxylate, m. p. and mixed m. p. 182°.

(*c*) When a mixture of ethyl 2-acetoxy-4 : 5-dimethoxybenzoylpyruvate (2 g.), sodium acetate (2 g.), and acetic anhydride (10 ml.) was warmed on the steam-bath for 5 minutes and diluted with water (150 ml.), a semi-crystalline solid (2 g.) separated which, on repeated purification from alcohol, benzene, and ethyl acetate, gave a small yield of ethyl 6 : 7-dimethoxy-2-methylchromone-3-glyoxylate, m. p. and mixed m. p. 182°.

Evaporation of the mother-liquors from the purification of the foregoing chromone-3-glyoxylate prepared by method (*c*), followed by slow crystallisation of the residue from ethyl acetate, gave *ethyl 6 : 7-dimethoxy-3-acetylchromone-2-carboxylate* (XI; R = Et) in thick, massive, colourless prisms (0·5 g.), m. p. 147°, after repeated purification (Found : C, 60·0; H, 5·0%). This compound (0·2 g.), which had a negative ferric reaction, was warmed on the steam-bath with concentrated sulphuric acid (3 ml.) for 5 minutes, the solution was treated with crushed ice, and the resulting precipitate was isolated by extraction with much chloroform. Crystallisation of the product from the same solvent yielded 6 : 7-*dimethoxy-3-acetylchromone-2-carboxylic acid* (XI; R = H) in colourless prisms (0·15 g.), m. p. 240—241° (decomp.), sparingly soluble in alcohol or chloroform, almost insoluble in benzene or light petroleum, readily soluble in 2N-aqueous sodium hydrogen carbonate (Found : C, 57·4; H, 4·2. $C_{14}H_{12}O_7$ requires C, 57·5; H, 4·1%). Decarboxylation of this acid appeared to give a mixture of non-acidic compounds which was not further investigated.

When heated on the steam-bath with concentrated sulphuric acid (5 ml.), ethyl 6 : 7-dimethoxy-2-methylchromone-3-glyoxylate (0·5 g.) evolved carbon monoxide and, after the effervescence had ceased, the reaction mixture was treated with ice. Crystallisation of the resulting precipitate from acetic acid (charcoal) or from chloroform–light petroleum (b. p. 60—80°) gave 6 : 7-*dimethoxy-2-methylchromone-3-carboxylic acid* in tiny colourless needles (0·38 g.), m. p. 224° (decomp.) (Found : C, 59·0; H, 4·5. $C_{13}H_{12}O_6$ requires C, 59·1; H, 4·6%).

[With G. W. K. Cavill.] *4-Hydroxy-6 : 7-dimethoxy-3-acetoacetylcoumarin* (XIV).—A solution of *O*-dimethylcitromycinone (Part III, *loc. cit.*) (1 g.) in concentrated hydrochloric acid (50 ml.) was heated on the steam-bath for 10 minutes, diluted with water (100 ml.), almost neutralised with 2N-aqueous sodium hydroxide, and extracted with ether (50 ml. × 5). During the extraction unchanged *O*-dimethylcitromycinone (0·8 g.), which is insoluble in ether, separated from the aqueous liquor. Evaporation of the dried ethereal extract left *4-hydroxy-6 : 7-dimethoxy-3-acetoacetylcoumarin* which formed colourless needles (0·05 g.), m. p. 208° (decomp.), from ethanol (Found : C, 58·8; H, 4·7. $C_{15}H_{14}O_7$ requires C, 58·8; H, 4·6%).

The yellow solution of the compound (0·04 g.) in concentrated sulphuric acid (2 ml.) was kept at room temperature for 24 hours and then poured into ice-water (30 ml.). The pale yellow solid, which slowly separated, was collected, well washed, and crystallised from acetic acid, giving *O*-dimethylcitromycinone in colourless prisms (0·02 g.), m. p. 314—316° (decomp.), undepressed on admixture with an authentic specimen.

6 : 7-*Dimethoxy-4′-methyl-α-pyrono*(5′ : 6′ : 3 : 4)*coumarin* (XVI).—A mixture of 4-hydroxy-6 : 7-dimethoxycoumarin (1 g.), phosphoric oxide (4 g.), ethyl acetoacetate (2 ml.), and acetic acid (20 ml.) was heated on the steam-bath for 20 minutes and the resulting brownish semi-solid was transferred portion-wise to an excess of water. After having been well washed with aqueous sodium hydrogen carbonate and water the resulting crystalline product was extracted with concentrated hydrochloric acid and then recrystallised from acetic acid (charcoal), giving the *α-pyrono-coumarin* in pale cream-coloured, thin prisms (0·9 g.), m. p. 292° (slight decomp.) [Found : C, 62·6; H, 4·3; OMe, 21·7. $C_{13}H_6O_4(OMe)_2$ requires C, 62·5; H, 4·2; OMe, 21·5%]. This compound dissolves slowly in hot 2N-aqueous sodium hydroxide and is precipitated unchanged on acidification of the yellow alkaline solution with dilute hydrochloric acid. An acetic acid solution of the coumarin exhibits an intense purple fluorescence.

When the phosphoric oxide was replaced by phosphorus oxychloride in the foregoing reaction the yield of coumarin was 0·35 g., whilst with concentrated sulphuric acid only a very small amount of the compound was formed.

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