579. *The Chemistry of Fungi. Part XII. The Synthesis of* 6′ : 7′-*Dimethoxy*-2 : 4-*dimethylchromeno*(3′ : 4′-5 : 6)*pyranol Identical with a Derivative of* O-*Dimethylcitromycin.*

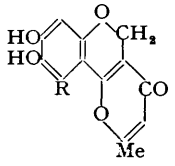
By J. B. D. Mackenzie, Alexander Robertson, and W. B. Whalley.

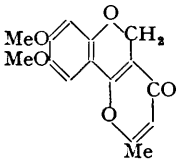
The revised structure (II) proposed for *O*-dimethylcitromycin (Part XI, *loc. cit.*), and hence those for citromycin (I; R = H) and citromycetin (I; R = CO_2H), have been confirmed by the synthesis of 6′ : 7′-dimethoxy-2 : 4-dimethylchromeno(3′ : 4′-5 : 6)pyranol (V). This pyranol, which was formed by the condensation of 6 : 7-dimethoxychromanone (VI) and acetylacetone with phosphoryl chloride, is identical with the base obtained by the interaction of *O*-dimethylcitromycin and methylmagnesium iodide. In the attempted preparation of 6′ : 7′-dimethoxy-4-phenyl-6-methylchromeno(3′ : 4′-3 : 2)pyranol (III) from *O*-dimethylcitromycin an anomalous product was obtained which appears to be 6′ : 7′-dimethoxy-6-methylchromeno(3′ : 4′-3 : 2)-pyranol.

The syntheses of 5 : 7-dimethoxy-2 : 4-dimethylbenzpyranol (IX) (two routes) and of 6 : 7-dimethoxy- (X; R = H) and 4-hydroxy-6 : 7-dimethoxy-3-benzoylcoumarin (X; R = OH) are described. Attempts to obtain 6 : 7-dimethoxy-3-benzoylchroman-4-one were unsuccessful.

On the basis of any one of the possible γ-pyrone type of formulæ developed for *O*-dimethylcitromycin in Part III (*J.*, 1949, 848; compare Part XI, *J.*, 1950, 1031) it appeared likely that the carbonyl group in the γ-pyrone residue would react with Grignard reagents, giving rise to pyranol bases of type (III) which could be suitably characterised by the formation of pyrylium

salts in the usual manner. Thus in a base of the type (III) the carbon atom originally present as the carbonyl group of the γ-pyrone residue on *O*-dimethylcitromycin is labelled by the attachment of a phenyl residue and hence its fate on degradation of the compound is more easily followed. Consequently, to obtain further analytical evidence in support of formula (II) for *O*-dimethylcitromycin (Part XI, *loc. cit.*) a study of the hydrolytic decomposition of the pyranol (III) was planned simultaneously with the experiments described in Parts IX (*J.*, 1950, 895), X (*J.*, 1950, 903), and XI (*loc. cit.*). Unexpected difficulties were encountered, however, in attempting the preparation of (III) by the interaction of *O*-dimethylcitromycin with phenylmagnesium bromide and the project was abandoned when an independent synthesis of the analogous pyranol (V) was discovered.


(I.)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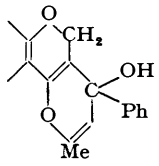
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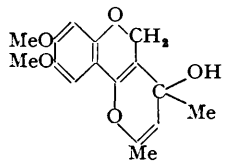
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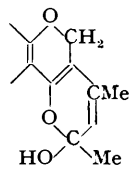
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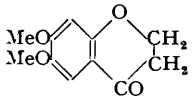
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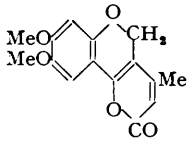
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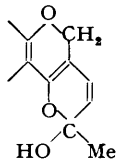
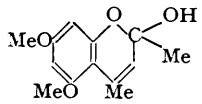

(VIII.)


(IX.)

The interaction of *O*-dimethylcitromycin with a molecular proportion of methylmagnesium iodide furnished a complex which on decomposition in the usual manner regenerated unchanged *O*-dimethylcitromycin, a result which is clearly due to the reactive methylene group taking up the Grignard reagent (cf. Part III, *loc. cit.*). When, however, an excess of methylmagnesium iodide was employed at room temperature a complex mixture was obtained from which 6′ : 7′-dimethoxy-2 : 4-dimethylchromeno(3′ : 4′-5 : 6)pyranol (V) could be isolated only by way of the picrate. In an attempt to isolate the parent pyranol base (V) from a solution of the crude picrate in benzene by chromatography on aluminium oxide two main zones were obtained which on elution furnished unchanged *O*-dimethylcitromycin and a remarkably stable picrate, m. p. 256°, respectively. This picrate, which was recovered unchanged after repeated crystallisation from solvents, gave anomalous analytical results and on treatment with perchloric acid and with hydroferric chloride was converted into a perchlorate and a ferrichloride, respectively, which also gave anomalous analytical results. Obtained from the perchlorate

Natural perchlorate (see Fig. 1).				*Synthetic perchlorate.*			
λ, max, mμ.	ε, max.	λ, min., mμ.	ε, min.	λ, max., mμ.	ε, max.	λ, min., mμ.	ε, min.
365	9,650	311	3,780	365	9,690	311	3,600
294	6,340	275	5,480	294	5,810	275	4,770
243	12,600	230	11,170	243	12,400	230	16,660

Natural picrate, m. p. 256° (decomp.) (see Fig. 2).				*Synthetic picrate*, m. p. 256° (decomp.).			
λ, max., mμ.	ε, max.	λ, min., mμ.	ε, min.	λ, max., mμ.	ε, max.	λ, min., mμ.	ε, min.
365	23,807	311	6,630	365	23,347	311	5,932
295	11,194	275	8,207	295	10,327	275	7,352
242	26,243	230	24,380	242	24,140	230	24,277

in the usual manner, 6′ : 7′-dimethoxy-2 : 4-dimethylchromeno(3′ : 4′-5 : 6)pyranol (V) formed a highly soluble chloride and with picric acid yielded a product which on chromatography followed by recrystallisation regenerated the picrate, m. p. 256° (decomp.). In the course of experiments on the synthesis of *O*-dimethylcitromycin and related compounds (unpublished work) it was found that this pyranol (V) was formed in small yield by the condensation of acetylacetone and 6 : 7-dimethoxychroman-4-one (VI) with phosphoryl chloride. The synthetic base (V) was isolated from the reaction mixture by the formation of a picrate which on chromatography furnished the characteristic picrate, m. p. 256° (decomp.), identical with the derivative obtained from *O*-dimethylcitromycin and forming the anomalous perchlorate

and ferrichloride derivatives. Prepared from its perchlorate, the synthetic pyranol (V) was identical with the natural derivative, and this identification was confirmed by a comparison of the ultra-violet absorption spectra of the natural and synthetical picrates (Fig. 2) and perchlorates (Fig. 1).

In conjunction with the analytical evidence described in Parts III and XI (*loc. cit.*) the synthesis of the pyranol (V) serves to confirm the angular structure (II) assigned to *O*-dimethylcitromycin (Part XI) and, *inter alia*, clearly shows that the easily oxidisable reactive methylene group is in the 2-position of the Δ^3-chromen residue. The formation of the pyranol (V) by the action of the Grignard reagent on *O*-dimethylcitromycin does not, however, rule out the possibility of the last-named compound having the α-pyrone structure (VII) but this alternative is entirely excluded by the observation that the hydration product of *O*-dimethylcitromycinone is a diketone and not a keto-acid in conjunction with the fact that 6 : 7-dimethoxy-4′-methyl-α-pyrono(5′ : 6′-3 : 4)coumarin is isomeric and not identical with the *O*-dimethylcitromycinone (Part X, *J.*, 1950, 903). Thus the structure (II) for *O*-dimethylcitromycin is conclusively established, and hence citromycin and citromycetin are represented by formulæ (I; R = H) and (I; R = CO_2H), respectively.

FIG. 1.

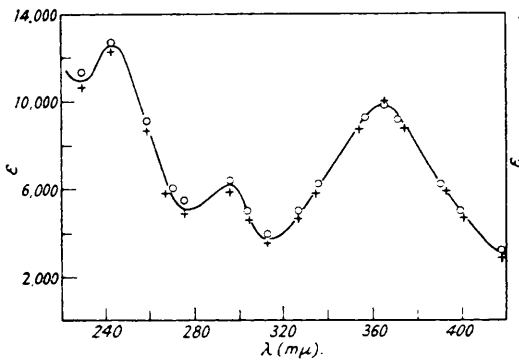
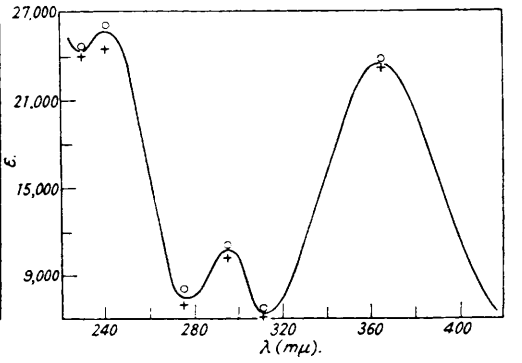


FIG. 2.



○ = *natural.* + = *synthetic.*

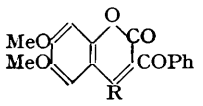
With regard to the question whether the base derived from *O*-dimethylcitromycin is an α- or a γ-pyranol, we consider that although the product originally formed by the hydrolysis of the Grignard complex may have formula (IV), the pyranol isolated from the perchlorate or chloride clearly has formula (V) (cf. Shriner and Moffett, *J. Amer. Chem. Soc.*, 1941, **63**, 1694).

It has been shown by Hetherington and Raistrick (*Phil. Trans.*, 1931, *B*, **220**, 209) that citromycin exhibits basic properties, forming a hydrobromide and a hydriodide, and in view of the anomalous composition of the oxonium salts derived from the pyranol (V) we examined the addition products formed from *O*-dimethylcitromycin and some acidic reagents. With picric acid and hydrochloric acid, respectively, this compound gave a normal picrate and hydrochloride, but with perchloric acid and hydroferric chloride the products were not simple addition compounds. From each of these derivatives unchanged *O*-dimethylcitromycin was readily recovered by treatment with aqueous sodium acetate or sodium hydrogen carbonate.

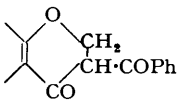
Although our studies on the interaction of *O*-dimethylcitromycin with phenylmagnesium bromide have not yet been completed it may be noted that, as in the case of methylmagnesium iodide, the interaction of molecular proportions of the compounds gave a complex which on decomposition furnished only unchanged *O*-dimethylcitromycin. With an excess of phenylmagnesium bromide a mixture was obtained from which basic material was separated by way of a picrate which on chromatography with aluminium oxide gave the remarkably stable picrate (A). Crystallisation of this compound from alcohol containing picric acid yielded a picrate (B) which on chromatography reverted to picrate (A). The parent base was regenerated from the chloride and from the perchlorate, respectively, which were prepared from picrate (A), but its analytical composition clearly showed that the compound was not a condensation product of type (III) containing a phenyl residue. Whilst this base, which appears to have the empirical formula $C_{15}H_{16}O_5$, can be clearly differentiated from *O*-dimethylcitromycin by its chemical properties, it closely resembles *O*-dimethylcitromycinol. In view of the established reduction of ketones by Grignard reagents in suitable circumstances (cf. Whitmore *et al.*,

J. Amer. Chem. Soc., 1941, **63**, 643; 1942, **64**, 1289) we believe that the γ-carbonyl group in the 4-position of *O*-dimethylcitromycin undergoes reduction with phenylmagnesium bromide giving the corresponding pyran-4-ol which is subsequently converted into the isomeride (VIII) by way of its salts.

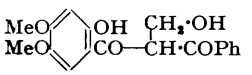
In model exploratory experiments 5 : 7-dimethoxy-2 : 4-dimethylbenzpyranol (IX) was synthesised by the two general routes employed for (V). 5 : 7-Dimethoxy-2-methylchromone was prepared by cyclisation of 2-hydroxy-4 : 6-dimethoxybenzoylacetone obtained from 2-hydroxy-4 : 6-dimethoxyacetophenone as well as by the simultaneous partial demethylation and cyclisation of 2 : 4 : 6-trimethoxybenzoylacetone. On treatment with methylmagnesium iodide, this chromone gave rise to a product from which the pyranol (IX) was isolated by chromatography. This base was unstable in air but was conveniently characterised by the formation of the well-defined 5 : 7-dimethoxy-2 : 4-dimethylbenzpyrylium picrate. The corresponding chloride was extremely soluble in hydrochloric acid, and attempts to convert the base into the pyrylium perchlorate or ferrichloride gave resinous products. The condensation of *O*-dimethylphloroglucinol with acetylacetone in hydrogen chloride–acetic acid gave rise to the same pyranol (IX), characterised by formation of the picrate.



(X.)



(XI.)



(XII.)

As possible reference compounds expected to be required in the hydrolysis of the pyranol (III), 6 : 7-dimethoxy- (X ; R = H) and 4-hydroxy-6 : 7-dimethoxy-3-benzoylcoumarin (X ; R = OH) were prepared by standard methods (cf. Part X, *loc. cit.*). In the course of numerous attempts to synthesise 6 : 7-dimethoxy-3-benzoylchroman-4-one (XI) it was found that the condensation of 6 : 7-dimethoxychroman-4-one and ethyl benzoate with sodium ethoxide gave rise to a small yield of a product which did not have the composition of the expected chromanone (XI). This substance, which did not form a 2 : 4-dinitrophenylhydrazone, was readily soluble in aqueous sodium hydroxide and gave an intense ferric reaction. It appears to be either a hydrated form of the enol of (XI) or, more likely, the hemihydrate of the compound (XII) formed by the scission of the dihydropyranone ring in (XI), but we were unable to obtain the anhydrous compound. In this connection it may be noted that in several investigations in these laboratories (unpublished work) it has been frequently observed that with alkaline reagents chromanones of type (VI) show a marked tendency to undergo scission and in this respect resemble the well-established behaviour of the flavanones. The failure to achieve a stepwise hydrolysis of citromycetin and citromycin or their dimethyl ethers is undoubtedly due in the main to the presence of the potential chromanone system in these compounds (cf. Hetherington and Raistrick, *loc. cit.*; and Part III, *loc. cit.*).

Experimental.

Salts of O-*Dimethylcitromycin.*—(*a*) A solution of *O*-dimethylcitromycin (1 g.), in benzene (200 ml.), was vigorously shaken with 10N-hydrochloric acid (20 ml.) for 10 minutes, and on being separated from the benzene layer the orange-red acidic liquor slowly deposited the *hydrochloride*, which was collected 24 hours later and recrystallised from 10N-hydrochloric acid, forming yellow rectangular prisms, m. p. 222° (decomp.) (Found : C, 58·2; H, 5·1. $C_{15}H_{15}O_5Cl$ requires C, 58·0; H, 4·8%).

(*b*) A warm saturated solution of picric acid in 50% aqueous alcohol was added to *O*-dimethylcitromycin (1 g.), dissolved in hot alcohol (25 ml.), until precipitation of the *picrate* appeared to be complete. 24 Hours later this compound was isolated and crystallised from benzene, forming clusters of irregular orange prisms, m. p. 180—181° (decomp.) (Found : C, 49·6; H, 3·3; N, 8·4. $C_{21}H_{17}O_{12}N_3$ requires C, 50·1; H, 3·3; N, 8·1%).

(*c*) A mixture of *O*-dimethylcitromycin (0·5 g.), perchloric acid (2 ml.), and acetic acid (2 ml.) was kept at about 40° until a clear solution was formed, and on being diluted with water (4 ml.) and kept at room temperature this mixture slowly deposited an anomalous perchlorate which formed golden-brown prisms, m. p. 238° (decomp.), from acetic acid (Found : C, 53·1; H, 4·6. Calc. for $C_{15}H_{15}O_9Cl$: C, 48·1; H, 4·0%).

(*d*) The addition of a concentrated solution of hydroferric chloride in hydrochloric acid to *O*-dimethylcitromycin in acetic acid gave a product which separated from acetic acid in slender, golden-brown prisms, m. p. 248° (decomp.) [Found : C, 46·9; H, 4·1; Cl, 18·2; Fe, 7·2. Calc. for $C_{15}H_{15}O_5Cl_4Fe$: C, 37·9; H, 3·2; Cl, 30·0; Fe, 12·0. Calc. for $(C_{15}H_{14}O_5)_2,HFeCl_4,2H_2O$: C, 47·1; H, 4·1; Cl, 18·7; Fe, 7·3%].

6′ : 7′-*Dimethoxy*-2 : 4-*dimethylchromeno*(3′ : 4′-5 : 6)*pyranol* (V).—(*a*) A solution of methylmagnesium iodide (from 0·8 g. of magnesium) in ether (50 ml.) was added to *O*-dimethylcitromycin

(3 g.) dissolved in benzene (1500 ml.). The mixture was occasionally shaken and 3 hours later was treated with a saturated aqueous solution of picric acid (200 ml.) containing 2N-hydrochloric acid (15 ml.). The orange benzene layer was separated, dried, and poured on a column of aluminium oxide, giving three zones on development with benzene: (1) a lower yellow zone of unchanged *O*-dimethylcitromycin (0·3 g.), washed through with an excess of benzene, (2) a middle zone of picrate (2·5 g.), eluted with benzene–methanol (3 : 1), and (3) an upper zone not removed by methanol. The recovered picrate was washed with water to remove traces of aluminium picrate and then crystallised from methanol or ethyl acetate–light petroleum, forming yellow needles (1·8 g.), m. p. 256° (decomp.) (Found: C, 48·4; H, 4·3; N, 9·2. Calc. for $C_{22}H_{19}O_{11}N_3$: C, 52·7; H, 3·8; N, 8·4%). Formed from this picrate, the perchlorate derivative separated from acetic acid in clusters of orange-brown rhombic prisms, m. p. 240—242° (decomp.) (Found: C, 53·8; H, 4·6. Calc. for $C_{16}H_{17}O_8Cl$: C, 51·6; H, 4·6%), and the ferrichloride derivative from acetic acid in dark reddish-brown prisms, m. p. 240—242° (decomp.) (Found: C, 46·8; H, 4·2; Fe, 7·5. Calc. for $C_{16}H_{17}O_4Cl_4Fe$: C, 40·9; H, 3·6; Fe, 12·0%).

Prepared from the foregoing perchlorate derivative by means of aqueous sodium acetate, 6′ : 7′-*dimethoxy*-2 : 4-*dimethylchromeno*(3′ : 4′-5 : 6)*pyranol* separated from aqueous methanol in almost colourless, slender needles, m. p. 225° (decomp.) (Found: C, 66·3; H, 6·4. $C_{16}H_{18}O_5$ requires C, 66·2; H, 6·2%). This compound was readily soluble in methanol or alcohol, sparingly soluble in benzene, and almost insoluble in light petroleum. The corresponding pyrylium chloride was readily soluble in cold dilute or concentrated hydrochloric acid and could not be isolated in the usual manner.

(*b*) A mixture of 6 : 7-dimethoxychroman-4-one (Robertson *et al.*, *J.*, 1936, 1832) (1 g.), acetylacetone (2 ml.), phosphoryl chloride (5 ml.), and acetic acid (10 ml.) was heated under reflux on the steam-bath for 90 minutes, and the resulting dark reddish-brown reaction mixture cooled to 0° and treated with ice-water (200 g.). After having been almost neutralised with aqueous sodium hydrogen carbonate, the mixture was mixed with saturated aqueous picric acid (50 ml.), and the yellow-brown curdy precipitate isolated by extraction with benzene (100 ml. × 3). The combined extracts were dried, and the picrate of the product isolated by chromatography on aluminium oxide and washed with water to remove a little aluminium picrate as in (*a*). Crystallised from methanol and then ethyl acetate–light petroleum, this compound formed pale, lemon-yellow needles (0·1—0·2 g.), m. p. 256° (decomp.) alone or admixed with the product prepared from natural *O*-dimethylcitromycin by method (a) (Found: C, 58·5; H, 4·5; N, 9·6%). As in (*a*) this picrate gave the perchlorate derivative, forming orange-brown rhombic prisms, m. p. and mixed m. p. 240—242° (decomp.) (Found: C, 54·1; H, 4·7; Cl, 6·8%), from acetic acid, and the ferrichloride derivative, which separated from the same solvent in dark reddish-brown prisms, had m. p. and mixed m. p. 240—242° (decomp.) (Found: C, 47·2; H, 4·3; Fe, 7·5%). Prepared from the perchlorate derivative, the pyranol base crystallised from aqueous methanol in almost colourless needles, m. p. and mixed m. p. 225° (decomp.), identical with the natural derivative and regenerating the picrate, m. p. and mixed m. p. 256° (decomp.), after purification by chromatography.

5 : 7-*Dimethoxy*-2-*methylchromone*.—(*a*) 2-Hydroxy-4 : 6-dimethoxyacetophenone was prepared by the following improved method (cf. Robertson *et al.*, *J.*, 1931, 1249). A solution of *O*-dimethylphloroglucinol (30 g.) in a mixture of acetic acid (10 ml.) and acetic anhydride (30 ml.) was saturated at 0° with boron trifluoride and 24 hours later the resulting yellow crystalline mass was treated with a solution of sodium acetate (60 g.) in water (500 ml.). From this reaction mixture 2-hydroxy-4 : 6-dimethoxyacetophenone, m. p. and mixed m. p. 82°, was separated by a current of steam and collected from the cooled distillate; yield, 20·5 g. The non-volatile solid consisted of 4-hydroxy-2 : 6-dimethoxyacetophenone, which crystallised from water in almost colourless plates (9 g.), m. p. 184—185°.

A mixture of 2-hydroxy-4 : 6-dimethoxyacetophenone (5 g.), ethyl acetate (10 ml.), and pulverised sodium (2 g.) was heated on the steam-bath for one hour, cooled, and treated with ice-water (30 g.). The precipitated crystalline sodium salt of 2-*hydroxy*-4 : 6-*dimethoxybenzoylacetone* was collected, washed with aqueous sodium chloride, and decomposed with dilute acetic acid, giving the diketone, which crystallised from light petroleum in colourless needles (3·2 g.), m. p. 82° (Found: C, 60·7; H, 6·3. $C_{13}H_{14}O_5$ requires C, 60·5; H, 6·0%). This compound gives an intense red ferric reaction in alcohol and is readily soluble in the usual organic solvents except light petroleum.

The diketone (3 g.) was cyclised by being boiled in a mixture of alcohol (30 ml.) and concentrated hydrochloric acid (2 ml.) for 2 minutes and the resulting 5 : 7-*dimethoxy*-2-*methylchromone* isolated with water and basified with aqueous sodium hydrogen carbonate. Crystallised from ligroin, this compound formed colourless prisms (2·6 g.), m. p. 124° (Found: C, 65·4; H, 5·6. $C_{13}H_{12}O_4$ requires C, 65·5; H, 5·5%). Condensed with piperonal (0·2 g.) and sodium ethoxide (from 0·2 g. of sodium) in alcohol (15 ml.), this chromone (0·2 g.) gave the 3′ : 4′-methylenedioxystyryl derivative, which formed golden-yellow prisms (0·1 g.), m. p. 164°.

(b) A mixture of 2 : 4 : 6-trimethoxyacetophenone (Friedlander and Schnell, *Ber.*, 1897, **30**, 2152) (10 g.), pulverised sodium (4 g.), and ethyl acetate (20 ml.) was heated on the steam-bath for 4 hours, and 24 hours later methanol (10 ml.) was added to destroy traces of residual sodium, followed by water (100 ml.). The mixture was acidified with acetic acid and extracted with chloroform (100 ml. × 3), and the combined extracts were washed with 2N-aqueous sodium hydroxide (50 ml. × 3). Acidification of the combined alkaline washings with acetic acid precipitated 2 : 4 : 6-*trimethoxybenzoylacetone*, which crystallised from aqueous methanol in colourless plates (8 g.), m. p. 106° (Found: C, 62·0; H, 6·2. $C_{13}H_{16}O_5$ requires C, 61·9; H, 6·3%). This diketone is readily soluble in ethyl acetate, benzene, or chloroform and sparingly soluble in alcohol or ether.

2 : 4 : 6-Trimethoxybenzoylacetone (2 g.) was refluxed with concentrated hydrochloric acid (75 ml.) for 4 hours and the mixture was basified with aqueous sodium hydrogen carbonate and extracted with chloroform (50 ml. × 3). The combined extracts were washed with dilute aqueous sodium hydroxide to remove traces of phenolic material and then with water, dried, and evaporated, leaving 5 : 7-di-

methoxy-2-methylchromone which formed colourless prisms (0·7 g.), m. p. 124°, from ligroin, identical with a specimen prepared by method (a).

5 : 7-*Dimethoxy*-2 : 4-*dimethylbenzpyranol* (IX).—(*a*) Methylmagnesium iodide (from 1 g. of magnesium) in ether (50 ml.) was added to a solution of the foregoing chromone (3 g.) in benzene (300 ml.), and 3 hours later the orange-yellow mixture was heated under reflux for one hour, cooled, and treated with saturated aqueous picric acid (100 ml.) followed by 2N-hydrochloric acid (50 ml.). The red benzene solution was separated, dried, and poured on a column of aluminium oxide, and the chromatogram developed with benzene, giving a dark upper and a yellow lower zone. Elution of the yellow zone with benzene–methanol (3 : 1) gave the benzpyranol, which crystallised from methanol in small, colourless prisms (0·4 g.), m. p. 155° (decomp.), which quickly darkened on exposure to air. Prepared from this base in the usual manner 5 : 7-*dimethoxy*-2 : 4-*dimethylbenzpyrylium picrate* separated from benzene in greenish-yellow prisms, m. p. 172—174° (decomp.) after darkening at 160° (Found : C, 51·2; H, 3·5; N, 9·1. $C_{19}H_{17}O_{10}N_3$ requires C, 51·3; H, 3·8; N, 9·4%). Owing to its extreme solubility in hydrochloric acid the chloride could not be purified and attempts to prepare the perchlorate and the ferrichloride from the base were unsuccessful, only dark resinous products being obtained.

(*b*) A solution of phloroglucinol dimethyl ether (5 g.) and acetylacetone (5 g.) in acetic acid (20 ml.) was saturated at 10° with hydrogen chloride, and next day the dark red reaction mixture was diluted with ether, the ethereal layer was decanted, and the dark brown residue washed with ether until almost all the acid had been removed. A solution of the residue in water was neutralised with 2N-ammonia, and the resulting dark red precipitate (4·5 g.) collected, dried, and dissolved in benzene. By chromatography on aluminium oxide 5 : 7-dimethoxy-2 : 4-dimethylbenzpyranol was isolated from this solution and crystallised from methanol, forming colourless squat prisms (3·5 g.), m. p. and mixed m. p. 155° (decomp.), which were unstable in air. The picrate separated from benzene in greenish-yellow prisms, m. p. and mixed m. p. 172—174° (decomp.) after darkening at 160° (Found : C, 51·3; H, 3·5; N, 9·4%).

6′ : 7′-*Dimethoxy*-2-*methylchromeno*(3′ : 4′-5 : 6)*pyranol* (VIII).—A solution of phenylmagnesium bromide (from 0·8 g. of magnesium and 5·5 g. of bromobenzene) in ether (50 ml.) was added to *O*-dimethylcitromycin (3 g.), dissolved in benzene (1500 ml.), and next day the mixture, which had deposited an amorphous yellow precipitate, was extracted with 5N-hydrochloric acid (25 ml. × 3). The combined acidic extracts were almost neutralised with 2N-ammonia (about 150 ml.) and were then mixed with a saturated aqueous solution of picric acid. 24 Hours later the resulting orange-yellow precipitate (5 g.) was collected, dried, and extracted with boiling benzene (1000 ml.). The cooled benzene extract was filtered to remove an intractable residue (1·5 g.) and poured on a column of aluminium oxide; the chromatogram was developed with benzene, giving a narrow upper zone not removed with methanol, a middle deep yellow zone, and a lower yellow zone. On elution with benzene–methanol (19 : 1) the lower zone gave unchanged *O*-dimethylcitromycin (0·5 g.), whilst with benzene–methanol (1 : 1) the middle zone gave picrate A, which was washed with water to remove traces of aluminium picrate and then crystallised from methanol or ethyl acetate–light petroleum, forming lemon-yellow needles, m.p. 254—255° (decomp.), which did not have the composition of a normal picrate of the pyranol (VIII) (Found : C, 51·0; H, 4·3; N, 6·8. Calc. for $C_{21}H_{17}O_{11}N_3$: C, 51·7; H, 3·5; N, 8·6%). The same picrate, m. p. 254—255°, was obtained when the benzene reaction-liquor containing the primary condensation product was shaken with a mixture of saturated aqueous picric acid (250 ml.) and dilute hydrochloric acid (20 ml.), and the resulting mixed solids were chromatographed. These results were not always reproducible and in some experiments the base or its picrate could not be isolated.

Crystallisation of picrate A from warm saturated alcoholic picric acid gave picrate B, which on recrystallisation from methanol containing a little picric acid formed clusters of orange-brown needles, m. p. 232° (decomp.) (Found : C, 48·6; H, 3·4; N, 9·1%). The addition of perchloric acid to a solution of picrate A in acetic acid gave a perchlorate which crystallised from acetic acid in yellow-brown prisms, m. p. 228—229° (decomp.) after darkening at 220° (Found : C, 49·5; H, 4·6; Cl, 7·3. Calc. for $C_{15}H_{15}O_8Cl$: C, 51·3; H, 4·2; Cl, 10·0%). Prepared in a similar manner, the ferrichloride derivative separated from acetic acid in long reddish-brown, glistening needles, m. p. 260—262° (decomp.) after darkening at about 240° (Found : C, 49·0; H, 4·2; Cl, 17·9; Fe, 7·4. Calc. for $C_{15}H_{15}O_4Cl_4Fe$: C, 39·4; H, 3·3; Cl, 31·1; Fe, 12·3%).

When a solution of the foregoing perchlorate in methanol was treated with aqueous sodium acetate and the resulting faintly coloured solution was diluted with water, 6′ : 7′-*dimethoxy*-2-*methylchromeno*-(3′ : 4′-5 : 6)*pyranol* was precipitated in almost colourless needles. Crystallised from ethyl acetate, this compound formed very pale fawn, squat rectangular prisms, m. p. 221—222° (decomp.) which on admixture with *O*-dimethylcitromycin melted about 200° (Found : C, 64·8; H, 5·3. $C_{15}H_{16}O_5$ requires C, 65·2; H, 5·8%). This compound was moderately soluble in methanol or alcohol and sparingly soluble in light petroleum. With perchloric acid the base gave the perchlorate, m. p. 228—229° (decomp.), and with alcoholic picric acid it gave picrate B, m. p. 232° (decomp.).

When a solution of the pyranol in ethyl acetate was saturated with hydrogen chloride an almost quantitative yield of a chloride was obtained in rosettes of orange-yellow needles, m. p. 217—218° (decomp.) after darkening at 210° (Found : C, 64·1; H, 5·6; Cl, 9·8. Calc. for $C_{15}H_{15}O_4Cl$: C, 61·1; H, 5·1; Cl, 12·1%). This compound was extremely soluble in dilute or concentrated hydrochloric acid and could not be recrystallised by the usual methods.

6 : 7-*Dimethoxy*-3-*benzoylcoumarin* (X; R = H).—Piperidine (0·5 ml.) was added to a solution of 2-hydroxy-4 : 5-dimethoxybenzaldehyde (Head and Robertson, *J.*, 1931, 32) (2 g.) and ethyl benzoylacetate (2·5 g.) in warm methanol, and 24 hours later the yellow product was isolated and crystallised from ethyl acetate, giving the 6 : 7-*dimethoxy*-3-*benzoylcoumarin* in lemon-yellow needles (2 g.), m. p. 206° (Found : C, 70·0; H, 4·4. $C_{18}H_{14}O_5$ requires C, 69·7; H, 4·5%). This compound, which had a negative ferric reaction in alcohol, was sparingly soluble in acetone or alcohol and gave a 2 : 4-*dinitro*-

phenylhydrazone, which separated from dioxan in crimson needles, m. p. 282° (decomp.) (Found : N, 11·1. $C_{24}H_{18}O_8N_4$ requires N, 11·4%).

4-Hydroxy-6 : 7-dimethoxy-3-benzoylcoumarin (X; R = H).—2-Acetoxy-4 : 5-dimethoxybenzoyl chloride was prepared by the interaction of the parent acid (Head and Robertson, *loc. cit.*) (3 g.) with phosphorus pentachloride (1·9 g.) in chloroform (100 ml.) and, after the evaporation of the solvent and phosphorus oxychloride, was treated with ether (200 ml.) containing ethyl sodiobenzoylacetate (from 4·8 g. of ethyl benzoylacetate and 0·7 g. of sodium). The mixture was heated under reflux for 4 hours, cooled, and treated with water (50 ml.). The aqueous alkaline layer was separated and acidified with 2N-hydrochloric acid, giving *4-hydroxy-6 : 7-dimethoxy-3-benzoylcoumarin* as a sticky precipitate (1 g.). Crystallised from alcohol and then ethyl acetate, the coumarin formed pale lemon-yellow needles, m. p. 252—253° (Found : C, 66·4; H, 4·3. $C_{18}H_{14}O_6$ requires C, 66·3; H, 4·3%). This compound, which gave a greenish colour with alcoholic ferric chloride, dissolved slowly in aqueous sodium hydrogen carbonate.

Condensation of 6 : 7-Dimethoxychroman-4-one with Ethyl Benzoate.—The condensation of this chroman-4-one (1 g.) with ethyl benzoate (5 ml.) was effected with sodium ethoxide (from 0·5 g. of sodium) in well-stirred ether (40 ml.) during 8 hours. After the addition of more ether (100 ml.) followed by ice-water (30 ml.), the mixture was vigorously shaken and the aqueous layer was isolated and acidified with 2N-hydrochloric acid. Next day the sticky precipitate was collected, triturated with a little methanol, and crystallised from dioxan, giving a substance in colourless squat prisms, m. p. 246° (Found, in a specimen dried in a vacuum at room temperature : C, 63·4; H, 5·2. Calc. for $C_{18}H_{18}O_6,0{\cdot}5H_2O$: C, 63·7; H, 5·6. Found, in a specimen dried in a high vacuum at 80° : C, 64·2; H, 5·7. Calc. for $C_{18}H_{18}O_6$: C, 65·5; H, 5·5%). The yield of this compound was very variable, the optimum being 0·3 g. from 1 g. of chromanone. It dissolves readily in N-aqueous sodium hydroxide and is recovered unchanged on acidification of the resulting yellow solution. With alcoholic ferric chloride the compound gives a blue-green colour, and with concentrated sulphuric acid a yellow solution which becomes bottle-green on being warmed.

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