447. *The Chemistry of Fungi. Part XV.* The Degradation of Methyl O-Dimethylcitromycetin.*

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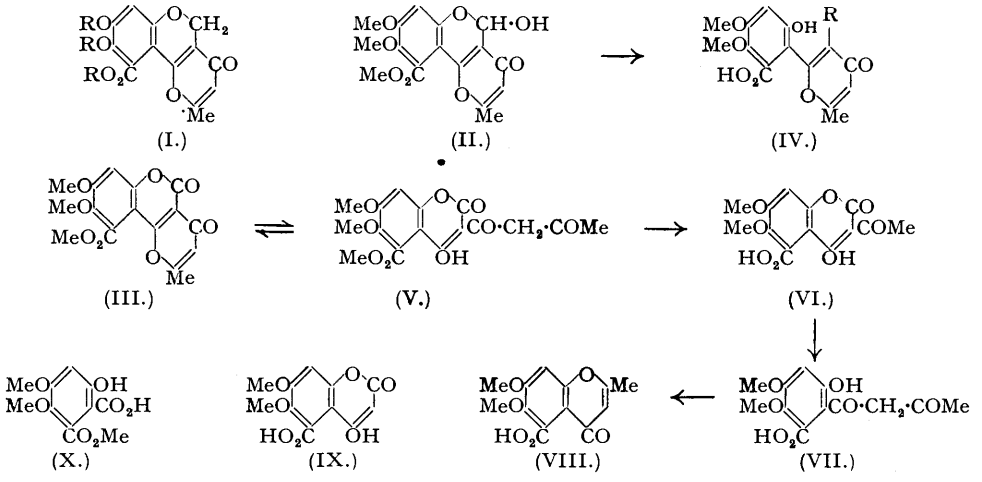
Methyl *O*-dimethylcitromycetin (I; R = Me), which is shown to have basic properties, is oxidised with lead tetra-acetate and chromic acid respectively to give methyl *O*-dimethylcitromycetinol (II) and methyl *O*-dimethylcitromycetinone (III). Unlike *O*-dimethylcitromycin, (I; R = Me) is not oxidised to give (II) and (III) with ozone. The phenylpyrone (IV; R = H) is formed from (II) with alkali, whilst with warm dilute acid (III) gives (V) which on cyclisation regenerates the parent compound. With warm alkali (III) gives rise to (VI), (VIII), and probably (IX), along with acetone and acetic acid.

Attempts to employ the ester (XIV; R = Me, R′ = OH) as the starting material for the synthesis of (VI), (VIII), and (IX) were unsuccessful because (XIV; R = Me, R′ = OH) could not be *C*-formylated or -acetylated. A new route to the synthesis of the acid (XIV; R = H, R′ = OH) is described.

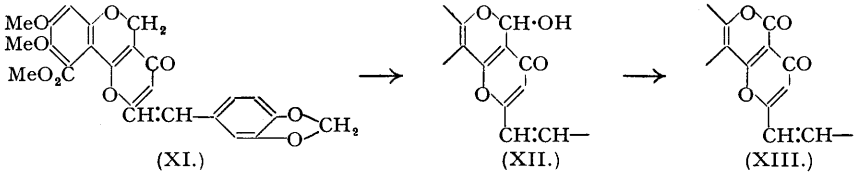
Since on oxidation with potassium permanganate methyl *O*-dimethylcitromycetin gave rise to methyl 2-carboxy-3-hydroxy-5 : 6-dimethoxybenzoate (X) (Part III, *J.*, 1949, 848), it became clear that on the basis of the structure established for citromycin (Part XI, *J.*, 1950, 1031; Part XII, *J.*, 1950, 2965) citromycetin was represented by formula (I; R = H). In view of the possibility that the decarboxylation of citromycetin to give citromycin might be accompanied by a fundamental change in the structure of the molecule, it seemed desirable to investigate the stepwise degradation of methyl *O*-dimethylcitromycetin by the methods employed for *O*-dimethylcitromycin with a view to obtaining an analogous series of products. Our efforts have only been partly successful and, though it has been possible to obtain the primary oxidation products (II) and (III) of methyl *O*-dimethylcitromycetin, their decomposition has proved somewhat unsatisfactory (cf. Part XI, *loc. cit.*), a result which is clearly due to the unexpectedly profound effect of the carboxyl (or carbmethoxy-) group present in the benzenoid system. Whilst the structures of the degradation products from (II) and (III) have been deduced primarily from our knowledge of the heterocyclic system in citromycin, the results obtained in the present work serve to support the view that the same heterocyclic system is present in citromycetin.

* Part XIV, *J.*, 1950, 3380.

The basic properties of methyl *O*-dimethylcitromycetin are established by the formation of a picrate, platinichloride, perchlorate, and hydroferric chloride, but the analytical results given by the last two salts are not in agreement with their being the normal derivatives. Like *O*-di-



methylcitromycin (Part VIII, *J.*, 1949, 1567), with lead tetra-acetate methyl *O*-dimethylcitromycetin gave a carbinol base, methyl *O*-dimethylcitromycetinol (II), which readily formed a chloride and on oxidation with chromic acid yielded methyl *O*-dimethylcitromycetinone (III), identical with the product obtained by oxidation of methyl *O*-dimethylcitromycetin with the same reagent; neither of these oxidation products can be obtained by means of ozone (cf. Part III, *loc. cit.*). Methyl *O*-dimethylcitromycetinone retains the basic properties of the parent compound, giving a hydroferric chloride and an abnormal platinichloride, and like *O*-dimethylcitromycinone it forms a dioximino-derivative and an anilide.



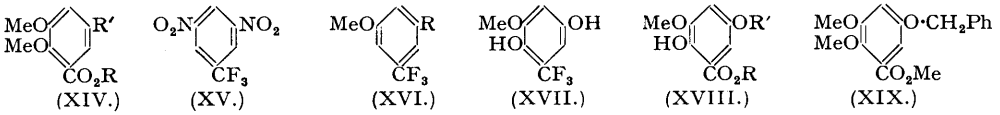
With piperonaldehyde and alcoholic sodium methoxide, methyl *O*-dimethylcitromycetin gives a piperonylidene derivative (XI), which on oxidation with lead tetra-acetate and with chromic acid gives the corresponding derivatives of methyl *O*-dimethylcitromycetinol (XII) and methyl *O*-dimethylcitromycetinone (XIII), respectively, thus showing that the reactive methyl group in the 2-position of the γ-pyrone ring is retained in the oxidation products.

On hydrolysis with warm alkali, methyl *O*-dimethylcitromycetinol (II) gave rise to formic acid and a product which is regarded as the phenyl-γ-pyrone (IV; R = H) formed by the opening of the carbinol ring by way of (IV; R = CHO). On the other hand, the hydrolysis of methyl *O*-dimethylcitromycetinone (III) with warm dilute hydrochloric acid primarily affects the γ-pyrone ring, giving the 3-acetoacetyl-4-hydroxycoumarin (V) which with concentrated sulphuric acid regenerates the parent compound (III) along with a trace of 3-acetyl-4-hydroxy-6 : 7-dimethoxycoumarin-5-carboxylic acid (VI). The hydrolytic decomposition of (III) was also effected with warm alkali under a variety of conditions, and in addition to acetic acid and acetone the main products obtained were the 3-acetyl-4-hydroxycoumarin (VI) and the chromone (VIII), along with small amounts of a substance which may be the 4-hydroxycoumarin (IX) but for which satisfactory analytical results were not obtained.

The structure of the chromone (VIII) is established by the formation of a piperonylidene derivative, confirming the presence of a methyl group in the 2-position, in conjunction with the fission by means of alkali to give two molecular proportions of acetic acid, and the acid (XIV; R = H, R′ = OH). Hydrolytic fission of the compound (VI), which was readily characterised by the formation of the methyl ester, gave the expected products, *viz.*, acetone, acetic acid, the

chromone (VIII), and a trace of the compound believed to be (IX). The chromone (VIII) clearly arises from (VI) and hence from (II) by way of the intermediate diketone (VII) which apparently undergoes cyclisation with remarkable ease.

It seemed desirable that the structures of (VI), (VII), (VIII), and (IX) should be confirmed by synthesis, and for this purpose the acid (XIV; R = H, R′ = OH) appeared to be a suitable starting material. This compound, which was originally obtained by Faltis and Kloiber



(XIV.) (XV.) (XVI.) (XVII.) (XVIII.) (XIX.)

(*Monatsh.*, 1929, **53**, 633) as a by-product during the preparation of 4 : 5-dimethoxybenzene-1 : 2 : 3-tricarboxylic acid from *m*-hemipinic acid, was prepared from (XIV; R = H, R′ = NO_2) by way of (XIV; R = H, R′ = NH_2) and (XIV; R = H, R′ = N_2Cl), but the method gave unsatisfactory results. Although the catalytic reduction of (XIV; R = H, R′ = NO_2) furnished much improved yields of the amine (XIV; R = H, R′ = NH_2), yet the conversion of the corresponding diazonium salt into the phenolic acid (XIV; R = H, R′ = OH) resulted in poor yields accompanied by much by-product. Accordingly, the following superior route was devised. By the action of methanolic sodium hydroxide 3 : 5-dinitrobenzotrifluoride (XV) was converted into 5-methoxy-3-nitrobenzotrifluoride (XVI; R = NO_2), and on catalytic reduction this gave the amine (XVI; R = NH_2) which furnished the 3-hydroxy-5-methoxybenzotrifluoride (XVI; R = OH) by the standard procedure. On oxidation with potassium persulphate this phenol (XVI; R = OH) gave 2 : 5-dihydroxy-3-methoxybenzotrifluoride (XVII), the trifluoromethyl group of which was hydrolysed with alkali (Whalley, *J.*, 1949, 3016) with the formation of the 2 : 5-dihydroxy-3-methoxybenzoic acid (XVIII; R = R′ = H). On monobenzylation, the ester (XVIII; R = Me, R′ = H) of the latter acid furnished the monobenzyl ether which, because of the resistance of phenolic hydroxyl groups in the *o*-position to carboxyl to benzylation, together with the fact that the ether gives a strong ferric reaction, has the orientation (XVIII; R = Me, R′ = Bz). Obtained by the methylation of (XVIII; R = Me, R′ = Bz), methyl 5-benzyloxy-2 : 3-dimethoxybenzoate (XIX) on debenzylation and hydrolysis gave 5-hydroxy-2 : 3-dimethoxybenzoic acid (XIV; R = H, R′ = OH), identical with the compound prepared by the method of Faltis and Kloiber (*loc. cit.*).

Attempts to synthesise (VI), (VIII), and (IX) had to be abandoned when it was found impossible to induce the ester (XIV; R = Me, R′ = OH) to undergo the Gattermann, Hoesch, or Friedel–Crafts reactions. Similarly, the benzotrifluoride (XVII) was equally unreactive.

Experimental.

Derivatives of Methyl O-Dimethylcitromycetin.—(*a*) When a mixture of this ester (1 g.), piperonaldehyde (1 g.), potassium ethoxide (from 0·25 g. of potassium), and alcohol (40 ml.) was heated on the steam-bath for ½ hour and then kept at room temperature for 7 days the *piperonylidene* derivative (0·8 g.) separated. Recrystallised from methanol, this formed bright yellow needles, m. p. 220° (Found: C, 64·8; H, 4·4. $C_{25}H_{20}O_9$ requires C, 64·7; H, 4·3%).

(*b*) Prepared with alcoholic picric acid, the *picrate* of methyl *O*-dimethylcitromycetin separated from methanol or benzene containing a little picric acid in yellow needles, m. p. 164° (Found: C, 49·3; H, 3·5; N, 7·2. $C_{17}H_{16}O_7,C_6H_3O_7N_3$ requires C, 49·2; H, 3·4; N, 7·5%).

(*c*) When a solution of methyl *O*-dimethylcitromycetin (1 g.) and platinum chloride (1 g.) in acetic acid was saturated with hydrogen chloride, the *platinichloride* separated during 2 days in tiny yellow needles, m. p. 191° (decomp.) [Found: C, 38·1; H, 3·5; Cl, 19·4; Pt, 18·1. $(C_{17}H_{16}O_7)_2,H_2PtCl_6$ requires C, 38·0; H, 3·2; Cl, 19·8; Pt, 18·2%].

(*d*) 60% Perchloric acid (1 ml.) was added to a solution of methyl *O*-dimethylcitromycetin (1 g.) in acetic acid (5 ml.), and the resulting *perchlorate*, m. p. 226° (decomp.), was collected 2 days later and washed with a little ether (Found: C, 46·6; H, 4·5; Cl, 20·9. $C_{17}H_{16}O_7,HClO_4$ requires C, 47·2; H, 3·9; Cl, 8·2%).

(*e*) When perchloric acid in (*d*) was replaced by concentrated hydroferrichloric acid, a *salt* separated in dark orange needles, m. p. 161—162° (decomp.), which was collected and washed with a little ether [Found: C, 43·4; H, 4·2; Cl, 19·7; Fe, 8·4. $C_{17}H_{16}O_7,HFeCl_4$ requires C, 38·4; H, 3·2; Cl, 26·7; Fe, 10·5%. $(C_{17}H_{16}O_7)_3,2HFeCl_4$ requires C, 43·9; H, 3·6; Cl, 20·4; Fe, 8·0%]. Attempts to recrystallise this compound or the perchlorate described in (*d*) were unsuccessful.

Methyl O-Dimethylcitromycetinol (II).—A mixture of powdered methyl *O*-dimethylcitromycetin (2 g.) and lead tetra-acetate (4 g.) was kept at 16—18° for 26 days, and the solid isolated from this dark liquor was washed and crystallised from methanol, giving *methyl O-dimethylcitromycetinol* (0·5 g.) in colourless needles, m. p. 234° (decomp.) (Found: C, 58·5; H, 4·8. $C_{17}H_{16}O_8$ requires C, 58·6; H, 4·6%). On addition of water (250 ml.) to the dark acetic acid reaction mixture a further quantity (0·35 g.) of this compound was obtained. Extraction of the aqueous acetic acid liquor with chloroform (100 ml. × 5)

and evaporation of the dried extracts gave a dark brown residue which on crystallisation from warm methanol gave a substance in pale yellow prisms (0·15 g.), m. p. 304—306° (decomp.) (Found: C, 61·3; H, 5·0%). A solution of this product in a little concentrated hydrochloric acid was warmed to 50° for 2 minutes and then diluted with water, giving methyl *O*-dimethylcitromycetinol, m. p. 234° (decomp.) after purification.

This carbinol readily dissolved in a small volume of concentrated hydrochloric acid and on being kept for 12 hours the solution deposited the *chloride* in rosettes of tiny, lemon-yellow prisms, m. p. 242—243° (decomp.) (Found: C, 55·4; H, 4·6; Cl, 9·7. $C_{17}H_{15}O_7Cl$ requires C, 55·6; H, 4·1; Cl, 9·7%). With much water or aqueous sodium acetate the salt regenerated the parent carbinol base.

Oxidation of the piperonylidene derivative of methyl *O*-dimethylcitromycetin (0·9 g.), dissolved in acetic acid (5 ml.), with lead tetra-acetate (2 g.) at room temperature for 28 days gave the *piperonylidene* derivative of methyl *O*-dimethylcitromycetinol, which was isolated with chloroform from the reaction mixture after dilution with water. This compound formed small yellow needles (0·2 g.), m. p. 196—198°, from dilute acetic acid (Found: C, 62·3; H, 4·2. $C_{25}H_{20}O_{10}$ requires C, 62·5; H, 4·2%).

Methyl O-*Dimethylcitromycetinone* (III).—Chromic oxide (0·75 g.) was gradually added to a solution of methyl *O*-dimethylcitromycetin (1 g.) in acetic acid (5 ml.) kept at 70—75°, and next day the green solution was diluted with water (100 ml.), and extracted with chloroform (100 ml. × 5). Evaporation of the combined dried extracts left *methyl* O-*dimethylcitromycetinone* as a brown viscous product which on purification from methanol was obtained in colourless stout prisms (0·6 g.), m. p. 240° (decomp.) [Found: C, 59·3; H, 3·9; OMe, 25·0. $C_{14}H_5O_5(OMe)_3$ requires C, 59·0; H, 4·0; OMe, 26·9%]. Oxidation of methyl *O*-dimethylcitromycetinol (0·4 g.) in acetic acid (2·5 ml.) with chromic oxide (0·3 g.) at 70—75° gave the same product (0·4 g.), m. p. 240° (decomp.), after purification.

Oximation of this compound by the pyridine or sodium acetate method gave a *dioximino*-derivative, which formed colourless flat needles, m. p. 210°, from methanol, having a red ferric reaction (Found: C, 54·4; H, 4·2; N, 7·6. $C_{17}H_{16}O_8N_2$ requires C, 54·3; H, 4·3; N, 7·5%). This compound dissolved in aqueous sodium hydroxide and was recovered unchanged by acidification of the solution. A mixture of methyl *O*-dimethylcitromycetinone (0·5 g.), aniline (1 ml.), and acetic acid (1 ml.) was heated on the steam-bath until a clear solution was formed (about 5 minutes). Treatment of this with an excess of 2N-hydrochloric acid gave an *anilide*, which separated from methanol in tiny, bright yellow needles (0·6 g.), m. p. 226° (Found: C, 63·1; H, 5·2; N, 3·6. $C_{23}H_{21}O_8N$ requires C, 62·9; H, 4·8; N, 3·2%).

Prepared in the usual manner, the *hydroferric chloride* of methyl *O*-dimethylcitromycetinone separated from acetic acid in dark orange prisms, m. p. 152—153° (decomp.) (Found: Cl, 26·1. $C_{17}H_{14}O_8,HFeCl_4$ requires Cl, 26·1%). With platinic chloride in acetic acid methyl *O*-dimethylcitromycetinone gave a complex salt decomposing at 203—204° with darkening at 190° [Found, in specimen dried in a high vacuum at 80°: C, 33·0; H, 3·7; Pt, 10·1. Calc. for $(C_{17}H_{14}O_8)_2,H_2PtCl_6$: C, 37·0; H, 2·7; Pt, 17·7%]. On decomposition with warm aqueous sodium acetate these derivatives gave methyl *O*-dimethylcitromycetinone.

Oxidation of the piperonylidene derivative of methyl *O*-dimethylcitromycetin (0·5 g.), dissolved in acetic acid (2·5 ml.), with chromic oxide (0·4 g.) at 75—80°, followed by the addition of water (100 ml.) gave the *piperonylidene* derivative of methyl *O*-dimethylcitromycetinone. Crystallised from methanol and then dilute acetic acid (charcoal), this compound formed yellow needles (0·3 g.), m. p. 170—172° with darkening [Found: C, 62·6; H, 3·8; OMe, 20·0. $C_{22}H_9O_7(OMe)_3$ requires C, 62·8; H, 3·8; OMe, 19·5%]. Similarly, the oxidation of the piperonylidene derivative of methyl *O*-dimethylcitromycetinol (0·1 g.) with chromic oxide (0·05 g.) in acetic acid (1 ml.) at 70—80° during 3 hours gave the corresponding derivative of methyl *O*-dimethylcitromycetinone, m. p. 170—172° with darkening.

When a solution of methyl *O*-dimethylcitromycetinone (0·5 g.) in methanol (10 ml.) and water (50 ml.) containing Raney nickel (1 g.) was heated under reflux for 2 hours, filtered, evaporated to a small bulk (10 ml.), and kept for 24 hours, a substance separated in pale yellow prisms which, after having been washed with dilute hydrochloric acid to remove a little unchanged material, formed colourless slender needles, m. p. 166°, from methanol, slowly soluble in 2N-aqueous sodium hydrogen carbonate and readily soluble in dilute sodium hydroxide (Found: C, 58·3, 58·3; H, 5·4, 5·3; OMe, 27·8%). When a solution of this compound in concentrated sulphuric acid was kept at room temperature for 2 hours and then poured on ice, methyl *O*-dimethylcitromycetinone, m. p. 240° (decomp.), was regenerated. On being heated with aniline, the substance, m. p. 166°, gave rise to the anilide, m. p. 226°, identical with that obtained from methyl *O*-dimethylcitromycetinone.

Degradation of Methyl O-*Dimethylcitromycetinol with Alkali.* (With G. W. K. Cavill.)—This compound (1·3 g.) was heated under reflux with 2N-aqueous sodium hydroxide (50 ml.) in an atmosphere of nitrogen for 1½ hours; the solid had dissolved in about 15 minutes, giving a clear amber solution. Acidification of the cooled reaction mixture with 2N-sulphuric acid (100 ml.) yielded a flocculent buff-coloured precipitate (0·6 g.) which was extracted with warm methanol, leaving 2-(6-*carboxy*-2-*hydroxy*-4 : 5-*dimethoxyphenyl*)-6-*methyl*-4-*pyrone* (0·1 g.). Crystallised from dioxan, this compound formed colourless prisms, m. p. 225—228° (decomp.) (Found: C, 58·6; H, 4·8. $C_{15}H_{14}O_7$ requires C, 58·8; H, 4·6%). This pyrone, which forms a yellow solution in a little concentrated hydrochloric acid, is soluble in 2N-aqueous sodium hydrogen carbonate and gives an incipient ferric reaction in alcohol.

From the methanolic extract of the precipitate 5-*carboxy*-6 : 7-*dimethoxy*-2-*methylchromone* (0·3 g.) separated in very pale yellow needles (0·3 g.), m. p. 156°, after recrystallisation (Found: C, 59·1; H, 4·6. $C_{13}H_{12}O_6$ requires C, 59·1; H, 4·6%). Treatment of the filtered acidic liquor left after the isolation of the precipitate with aqueous 2 : 4-dinitrophenylhydrazine sulphate gave a yellow precipitate from which acetone 2 : 4-dinitrophenylhydrazone (0·15 g.) was isolated by chromatography from light petroleum on aluminium oxide and identified by comparison with an authentic specimen. Distillation of the aqueous filtrate from the crude hydrazone gave formic acid, which was identified by conversion into the benziminazole (0·2 g.), m. p. 168—170°, after purification (Found: N, 23·3. Calc. for $C_7H_6N_2$:

N, 23·7%). A portion of the benziminazole was converted into the picrate, m. p. 223—225° (decomp.), identical with an authentic specimen.

Hydrolysis of Methyl O-*Dimethylcitromycetinone.*—(*a*) A solution of this compound (1 g.) in concentrated hydrochloric acid (50 ml.) was heated on the steam-bath for 1½ hours, cooled, diluted with water (100 ml.), almost neutralised with 2N-aqueous sodium hydroxide (150 ml.), and quickly extracted with ether (50 ml. × 20). The residue left on the evaporation of the combined dried extracts was washed several times with cold dilute hydrochloric acid to remove traces of methyl *O*-dimethylcitromycetinone and then crystallised from ethyl acetate–light petroleum, giving *methyl* 3-*acetoacetyl*-4-*hydroxy*-6 : 7-*dimethoxycoumarin*-5-*carboxylate* (V) in colourless needles, m. p. 165·5° (decomp.) (Found : C, 55·8; H, 4·6. $C_{17}H_{16}O_9$ requires C, 56·0; H, 4·4%); the yield of this product varied from about 50 to 100 mg. This diketone, which had a pale yellow-orange ferric reaction in alcohol, dissolved readily in 2N-aqueous sodium carbonate or hydroxide and slowly in aqueous 2N-sodium hydrogen carbonate. Treatment of the compound (50 mg.) with concentrated sulphuric acid (5 ml.) at room temperature for 24 hours followed by the addition of ice regenerated methyl *O*-dimethylcitromycetinone (40 mg.), m. p. and mixed m. p. 240° (decomp.), after purification (Found : C, 59·0; H, 4·3%).

(*b*) Methyl *O*-dimethylcitromycetinone (1 g.) was warmed with 2N-aqueous sodium hydroxide (50 ml.) on the steam-bath for 10 minutes and the resulting deep orange solution was cooled and acidified with 2N-sulphuric acid. After having been washed and dried, the yellow precipitate (0·6 g.) was extracted with hot methanol, giving 6 : 7-*dimethoxy*-2-*methylchromone*-5-*carboxylic acid* in pale yellow needles (0·36 g.), m. p. 156°, readily soluble in aqueous sodium hydrogen carbonate or ether, and moderately soluble in water or warm methanol [Found : C, 59·0; H, 5·0; OMe, 24·8. $C_{11}H_6O_4(OMe)_2$ requires C, 59·1; H, 4·6; OMe, 23·5%]. Interaction of a solution of the sodium salt of this acid (from 0·2 g. of acid) in 50% methanol (10 ml.) with *p*-nitrobenzyl bromide (0·3 g.) on the steam-bath for 1½ hours gave rise to the p-*nitrobenzyl* ester, which formed almost colourless needles, m. p. 168°, from alcohol (Found : C, 60·5; H, 4·1. $C_{20}H_{17}O_8N$ requires C, 60·1; H, 4·3%). Condensation of 6 : 7-dimethoxy-2-methylchromone-5-carboxylic acid (0·5 g.) and piperonaldehyde (0·5 g.) with methanolic sodium methoxide (from 0·25 g. of sodium and 50 ml. of methanol) on the steam-bath during 1 hour furnished a *piperonylidene* derivative which separated from benzene in clusters of pale yellow needles (0·15 g.), m. p. 225·5°, slowly soluble in aqueous sodium hydrogen carbonate (Found, in specimen dried in a high vacuum at 80° : C, 61·1; H, 3·9. $C_{21}H_{18}O_9$ requires C, 60·9; H, 4·4%).

The residue left after the extraction of 6 : 7-dimethoxy-2-methylchromone-5-carboxylic acid was crystallised from a large volume of methanol, giving 3-*acetyl*-4-*hydroxy*-6 : 7-*dimethoxycoumarin*-5-*carboxylic acid* in colourless needles (0·2 g.), m. p. 314° (decomp.), soluble in aqueous sodium hydrogen carbonate and giving a brownish ferric reaction in alcohol [Found : C, 54·8; H, 4·9; OMe, 18·5. $C_{12}H_6O_6(OMe)_2$ requires C, 54·6; H, 3·9; OMe, 19·8%]. This compound did not react with 2 : 4-dinitrophenylhydrazine but on methylation with ethereal diazomethane or methyl iodide–potassium carbonate gave *methyl* 3-*acetyl*-4-*hydroxy*-6 : 7-*dimethoxycoumarin*-5-*carboxylate*, which formed colourless prisms, m. p. 229° (decomp.), from methanol [Found : C, 55·9; H, 4·5; OMe, 26·6. $C_{12}H_5O_5(OMe)_3$ requires C, 55·9; H, 4·4; OMe, 28·3%].

The acidic liquor remaining after the separation of the solid precipitate was diluted with water and repeatedly extracted with ether, giving more 6 : 7-dimethoxy-2-methylchromone-5-carboxylic acid (0·32 g.). From the aqueous liquor, acetone, as its 2 : 4-dinitrophenylhydrazone, and acetic acid, as 2-methylbenziminazole (Brown and Campbell, *J.*, 1937, 1699), were isolated.

(*c*) Methyl *O*-dimethylcitromycetinone (8 g.) was heated under reflux with 2N-sodium hydroxide (400 ml.) for 1½ hours, and the cooled solution acidified with 2N-sulphuric acid (500 ml.), giving a precipitate of 6 : 7-dimethoxy-2-methylchromone-5-carboxylic acid (2·3 g.), m. p. 156°, after purification from methanol. From portions of the aqueous filtrate the acetone and acetic acid were isolated, whilst extraction with ether yielded more 6 : 7-dimethoxy-2-methylchromone-5-carboxylic acid along with a small amount of a white solid (0·05 g.) which on repeated crystallisation from methanol gave a compound in rhombic prisms, m. p. 255°, which may be impure 4-hydroxy-6 : 7-dimethoxycoumarin-5-carboxylic acid (Found : C, 55·5; H, 5·1; OMe, 15·8%).

Degradation of 3-*Acetyl*-4-*hydroxy*-6 : 7-*dimethoxycoumarin*-5-*carboxylic Acid.*—The coumarin (1 g.) was refluxed with 10% aqueous sodium hydroxide (50 ml.) in a stream of nitrogen which was led into aqueous-alcoholic 2 : 4-dinitrophenylhydrazine sulphate for 1½ hours. The latter solution gave a precipitate of acetone 2 : 4-dinitrophenylhydrazone, m. p. 128°, after purification. The cooled alkaline hydrolysate was acidified with 2N-sulphuric acid, giving a precipitate of 6 : 7-dimethoxy-2-methylchromone-5-carboxylic acid (0·05 g.), m. p. 156°, after sublimation in a high vacuum. Extraction of the acidic liquor with ether gave a product containing more of this chromone along with a small amount of the compound, m. p. 255°, believed to be 4-hydroxy-6 : 7-dimethoxycoumarin-5-carboxylic acid. In another experiment acetic acid was isolated and converted into 2-methylbenziminazole, m. p. 170—173°, and the picrate, m. p. 212—213° (decomp.).

Degradation of 6 : 7-*Dimethoxy*-2-*methylchromone*-5-*carboxylic Acid.*—A mixture of the chromone (1·8 g.) and 50% aqueous potassium hydroxide (20 ml.) was kept at 120—130° for ½ hour and then at 310—320° for 30 minutes in a stream of nitrogen which was led through aqueous-alcoholic 2 : 4-dinitrophenylhydrazine sulphate. From the latter, only a trace of a 2 : 4-dinitrophenylhydrazone was obtained. The alkaline melt was dissolved in water (100 ml.) and acidified with 2N-sulphuric acid. From a portion of the aqueous liquor, acetic acid equivalent to two molecular proportions was isolated and converted into methylbenziminazole, m. p. 170—173°, and thence into its picrate, m. p. 213° (decomp.). From the remainder of the filtrate 2 : 3-dimethoxy-5-hydroxybenzoic acid, m. p. 175—178°, after purification, was isolated and identified by comparison with an authentic specimen.

3-*Amino*-5-*methoxybenzotrifluoride.*—A mixture of 3 : 5-dinitrobenzotrifluoride (Finger and Reed, *J. Amer. Chem. Soc.*, 1944, **66**, 1972) (10 g.), sodium methoxide (5·4 g.), and methanol (50 ml.) was heated

under reflux for 1 hour, most of the solvent was distilled, and after the addition of water (120 ml.) the mixture was extracted with ether, giving an orange-red product. Distillation of this in a high vacuum gave 3-*methoxy*-5-*nitrobenzotrifluoride*, which formed colourless rectangular prisms (8·5 g.), m. p. 37·5°, from light petroleum (b. p. 60—80°) (Found : C, 42·8; H, 3·5; N, 6·5; F, 25·9. $C_8H_6O_3NF_3$ requires C, 43·4; H, 2·7; N, 6·3; F, 25·8%). This product was identical with that prepared by methylation of 3-hydroxy-5-nitrobenzotrifluoride (Whalley, *loc. cit.*).

Reduction of this compound (5 g.), dissolved in methanol (100 ml.), with hydrogen and palladium–charcoal catalyst (from 1 g. of charcoal and 0·1 g. of palladium chloride) gave 3-*amino*-5-*methoxybenzotrifluoride*, which formed long, colourless, silky needles, m. p. 151°, from light petroleum (b. p. 60—80°), soluble in dilute hydrochloric acid, water, and organic solvents (Found : N, 7·3. $C_8H_8ONF_3$ requires N, 7·3%). Prepared with acetic anhydride, the *acetyl* derivative separated from benzene in long, colourless needles, m. p. 120° (Found : C, 51·5; H, 4·2; N, 6·2; F, 24·8. $C_{10}H_{10}O_2NF_3$ requires C, 51·5; H, 4·3; N, 6·0; F, 24·5%).

3-*Hydroxy*-5-*methoxybenzotrifluoride*.—3-Amino-5-methoxybenzotrifluoride (5 g.) was dissolved in 2N-hydrochloric acid (100 ml.) at 0° and converted into the diazonium chloride with a solution of sodium nitrite (1·95 g.) in water (10 ml.). After 15 minutes the excess of nitrous acid was destroyed with urea, and the solution mixed with sulphuric acid (from 200 ml. of concentrated acid and 200 ml. of water) and heated to 95° for 1½ hours. On isolation with ether the resulting 3-*hydroxy*-5-*methoxybenzotrifluoride* was purified by distillation, crystallisation from light petroleum, and finally by sublimation at 100°/14 mm., forming rectangular prisms (3·4 g.), m. p. 75° (Found : C, 49·7; H, 4·2; F, 30·4. $C_8H_7O_2F_3$ requires C, 50·0; H, 3·7; F, 29·7%). The p-*nitrobenzoate* formed clusters of slender, pale yellow needles, m. p. 115° (Found : N, 4·2. $C_{15}H_{10}O_5NF_3$ requires N, 4·1%).

2 : 5-*Dihydroxy*-3-*methoxybenzotrifluoride*.—Saturated aqueous solution containing potassium persulphate (14·1 g.) was added to a stirred solution of 3-hydroxy-5-methoxybenzotrifluoride (10 g.) in 10% aqueous sodium hydroxide at 18° in the course of 3—4 hours. After 24 hours the mixture was acidified (Congo-red) with hydrochloric acid, extracted with ether to remove unchanged phenol (5 g.), and after the addition of concentrated hydrochloric acid was again extracted with ether, giving 2 : 5-*dihydroxy*-3-*methoxybenzotrifluoride* (4 g.) which was sublimed at 140°/0·2 mm. Crystallised from benzene, this quinol formed colourless flat prisms, m. p. 131°, giving a red-brown ferric reaction (Found : C, 46·2; H, 3·4; F, 27·5. $C_8H_7O_3F_3$ requires C, 46·2; H, 3·4; F, 27·4%). The *di*-p-*nitrobenzoate* separated from dilute methanol in almost colourless prisms, m. p. 194° (Found : N, 5·6. $C_{22}H_{13}O_9N_2F_3$ requires N, 5·5%).

2 : 5-*Dihydroxy*-3-*methoxybenzoic Acid*.—A solution of 2 : 5-dihydroxy-3-methoxybenzotrifluoride (7·7 g.) in 2N-aqueous sodium hydroxide (100 ml.) was kept for 24 hours, acidified, and extracted with ether. From the combined ethereal extracts 2 : 5-*dihydroxy*-3-*methoxybenzoic acid* (5·6 g.) was isolated by means of aqueous sodium hydrogen carbonate and purified by sublimation at 210°/0·2 mm. and then by crystallisation from light petroleum, forming colourless needles, m. p. 221°, with an olive-green ferric reaction in alcohol (Found : C, 52·0; H, 4·6. $C_8H_8O_5$ requires C, 52·2; H, 4·3%). Formed with ethereal diazomethane, the *methyl* ester separated from benzene–light petroleum in colourless prisms, m. p. 163·5°, having a dark green ferric reaction in alcohol [Found : C, 54·7; H, 5·1; OMe, 30·0. $C_7H_4O_3(OMe)_2$ requires C, 54·5; H, 5·1; OMe, 31·3%]. The *di*-p-*nitrobenzoate* crystallised from methanol in fawn-coloured prisms, m. p. 209° (Found : C, 55·8; H, 3·5; N, 5·5. $C_{23}H_{16}O_{11}N_2$ requires C, 55·6; H, 3·2; N, 5·6%).

Methyl 5-*Hydroxy*-2 : 3-*dimethoxybenzoate*.—Benzylation of methyl 2 : 5-dihydroxy-3-methoxybenzoate (25 g.) with benzyl bromide (18 ml.) and potassium carbonate (25 g.) in boiling acetone (1·5 l.) was accomplished during 5 hours. On isolation, the *methyl* 5-*benzyloxy*-2-*hydroxy*-3-*methoxybenzoate* was purified by chromatography from ether (1 l.) on aluminium oxide, followed by distillation at 180—182°/0·1 mm., and then by crystallisation from light petroleum, and obtained in colourless needles (18 g.), m. p. 102°, having a dark green ferric reaction (Found : C, 66·4; H, 5·5. $C_{16}H_{16}O_5$ requires C, 66·7; H, 5·6%). The p-*nitrobenzoate* separated from benzene–light petroleum (b. p. 60—80°) in colourless plates, m. p. 182° (Found : N, 3·6. $C_{23}H_{19}O_6N$ requires N, 3·2%).

Methylation of this benzyl ether (18 g.) with potassium carbonate (20 g.) and an excess of methyl iodide in boiling acetone (1 l.) during 20 hours and distillation of the product gave *methyl* 5-*benzyloxy*-2 : 3-*dimethoxybenzoate* as a pale yellow oil (18 g.), b. p. 195—196°/0·3 mm. [Found : C, 67·0; H, 5·3; OMe, 28·4. $C_{14}H_9O_2(OMe)_3$ requires C, 67·6; H, 6·0; OMe, 30·8%]. Debenzylation of this compound (5 g.), dissolved in acetic acid (100 ml.), with hydrogen and a palladium–charcoal catalyst (from 0·2 g. of palladium chloride and 2 g. of charcoal) was complete in 2 hours and gave *methyl* 5-*hydroxy*-2 : 3-*dimethoxybenzoate* as a pale yellow oil (3·4 g.), b. p. 145°/0·4 mm. (Found : C, 56·8; H, 5·6. $C_{10}H_{12}O_5$ requires C, 56·6; H, 5·7%). This product was readily soluble in dilute aqueous sodium hydroxide and gave a transient pale green ferric reaction. The p-*nitrobenzoate* formed pale yellow prisms, m. p. 126°, from benzene–light petroleum (Found : N, 3·9. $C_{17}H_{15}O_8N$ requires N, 3·9%). When the debenzylation was carried out with half the amount of catalyst during 7 hours the product was unexpectedly 5-hydroxy-2 : 3-dimethoxybenzoic acid, pale yellow irregular prisms, m. p. 178° (Found : C, 54·7; H, 5·1. Calc. for $C_9H_{10}O_5$: C, 54·5; H, 5·1%). A specimen prepared according to Faltis and Kloiber (*loc. cit.*), who give m. p. 186—188°, had m. p. 178°, and was identical with the foregoing acid.

Debenzylation of methyl 5-benzyloxy-2 : 3-dimethoxybenzoate (1 g.) with acetic acid (2 ml.) and concentrated hydrochloric acid (2 ml.) during 10 minutes gave rise to a mixture of unchanged compound and 5-hydroxy-2 : 3-dimethoxybenzoic acid, m. p. 178°.

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