Usnic Acid. Part X. The Exploration of a Route to 4 : 6-Dimethoxy-3 : 5-dimethylcoumarilic Acid.*

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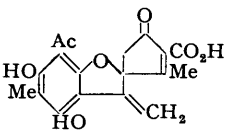
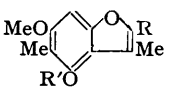
It has been shown that in coumarins prepared by Pechmann condensation of alkyl and acyl derivatives of phloroglucinol with ethyl acetoacetate and with ethyl α-chloroacetoacetate the alkyl groups occupy the 8- and the acyl groups the 6-position. With sulphuric acid as the condensing agent, *C*-methylphloroglucinol and ethyl acetoacetate gave a mixture of 5 : 7-dihydroxy-4 : 6- and -4 : 8-dimethylcoumarin, the dimethyl ethers of which have been converted into 4 : 6-dimethoxy-3 : 5- and -3 : 7-dimethylcoumarilic acid.

To attempt the synthesis of usnolic acid (I) or an immediate derivative by the route implicit in previous work (Parts VI, VII, and IX; *J.*, 1938, 306; 1939, 1594; 1953, 1250), it was necessary to obtain relatively large quantities of 4 : 6-dimethoxy-3 : 5- (II; R = H, R′ = Me) and -3 : 7-dimethylcoumarone (III; R = H, R′ = Me) or suitable related compounds. The coumarilic acid (II; R = CO_2H, R′ = Me) is a degradation product of usnic acid and has been decarboxylated to the corresponding coumarone (II; R = H, R′ = Me) by Asahina and Yanagita (*Ber.*, 1937, **70**, 66). These authors synthesised this coumarone by the cyclisation of 3 : 5-dimethoxy-4-methylphenoxyacetone (IV), which, however, is not easily accessible. The same coumarone has now been prepared from 2 : 6-dihydroxy-4-methoxy-3-methylacetophenone (V; R = H) by standard methods.



(I)



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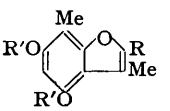


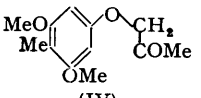
(III)

Cyclisation of the phenoxy-acid (V; R = $CH_2 \cdot CO_2H$) with acetic anhydride gave 4-acetoxy-6-methoxy-3 : 5-dimethylcoumarone (II; R = H, R′ = Ac), which on deacetylation followed by methylation furnished the dimethoxy-compound (II; R = H, R′ = Me). This conversion and the unreactive nature of the 3-hydroxyl group prove the orientation of the phenoxy-acid. As this route was but little more convenient, attention was directed to the preparation of coumarones from *C*-methylphloroglucinol. Condenation of phloroglucinol with ethyl α-chloroacetoacetate in basic media has been stated to give very poor yields of ethyl 4 : 6-dihydroxy-3-methylcoumarilate (VI) (Lang, *Ber.*, 1886, **19**, 2934; Kostanecki and Tambor, *Ber.*, 1909, **42**, 901) and it was therefore considered better to employ the Pechmann reaction and to convert the resulting coumarins into coumarilic acids by Perkin's method (*J.*, 1871, **24**, 37). Induced by hydrogen chloride, the condensation of *C*-methylphloroglucinol with ethyl α-chloroacetoacetate gave a single product which is clearly 3-chloro-5 : 7-dihydroxy-4 : 8-dimethylcoumarin (VII; R = Cl, R′ = H) since its dimethyl ether was identical with the product obtained when *C*-methylphloroglucinol was replaced by 2-hydroxy-4 : 6-dimethoxytoluene (VIII; R = Me) in the Pechmann condensation. The same orientation of substituents in the phloroglucinol residue was observed with ethyl acetoacetate in place of the chloro-ester. In this way 5 : 7-dihydroxy-4 : 8-dimethylcoumarin (VII; R = R′ = H) was prepared from *C*-methylphloroglucinol, whilst 5-hydroxy-7-methoxy-4 : 8-dimethylcoumarin (IX) was obtained from (VIII; R = H).

The dimethoxycoumarin (VII; R = H, R′ = Me), resulting from methylation of either

* Part IX, *J.*, 1953, 1250.

(VII; R = R′ = H) or (IX), reacted readily with bromine, giving the 3-bromocoumarin (VII; R = Br, R′ = Me). Neither this nor the corresponding chlorocoumarin was affected by alcoholic alkali under the standard conditions, but when treated with potassium hydroxide in boiling Carbitol both compounds gave good yields of 4 : 6-dimethoxy-3 : 7-dimethylcoumarilic acid (III; R = CO_2, R′ = Me) together with small amounts of 4 : 6-dimethoxy-3 : 7-dimethylcoumarone (III; R = H, R′ = Me), a reaction which also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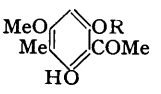
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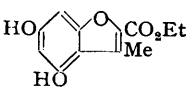
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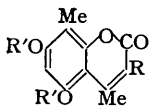
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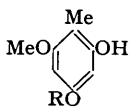
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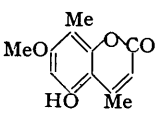
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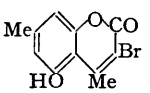
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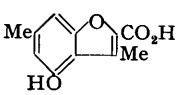
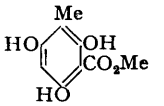

(XI)

defined the position of the halogen atoms. Attempted monobromination of 5 : 7-dihydroxy-4 : 8-dimethylcoumarin (VII; R = R′ = H) led only to the 3 : 6-dibromo-compound. Although Desai and Gaitonde's observation (*Proc. Indian Acad. Sci.*, 1947, **25**, *A*, 364) that 3-bromo-5-hydroxy-4 : 7-dimethylcoumarin (X) is smoothly converted into 5-hydroxy-3 : 6-dimethylcoumarilic acid (XI) by aqueous alkali has been confirmed, the application of this method to 3-chloro-5 : 7-dihydroxy-4 : 8-dimethylcoumarin (VII; R = Cl, R′ = H), which might have afforded a dihydroxycoumarilic acid related to (II), failed to give any recognisable product.

That the methoxycarbonyl group of methyl 2 : 4 : 6-trihydroxy-3-methylbenzoate (XII) had no effect on orientation in the Pechmann reaction with ethyl acetoacetate was indicated by the isolation of only one product (XIII; R = R″ = H, R′ = Me). The corresponding dimethyl ether was oriented by hydrolysis to an acid (XIII; R = R′ = H, R″ = Me), giving 5 : 7-dimethoxy-4 : 8-dimethylcoumarin (VII; R = H, R′ = Me) on decarboxylation. Methyl 3-chloro-5 : 7-dihydroxy-4 : 8-dimethylcoumarin-6-carboxylate (XIII; R = Cl, R′ = Me, R″ = H), obtained from a rather sluggish condensation with ethyl α-chloroacetoacetate, was similarly oriented by conversion into (VII; R = Cl, R′ = Me).

Whilst bromination of the ester (XIII; R = R″ = H, R′ = Me) resulted in the expected 3-bromocoumarin ester (XIII; R = Br, R′ = Me, R″ = H), the condensation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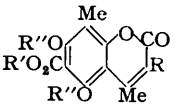
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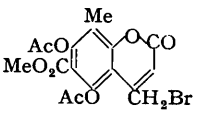
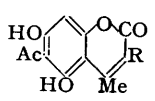

(XIV)

of (XII) and ethyl α-bromoacetoacetate with hydrogen bromide gave a complex mixture from which, after acetylation, a compound isomeric with (XIII; R = Br, R′ = Me, R″ = Ac) was isolated. Since Hantzsch (*Ber.*, 1894, **27**, 3168) has found that ethyl α-bromoacetoacetate is transformed into the γ-isomeride by acids, the new compound is considered to be the 4-bromomethylcoumarin (XIV).

6-Acetyl-5 : 7-dihydroxy-4-methylcoumarin (XV; R = H) was prepared by the interaction of phloroacetophenone and ethyl acetoacetate and on Clemmensen reduction readily furnished 6-ethyl-5 : 7-dihydroxy-4-methylcoumarin (XVI; R = R′ = H), isomeric with the 8-ethylcoumarin (XVII; R = R′ = H) obtained from *C*-ethylphloroglucinol. Orientation in this series was effected through 8-ethyl-5 : 7-dimethoxy-4-methylcoumarin (XVII; R = H, R′ = Me) which was obtained from both (XVII; R = R′ = H) and (XVIII).

Similar studies with phloroglucinaldehyde were not pursued owing to the very variable nature of the initial condensation product. Surprisingly, the reaction between phloroacetophenone and ethyl α-chloroacetoacetate gave both 6- (XV; R = Cl) and 8-acetyl-3-chloro-5 : 7-dihydroxy-4-methylcoumarin (XIX) which could be separated only as their dimethyl ethers. The chlorine atom exerted a more striking effect in the Fries rearrangement with boron trifluoride because 5 : 7-diacetoxy-4-methylcoumarin gave only the 6-acetylcoumarin (XV; R = H) whilst 5 : 7-diacetoxy-3-chloro-4-methylcoumarin gave the 8-acetylcoumarin (XIX). As before, the acetyl group of (XIX) was located by Clemmensen reduction followed by methylation to the 5 : 7-dimethoxy-compound (XVII; R = Cl, R′ = Me), identical with the coumarin from (XVIII) and ethyl α-chloroacetoacetate. Unfortunately, this orienting effect of chlorine could not be exploited because *C*-methylphloroacetophenone failed to react with ethyl α-chloroacetoacetate, although with the more reactive parent ester 6-acetyl-5 : 7-dihydroxy-4 : 8-dimethylcoumarin (XX; R = H) was produced. The Fries rearrangement of the acetate (VII; R = H, R′ = Ac) also gave (XX; R = H) and this was easily brominated, but both the resulting 3-bromocoumarin (XX; R = Br) and the corresponding 3-chlorocoumarin [XX; R = Cl; produced from (VII; R = Cl, R′ = Ac) by the action of aluminium chloride] were resinified by alkali.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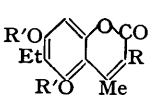
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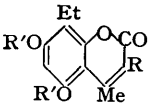
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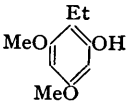
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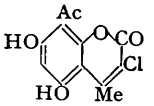
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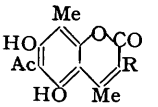
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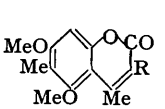
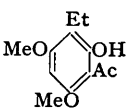

(XXI)


(XXII)

Since the above variations had failed to produce a 6-methylcoumarin, other condensing agents were examined. Fujise and Wayarama (*J. Chem. Soc. Japan*, 1934, **55**, 1016; *Chem. Abs.*, 1935, **29**, 4008) reported the preparation of an unoriented coumarin by the action of sulphuric acid on a mixture of *C*-methylphoroglucinol and ethyl acetoacetate. At first this coumarin appeared to be identical with the product formed with hydrogen chloride as the condensing agent, but closer examination showed that two coumarins were present which were separated as their dimethyl ethers. The major component was the ether (VII; R = H, R′ = Me); the other was considered to be 5 : 7-dimethoxy-4 : 6-dimethylcoumarin (XXI; R = H), a view substantiated by the smooth conversion of the corresponding 3-bromocoumarin (XXI; R = Br) into 4 : 6-dimethoxy-3 : 5-dimethylcoumarilic acid (II; R = CO_2H, R′ = Me), identical with the acid prepared by Asahina and Yanagita (*loc. cit.*).

Difficulties were encountered in the preparation of authentic *C*-ethylphloroglucinol and its 2 : 4-dimethyl ether (XVIII) necessary for the above work. A slight modification of Späth and Gruber's method (*Ber.*, 1941, **74**, 1492) furnished crystalline *C*-ethylphloroglucinol of m. p. 165° instead of the amorphous powder, m. p. 125°, obtained previously, but this material gave neither satisfactory analytical results nor crystalline derivatives with phenyl *iso*cyanate, benzoyl chloride, or *p*-nitrobenzoyl chloride. However, in the Gattermann reaction the crystalline material furnished an excellent yield of *C*-ethylphloroglucinaldehyde, identical with that described by Späth and Gruber (*loc. cit.*). Although Gruber and Traube (*Monatsh.*, 1947, **77**, 414) mention the 2 : 4-dimethyl ether of *C*-ethylphloroglucinol, its preparation and properties do not appear to have been described. When prepared by Clemmensen reduction of the corresponding ketone, the ether (XVIII) decomposed too rapidly to allow accurate analysis, but it formed a stable, characteristic phenylurethane, and in the Hoesch synthesis furnished the ketone (XXII) described by Gruber and Traube (*loc. cit.*).

Experimental

The light petroleum employed had b. p. 60—80°.

2-Acetyl-3-hydroxy-5-methoxy-4-methylphenoxyacetic Acid (V; R = $CH_2 \cdot CO_2H$).—Interaction of 2 : 6-dihydroxy-4-methoxy-3-methylacetophenone (4 g.), methyl bromoacetate (3·1 g.), and potassium carbonate (6 g.) in boiling acetone (150 ml.) for 8 hr. gave rise to *methyl 2-acetyl-3-hydroxy-5-methoxy-4-methylphenoxyacetate* (V; R = $CH_2 \cdot CO_2Me$) which separated from methanol in felted needles (3·1 g.), m. p. 159—160°, with a brownish-purple ferric reaction in alcohol [Found : OMe, 22·8. $C_{11}H_{10}O_4(OMe)_2$ requires OMe, 23·1%]. This ester (2 g.) was heated in 2N-aqueous sodium hydroxide (7·6 ml.) on the steam-bath for 15 min. and the cooled yellow solution acidified with hydrochloric acid, liberating *2-acetyl-3-hydroxy-5-methoxy-4-methylphenoxyacetic acid* which crystallised from 50% dioxan–ethyl acetate in prisms (1·6 g.), m. p. 228°, sparingly soluble in benzene and having a brownish-purple ferric reaction (Found : C, 56·9; H, 5·6; OMe, 11·3. $C_{11}H_{11}O_5 \cdot OMe$ requires C, 56·7; H, 5·6; OMe, 12·2%). With ethereal diazomethane, this acid regenerated the methyl ester, m. p. and mixed m. p. 159°.

4 : 6-Dimethoxy-3 : 5-dimethylcoumarone (II; R = H, R′ = Me) (cf. Asahina and Yanagita, *loc. cit.*).—The foregoing acid (4 g.), anhydrous sodium acetate (4 g.), and acetic anhydride (40 ml.) were heated under reflux for 1 hr., cooled, and treated with water (200 ml.). Next day the solid was collected, washed with water, dried, and extracted with light petroleum. The residue left on evaporation of the extract was distilled and the resulting oil (3·3 g.), b. p. 117—119°/0·01 mm., crystallised from light petroleum, giving *4-acetoxy-6-methoxy-3 : 5-dimethylcoumarone* (II; R = H, R′ = Ac) in prisms, m. p. 71° (Found : C, 66·3; H, 5·7. $C_{13}H_{14}O_4$ requires C, 66·7; H, 6·0%). Deacetylation of this acetoxycoumarone (0·15 g.) with 2N-sodium hydroxide (5 ml.) on the steam-bath for 3 hr. gave *4-hydroxy-6-methoxy-3 : 5-dimethylcoumarone* (II; R = R′ = H) which separated from methanol in plates (0·08 g.), m. p. 119°, with a negative ferric reaction and giving a red colour in warm concentrated sulphuric acid (Found : OMe, 16·6. $C_{10}H_9O_2 \cdot OMe$ requires OMe, 16·1%). Prepared by interaction of this hydroxycoumarone (1 g.), methyl iodide (2 ml.), and potassium carbonate (2 g.) in boiling acetone for 15 hr., 4 : 6-dimethoxy-3 : 5-dimethylcoumarone was an oil, b. p. 80—85°/0·005 mm. [Found : OMe, 27·0. Calc. for $C_{10}H_8O(OMe)_2$: OMe, 30·0%], forming a bright red *picrate* which crystallised from 90% alcohol in prisms, m. p. 95° (Found : N, 10·4. $C_{18}H_{17}O_{10}N_3$ requires N, 9·7%).

5 : 7-Dihydroxy-4 : 8-dimethylcoumarin (VII; R = R′ = H).—A solution of *C*-methylphloroglucinol (5 g.) and ethyl acetoacetate (3·5 ml.) in glacial acetic acid (25 ml.) was saturated with hydrogen chloride without external cooling. When the separation of solid appeared to be complete, this was isolated and crystallised from methanol, giving the *hemihydrate* of 5 : 7-dihydroxy-4 : 8-dimethylcoumarin in pale yellow needles (7 g.), m. p. 285° (decomp.), which were soluble in acetone, slightly soluble in methanol or acetic acid, and gave a bright yellow solution with 2N-sodium carbonate (Found : C, 58·8; H, 5·7. $C_{10}H_{10}O_4, 0{\cdot}5H_2O$ requires C, 59·1; H, 5·5%). With acetic anhydride–pyridine this coumarin afforded the *diacetate* (VII; R = H, R′ = Ac) which separated from methanol in needles, m. p. 208° (Found : C, 61·7; H, 5·0. $C_{15}H_{14}O_6$ requires C, 62·1; H, 4·9%), and by the methyl sulphate–potassium carbonate method afforded *5 : 7-dimethoxy-4 : 8-dimethylcoumarin* (VII; R = H, R′ = Me) which formed needles, m. p. 191°, from methanol or benzene; its alcoholic solution exhibited a pale blue fluorescence [Found : C, 66·6; H, 6·0; OMe, 27·0. $C_{11}H_8O_2(OMe)_2$ requires C, 66·6; H, 6·0; OMe, 26·5%].

5-Hydroxy-7-methoxy-4 : 8-dimethylcoumarin (IX).—Formed from 2 : 4-dihydroxy-6-methoxytoluene (1 g.) and ethyl acetoacetate (0·9 ml.) in acetic acid at 50° saturated with hydrogen chloride, *5-hydroxy-7-methoxy-4 : 8-dimethylcoumarin* was precipitated with methanol and purified from acetic acid, forming needles (1 g.), m. p. 278° (decomp.) (Found : C, 65·0; H, 5·8; OMe, 14·2. $C_{11}H_9O_3 \cdot OMe$ requires C, 65·4; H, 5·5; OMe, 14·1%), readily converted on methylation into 5 : 7-dimethoxy-4 : 8-dimethylcoumarin, m. p. and mixed m. p. 190°.

3-Chloro-5 : 7-dimethoxy-4 : 8-dimethylcoumarin (VII; R = Cl, R′ = Me).—(*a*) When saturated with hydrogen chloride a solution of 2-hydroxy-4 : 6-dimethoxytoluene (0·4 g.) and ethyl α-chloroacetoacetate (0·5 ml.) in dry ether (10 ml.) deposited *3-chloro-5 : 7-dimethoxy-4 : 8-dimethylcoumarin*, which formed needles (0·4 g.), m. p. 264°, from dioxan or acetic acid [Found : C, 57·9; H, 5·0; OMe, 22·6. $C_{11}H_7O_2Cl(OMe)_2$ requires C, 58·0; H, 4·9; OMe, 23·0%].

(*b*) A solution of *C*-methylphloroglucinol (3·9 g.) and ethyl α-chloroacetoacetate (4·6 g.) in warm acetic acid (50 ml.) was saturated with hydrogen chloride and kept until precipitation was complete. Recrystallised from a large volume of acetic acid, the resulting solid supplied the *hemihydrate* of 3-chloro-5 : 7-dihydroxy-4 : 8-dimethylcoumarin (VII; R = Cl, R′ = H) in

yellow needles (4·1 g.), m. p. 310° (decomp.), giving a bright yellow solution in 2N-sodium carbonate (Found: C, 53·0; H, 4·0; Cl, 13·9. $C_{11}H_9O_4Cl,0·5H_2O$ requires C, 52·8; H, 4·0; Cl, 14·2%). Prepared with acetic anhydride and either pyridine or boron trifluoride, the *diacetate* separated from alcohol in felted needles, m. p. 196°, slowly soluble in hot aqueous sodium hydroxide (Found: C, 55·9; H, 4·0. $C_{15}H_{13}O_6Cl$ requires C, 55·4; H, 4·0%). On methylation with methyl sulphate (6 ml.) and potassium carbonate (5·6 g.) in boiling acetone (150 ml.) for 8 hr. the dihydroxycoumarin (VII; R = Cl, R = H) gave 3-chloro-5 : 7-dimethoxy-4 : 8-dimethylcoumarin (2·1 g.), m. p. and mixed m. p. 264°.

3-Bromo-5 : 7-dimethoxy-4 : 8-dimethylcoumarin (VII; R = Br, R′ = Me).—Bromination of 5 : 7-dimethoxy-4 : 8-dimethylcoumarin (5 g.) in acetic acid (50 ml.) with a 10% solution (45 ml.) of bromine in the same solvent was rapid at 60°. The resulting *3-bromo-5 : 7-dimethoxy-4 : 8-dimethylcoumarin* separated from the cooled mixture and was crystallised from benzene, forming needles (7·3 g.), m. p. 242° [Found: C, 50·0; H, 4·2; Br, 25·5; OMe, 20·0. $C_{11}H_7O_2Br(OMe)_2$ requires C, 49·8; H, 4·2; Br, 25·6; OMe, 19·8%].

3 : 6-Dibromo-5 : 7-dimethoxy-4 : 8-dimethylcoumarin.—The gradual addition of a 10% solution (40 ml.) of bromine in chloroform to 5 : 7-dihydroxy-4 : 8-dimethylcoumarin (5 g.) in warm chloroform (50 ml.) was accompanied by the rapid evolution of hydrogen bromide. When the colour of bromine had disappeared, the solution was boiled to expel hydrogen bromide, and on cooling then deposited *3 : 6-dibromo-5 : 7-dihydroxy-4 : 8-dimethylcoumarin* which separated from methanol in needles, m. p. 212° (decomp.) (Found: C, 36·0; H, 2·2. $C_{11}H_8O_4Br_2$ requires C, 36·2; H, 2·2%). The *diacetate* formed needles, m. p. 208°, from acetic acid–benzene [Found: C, 40·2; H, 2·8; Br, 35·6; OAc, 23·9. $C_{15}H_8O_2Br_2(OAc)_2$ requires C, 40·0; H, 3·1; Br, 35·6; OAc, 24·0%]. The *dimethyl ether* crystallised from methanol in needles, m. p. 176° [Found: C, 39·4; H, 3·4; Br, 41·7; OMe, 16·0. $C_{11}H_6O_2Br_2(OMe)_2$ requires C, 39·8; H, 3·1; Br, 43·1; OMe, 15·8%].

4 : 6-Dimethoxy-3 : 7-dimethylcoumarilic acid (III; R = CO_2H, R′ = Me).—Powdered 3-chloro-5 : 7-dimethoxy-4 : 8-dimethylcoumarin (1 g.) (or the equivalent amount of the corresponding 3-bromocoumarin) was sifted into a boiling solution of potassium hydroxide (3 g.) in Carbitol (diethylene glycol monoethyl ether) (30 ml.). Potassium chloride was rapidly precipitated and 15 min. later the mixture was cooled, diluted with water (40 ml.), extracted with ether, and acidified. The gelatinous precipitate, which was allowed to coagulate before being collected, was washed with water and crystallised from acetic acid, giving *4 : 6-dimethoxy-3 : 7-dimethylcoumarilic acid* in needles (0·7 g.), m. p. 264° (decomp.) [Found: C, 61·9; H, 5·7; OMe, 25·3. $C_{11}H_8O_3(OMe)_2$ requires C, 62·4; H, 5·7; OMe, 24·8%]. With ethereal diazomethane this furnished the *methyl ester* (III; R = CO_2Me, R′ = Me), forming needles, m. p. 145°, from methanol [Found: OMe, 35·0. $C_{11}H_7O_2(OMe)_3$ requires OMe, 35·2%]. Evaporation of the combined ethereal extracts from a large number of experiments left an oil, which on distillation gave *4 : 6-dimethoxy-3 : 7-dimethylcoumarone* (III; R = H, R′ = Me), in prisms, b. p. 142°/20 mm., m. p. 69—71°, with a violet sulphuric acid reaction (Found: C, 70·5; H, 7·0. $C_{12}H_{14}O_3$ requires C, 70·0; H, 6·9%). The *picrate* separated from 80% alcohol in chocolate-coloured prisms, m. p. 94—95°, depressed on admixture with the picrate of 4 : 6-dimethoxy-3 : 5-dimethylcoumarone (Found: N, 9·4. $C_{18}H_{17}O_{10}N_3$ requires N, 9·7%).

5 : 7-Dimethoxy-4 : 6-dimethylcoumarin (XXI; R = H).—An intimate mixture of *C*-methylphloroglucinol (2 g.) and ethyl acetoacetate (1·9 ml.) was treated with sulphuric acid monohydrate (7 ml.) at 0°, kept in an ice-chest for 2 days, and mixed with crushed ice. The resulting solid was washed with 50% methanol and methylated by the methyl sulphate–potassium carbonate method (8 hr.), and the product extracted with light petroleum, leaving a residue of 5 : 7-dimethoxy-4 : 8-dimethylcoumarin (1·1 g.), m. p. and mixed m. p. 190°, after purification from methanol. Crystallised from methanol or from light petroleum, the extract gave *5 : 7-dimethoxy-4 : 6-dimethylcoumarin* in needles (0·8 g.), m. p. 160° [Found: C, 66·2; H, 6·3; OMe, 26·6. $C_{11}H_8O_2(OMe)_2$ requires C, 66·6; H, 6·0; OMe, 26·5%].

By bromination as above, this gave *3-bromo-5 : 7-dimethoxy-4 : 6-dimethylcoumarin* (XXI; R = Br), needles (0·2 g. from 0·2 g.), m. p. 176° (from dilute acetic acid) [Found: C, 49·2; H, 4·3; OMe, 19·9. $C_{11}H_7O_2Br(OMe)_2$ requires C, 49·8; H, 4·2; OMe, 19·8%].

4 : 6-Dimethoxy-3 : 5-dimethylcoumarilic acid (II; R = CO_2H, R′ = Me).—The foregoing bromocoumarin (0·2 g.) was added to a solution of potassium hydroxide (0·6 g.) in boiling Carbitol (7 ml.) and the mixture boiled for 3 min., cooled, diluted with water (50 ml.), and acidified with hydrochloric acid, giving 4 : 6-dimethoxy-3 : 5-dimethylcoumarilic acid which, on purification from dilute acetic acid, formed needles (0·1 g.), m. p. 220°, with a purple sulphuric acid reaction [Found: C, 62·5; H, 6·0; OMe, 24·8. Calc. for $C_{11}H_8O_3(OMe)_2$: C, 62·4; H,

5·7; OMe, 24·8%] (Asahina and Yanagita, *loc. cit.*, give m. p. 220°). Prepared with ethereal diazomethane the *methyl ester* separated from methanol in rectangular prisms, m. p. 127° [Found : C, 63·4; H, 6·0; OMe, 35·1. $C_{10}H_7O_2(OMe)_3$ requires C, 63·7; H, 6·1; OMe, 36·0%].

5 : 7-*Dimethoxy*-4 : 8-*dimethylcoumarin*-6-*carboxylic Acid* (XIII; R = R′ = H, R″ = Me).—Methyl 2 : 4 : 6-trihydroxy-3-methylbenzoate (4 g.) and ethyl acetoacetate (4 ml.) in acetic acid (25 ml.), when saturated with hydrogen chloride, gave *methyl* 5 : 7-*dihydroxy*-4 : 8-*dimethylcoumarin*-6-*carboxylate* which crystallised from acetic acid or methanol in small needles (4·2 g.), m. p. 249° (decomp.), with a blue ferric reaction (Found : C, 59·2; H, 4·7; OMe, 11·7. $C_{12}H_9O_5$·OMe requires C, 59·1; H, 4·6; OMe, 11·7%). By the methyl sulphate–potassium carbonate method this coumarin readily furnished *methyl* 5 : 7-*dimethoxy*-4 : 8-*dimethylcoumarin*-6-*carboxylate* (XIII; R = H, R′ = R″ = Me) which separated from light petroleum in needles, m. p. 113° [Found : C, 61·6; H, 5·5; OMe, 31·6. $C_{12}H_7O_3(OMe)_3$ requires C, 61·6; H, 5·5; OMe, 31·8%]. Hydrolysis of this ester (1·25 g.) with boiling 5% aqueous (25 ml.) sodium hydroxide for 1 hr. gave 5 : 7-*dimethoxy*-4 : 8-*dimethylcoumarin*-6-*carboxylic acid* which formed stout prisms, m. p. 220°, from benzene, soluble in methanol, ether, or aqueous sodium hydrogen carbonate, and regenerated the parent ester with diazomethane [Found : C, 60·5; H, 5·7; OMe, 22·0. $C_{12}H_8O_4(OMe)_2$ requires C, 60·4; H, 5·1; OMe, 22·3%]. On decarboxylation in boiling diethylene glycol (15 ml.) during 30 min. this acid (1 g.) furnished 5 : 7-dimethoxy-4 : 8-dimethylcoumarin, needles (0·7 g.), m. p. and mixed m. p. 189° (from benzene).

Methyl 3-*Chloro*-5 : 7-*dimethoxy*-4 : 8-*dimethylcoumarin*-6-*carboxylate* (XIII; R = Cl, R′ = R″ = Me).—Under the standard conditions the interaction of methyl 2 : 4 : 6-trihydroxy-3-methylbenzoate (4 g.) and ethyl α-chloroacetoacetate (3·5 ml.) continued for 4 days and furnished *methyl* 3-*chloro*-5 : 7-*dihydroxy*-4 : 8-*dimethylcoumarin*-6-*carboxylate* (XIII; R = Cl, R′ = Me, R″ = H) which separated from acetic acid in rectangular prisms (3·8 g.), m. p. 228° (decomp.), with a purple ferric reaction and forming a yellow solution in aqueous sodium carbonate (Found : C, 52·4; H, 3·9; OMe, 10·4. $C_{12}H_8O_5Cl$·OMe requires C, 52·2; H, 3·7; OMe, 10·4%). By the methyl sulphate–potassium carbonate method this coumarin gave *methyl* 3-*chloro*-5 : 7-*dimethoxy*-4 : 8-*dimethylcoumarin*-6-*carboxylate*, forming needles, m. p. 140°, from light petroleum [Found : C, 54·8; H, 4·7; OMe, 28·4. $C_{12}H_6O_3Cl(OMe)_3$ requires C, 55·1; H, 4·6; OMe, 28·5%]. Obtained by hydrolysis of this ester (0·75 g.) with hot 1·2% aqueous sodium hydroxide, the crude acid was amorphous, but with diazomethane regenerated the parent ester, m. p. and mixed m. p. 140°, and on decarboxylation with boiling diethylene glycol for 10 min. furnished 3-chloro-5 : 7-dimethoxy-4 : 8-dimethylcoumarin, m. p. and mixed m. p. 263° (yield, 50%).

Methyl 3-*Bromo*-5 : 7-*dihydroxy*-4 : 8-*dimethylcoumarin*-6-*carboxylate* (XIII; R = Br, R′ = Me, R″ = H).—A 10% solution (6 ml.) of bromine in acetic acid was added to methyl 5 : 7-dihydroxy-4 : 8-dimethylcoumarin-6-carboxylate (2 g.) in warm acetic acid (100 ml.) (agitate). After being heated to eject hydrogen bromide and then diluted with water, the solution slowly deposited *methyl* 3-*bromo*-5 : 7-*dihydroxy*-4 : 8-*dimethylcoumarin*-6 *carboxylate* which formed needles (2·2 g.), m. p. 232°, from acetic acid, having a blue ferric reaction (Found : C, 45·9; H, 3·3; Br, 23·4; OMe, 9·3. $C_{12}H_8O_5Br$·OMe requires C, 45·5; H, 3·2; Br, 23·3; OMe, 9·3%). The *diacetate* separated from light petroleum in needles, m. p. 164° (Found : C, 47·6; H, 3·6; Br, 18·9. $C_{17}H_{15}O_8Br$ requires C, 47·8; H, 3·5; Br, 18·7%).

Prepared from methyl 5 : 7-dimethoxy-4 : 8-dimethylcoumarin-6-carboxylate (0·67 g.) by the same method, *methyl* 3-*bromo*-5 : 7-*dimethoxy*-4 : 8-*dimethylcoumarin*-6-*carboxylate* (XIII; R = Br, R′ = R″ = Me) separated from light petroleum in needles (0·7 g.), m. p. 132° [Found : C, 48·9; H, 4·1; Br, 23·3; OMe, 24·8. $C_{12}H_6O_3Br(OMe)_3$ requires C, 48·5; H, 4·1; Br, 21·8; OMe, 25·1%].

Methyl 5 : 7-*Diacetoxy*-4-*bromomethyl*-8-*methylcoumarin*-6-*carboxylate* (XIV).—Condensation of methyl 2 : 4 : 6-trihydroxy-3-methylbenzoate (2 g.) and ethyl α-bromoacetoacetate (2 ml.) was effected with hydrogen bromide, and the crude product acetylated with acetic anhydride and a trace of sulphuric acid. Crystallised from benzene–light petroleum, the *diacetate* formed needles, m. p. 154° [Found : C, 48·2; H, 3·8; Br, 18·4; OAc, 26·2. $C_{13}H_9O_4Br(OAc)_2$ requires C, 47·8; H, 3·5; Br, 18·7; OAc, 27·6%].

6-*Acetyl*-5 : 7-*dihydroxy*-4-*methylcoumarin* (XV; R = H).—(*a*) Formed by the hydrogen chloride method from phloroacetophenone (5 g.) and ethyl acetoacetate (5 ml.) in acetic acid (50 ml.), 6-*acetyl*-5 : 7-*dihydroxy*-4-*methylcoumarin* separated from acetic acid in needles (6·0 g.), m. p. 288° (decomp.), with a red-brown ferric reaction (Found : C, 60·9; H, 4·2. $C_{12}H_{10}O_5$ requires C, 61·4; H, 4·3%), and on methylation yielded 6-*acetyl*-5 : 7-*dimethoxy*-4-*methylcoumarin* which crystallised from benzene and then acetic acid in prisms, m. p. 180° [Found : C, 64·0; H, 5·3; OMe, 23·8. $C_{12}H_8O_3(OMe)_2$ requires C, 64·1; H, 5·4: OMe, 23·7%].

(*b*) 5 : 7-Diacetoxy-4-methylcoumarin (Carter *et al.*, *J.*, 1931, 1255) (1 g.) in acetic acid (5 ml.) was treated with an excess of boron trifluoride without external cooling, and next day the yellow solution was poured on ice, giving the coumarin (XV; R = H) (0·8 g.), m. p. and mixed m. p. 290° after purification.

8-*Acetyl*-3-*chloro*-5 : 7-*dihydroxy*-4-*methylcoumarin* (XIX).—A solution of 5 : 7-diacetoxy-3-chloro-4-methylcoumarin (Dey, *J.*, 1915, 1606) (1 g.) in acetic acid (10 ml.) was saturated with boron trifluoride without cooling and poured into water (100 ml.) next day. Crystallised from acetic acid, the solid furnished 8-*acetyl*-3-*chloro*-5 : 7-*dihydroxy*-4-*methylcoumarin* in needles (0·8 g.), m. p. 270° (decomp.), with a red-brown ferric reaction and forming a yellow solution in aqueous alkali (Found : C, 53·9; H, 3·3; Cl, 12·8. $C_{12}H_9O_5Cl$ requires C, 53·6; H, 3·4; Cl, 13·2%). The *dimethyl ether* separated from benzene in plates, m. p. 222° [Found : C, 56·6; H, 4·4; Cl, 11·8; OMe, 19·7. $C_{12}H_7O_3Cl(OMe)_2$ requires C, 56·7; H, 4·4; Cl, 12·0; OMe, 21·0%].

6-*Acetyl*-3-*chloro*-5 : 7-*dimethoxy*-4-*methylcoumarin* (XV; R = Cl).—Interaction of phloroacetophenone (5 g.) and ethyl α-chloroacetoacetate under the standard conditions gave a solid (6 g.). which was methylated by the methyl sulphate–potassium carbonate method. Fractional crystallisation of the product from benzene yielded the less soluble 8-acetyl-3-chloro-5 : 7-dimethoxy-4-methylcoumarin (3·7 g.), m. p. and mixed m. p. 222°, and the more soluble 6-*acetyl*-3-*chloro*-5 : 7-*dimethoxy*-4-*methylcoumarin*, which separated from light petroleum in plates (2·3 g.), m. p. 140° [Found : C, 56·7; H, 4·5; Cl, 12·1; OMe, 20·7. $C_{12}H_7O_3Cl(OMe)_2$ requires C, 56·7; H, 4·4; Cl, 12·0; OMe, 19·7%].

6-*Acetyl*-5 : 7-*dihydroxy*-4 : 8-*dimethylcoumarin* (XX; R = H).—(*a*) Obtained from the condensation of *C*-methylphloroacetophenone (1·5 g.) and ethyl acetoacetate (1·2 ml.) in acetic acid (30 ml.) with sulphuric acid (1 ml.) or an excess of hydrogen chloride during 24 hr., 6-*acetyl*-5 : 7-*dihydroxy*-4 : 8-*dimethylcoumarin* separated from methanol in needles (1·7 g.), m. p. 240—241° (decomp.) (Found : C, 62·9; H, 5·0. $C_{13}H_{12}O_5$ requires C, 62·9; H, 4·9%), having a red-brown ferric reaction in alcohol. The *dimethyl ether* formed needles, m. p. 132°, from light petroleum [Found : C, 65·6; H, 6·1; Cl, 12·1; OMe, 22·3. $C_{13}H_{10}O_3(OMe)_2$ requires C, 65·2; H, 5·8; Cl, 12·0; OMe, 22·5%].

(*b*) A few drops of nitrobenzene initiated the interaction of 5 : 7-diacetoxy-4 : 8-dimethylcoumarin (1·5 g.) and aluminium chloride (1·2 g.) (intimately mixed), and the mixture was then kept at 100° for 20 min. Decomposition of the product with ice and concentrated hydrochloric acid gave 6-acetyl-5 : 7-dihydroxy-4 : 8-dimethylcoumarin, forming needles (1 g.), m. p. and mixed m. p. 241°, from acetic acid.

6-*Acetyl*-3-*chloro*-5 : 7-*dihydroxy*-4 : 8-*dimethylcoumarin* (XX; R = Cl).—The reaction between 5 : 7-diacetoxy-3-chloro-4 : 8-dimethylcoumarin (2 g.) and powdered aluminium chloride (5·2 g.) was initiated by a little nitrobenzene and completed on the steam-bath during 30 min. Decomposition of the complex with ice and hydrochloric acid gave a product from which 6-*acetyl*-3-*chloro*-5 : 7-*dihydroxy*-4 : 8-*dimethylcoumarin* was extracted with boiling acetic acid. This coumarin separated from alcohol in yellow needles (1·1 g.), m. p. 285°, giving a green ferric reaction and a yellow solution in aqueous sodium carbonate (Found : C, 55·4; H, 4·0; Cl, 12·6. $C_{13}H_{11}O_5Cl$ requires C, 55·1; H, 3·9; Cl, 12·5%).

6-*Acetyl*-3-*bromo*-5 : 7-*dihydroxy*-4 : 8-*dimethylcoumarin* (XX; R = Br).—Addition of bromine (0·7 g.) in acetic acid (5 ml.) to 6-acetyl-5 : 7-dihydroxy-4 : 8-dimethylcoumarin (1 g.) in hot acetic acid (60 ml.) caused the immediate separation of the 3-*bromocoumarin*, which formed yellow prisms (1·3 g.), m. p. 250°, from alcohol–dioxan, with a green ferric reaction (Found : C, 47·3; H, 3·4. $C_{13}H_{11}O_5Br$ requires C, 47·7; H, 3·4%). The *diacetate* crystallised from acetic acid in needles, m. p. 198° (Found : C, 49·7; H, 3·8. $C_{17}H_{15}O_7Br$ requires C, 49·6; H, 3·7%).

C-Ethylphloroglucinol.—A mixture of powdered phloroacetophenone (20 g.), amalgamated zinc dust (20 g.), concentrated hydrochloric acid (30 ml.), and water (20 ml.) was kept at 0° for 36 hr. and filtered. The filtrate was repeatedly extracted with ether and the combined, dried extracts were evaporated to a small volume and diluted with an equal volume of benzene. The resulting crystalline deposit was purified from anisole, giving *C*-ethylphloroglucinol in prisms, m. p. 165°, with a blue ferric reaction in water and a negative reaction in alcohol (Found : C, 63·7; H, 6·6. Calc. for $C_8H_{10}O_3$: C, 62·3; H, 6·5%). Distillation of the crude reduction product as described by Späth and Gruber (*loc. cit.*) gave a brittle glass which had the m. p. 125° as recorded by these authors but on crystallisation from anisole formed prisms, m. p. and mixed m. p. 165°, and furnished 3-ethylphloroglucinaldehyde, m. p. 176° (decomp.), by the Gattermann method.

2-*Ethyl*-3 : 5-*dimethoxyphenol* (XVIII).—2-Hydroxy-4 : 6-dimethoxyacetophenone (5 g.),

amalgamated zinc dust (2 g.), methanol (50 ml.), and concentrated hydrochloric acid (5 ml.) were heated under reflux for 2 hr., cooled, filtered, diluted with water (150 ml.), and extracted with ether. Evaporation of the extract left an oil, which on distillation solidified to a waxy mass, b. p. 164°/20 mm., m. p. 43°, rapidly darkening on being kept. This was considered to be mainly 2-ethyl-3 : 5-dimethoxyphenol since (*a*) with phenyl *iso*cyanate at 100° it furnished a *phenylurethane* which separated from methanol in plates, m. p. 165° [Found : C, 67·9; H, 6·4; N, 4·7; OMe, 20·6. $C_{15}H_{13}O_2N(OMe)_2$ requires C, 67·8; H, 6·4; N, 4·7; OMe, 20·6%], and (*b*) by the Hoesch reaction with methyl cyanide it gave the ketone (XXII), m. p. 111° (Gruber and Traube, *loc. cit.*) [Found : C, 64·3; H, 7·2; OMe, 28·0. Calc. for $C_{10}H_{10}O_2(OMe)_2$: C, 64·3; H, 7·2; OMe, 27·7%].

6-*Ethyl*-5 : 7-*dihydroxy*-4-*methylcoumarin* (XVI; R = R′ = H).—6-Acetyl-5 : 7-dihydroxy-4-methylcoumarin (1 g.) was reduced with amalgamated zinc (2 g.) and concentrated hydrochloric acid (4 ml.) in boiling methanol (25 ml.) for 1 hr. The resulting 6-*ethyl*-5 : 7-*dihydroxy*-4-*methylcoumarin* separated from the cooled solution and then formed small needles (0·8 g.), m. p. 240°, from alcohol, giving a negative ferric reaction and a yellow solution in alkali (Found : C, 60·0; H, 5·8. $C_{12}H_{12}O_4,H_2O$ requires C, 60·5; H, 5·9%). The *dimethyl ether* crystallised from benzene–light petroleum in needles, m. p. 136° [Found : C, 67·2; H, 6·5; OMe, 28·8. $C_{12}H_{10}O_2(OMe)_2$ requires C, 67·7; H, 6·5; OMe, 25·0%].

8-*Ethyl*-5 : 7-*dimethoxy*-4-*methylcoumarin* (XVII; R = H, R′ = Me).—8-Ethyl-5 : 7-dihydroxy-4-methylcoumarin rapidly separated from a solution of *C*-ethylphloroglucinol (1 g.) and ethyl acetoacetate (1 ml.) in acetic acid (25 ml.) saturated with hydrogen chloride and, on purification from alcohol, formed yellow needles (1·3 g.), m. p. 255°, with a negative ferric reaction; they formed a yellow solution in aqueous sodium carbonate (Found : C, 60·9; H, 6·3. $C_{12}H_{12}O_4,H_2O$ requires C, 60·5; H, 6·0%). The *dimethyl ether* separated from methanol in needles, m. p. 151° [Found : C, 67·9; H, 6·7; OMe, 24·8. $C_{12}H_{10}O_2(OMe)_2$ requires C, 67·7; H, 6·5; OMe, 25·0%]; the methanolic solution exhibited an intense blue fluorescence. This ether, m. p. and mixed m. p. 151°, was also formed by the interaction of 2-ethyl-3 : 5-dimethoxyphenol (1 g.) and ethyl acetoacetate (1 ml.) in dry ether (25 ml.) saturated with hydrogen chloride during 4 hr.

3-*Chloro*-8-*ethyl*-5 : 7-*dihydroxy*-4-*methylcoumarin* (XVII; R = Cl, R′ = H).—8-Acetyl-3-chloro-5 : 7-dihydroxy-4-methylcoumarin (2 g.), methanol (25 ml.), amalgamated zinc (2 g.), and concentrated hydrochloric acid (5 ml.) were heated under reflux temperature for 40 min. and filtered whilst hot. Diluted with water (25 ml.), the filtrate slowly deposited 3-*chloro*-8-*ethyl*-5 : 7-*dihydroxy*-4-*methylcoumarin* which separated from acetic acid or methanol in yellow needles (1·2 g.), m. p. 254°, with a negative ferric reaction, giving a yellow solution in 2N-aqueous sodium carbonate (Found : C, 52·4; H, 4·7. $C_{12}H_{11}O_4Cl,H_2O$ requires C, 52·5; H, 4·8%). This coumarin (1·1 g.), m. p. and mixed m. p. 253°, was also prepared from *C*-ethylphloroglucinol (1 g.) and ethyl α-chloroacetoacetate (1 ml.) by the general method.

Methylation (of 0·5 g.) gave 3-*chloro*-8-*ethyl*-5 : 7-*dimethoxy*-4-*methylcoumarin* (XVII; R = Cl, R′ = Me), forming long needles (0·5 g.), m. p. 192°, from methanol [Found : C, 59·6; H, 5·6; OMe, 21·8. $C_{12}H_9O_2Cl(OMe)_2$ requires C, 59·5; H, 5·3; OMe, 22·0%]. The same ether (1·4 g.), m. p. and mixed m. p. 192°, was prepared from 2-ethyl-3 : 5-dimethoxyphenol (1 g.) and ethyl α-chloroacetoacetate (1 ml.) by the standard method.

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