644. *A New Synthesis of 4-Hydroxycoumarins.*

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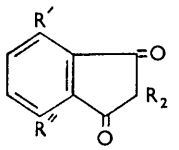
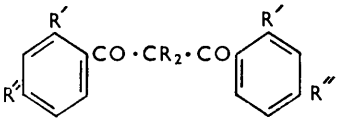
It is shown that phenol ethers condense with malonyl chlorides to form 4-hydroxycoumarins, and not the indane-1 : 3-diones reported by Walker and his associates. Under the same conditions, resorcinol dimethyl ether and malonyl chloride yield tetramethoxydibenzoylmethane.

A GENERAL method for the preparation of indane-1 : 3-diones (I), elaborated by Freund, Fleischer, and their co-workers,[1] is the condensation of malonyl chlorides with aromatic hydrocarbons in the presence of aluminium chloride. By-products include, according to the conditions used, dibenzoylmethanes (II) and compounds which were regarded as β-lactones (III). Applying this procedure to the interaction of various malonyl chlorides with resorcinol dimethyl ether,[2] methyl *p*-tolyl ether,[3] and other alkylated phenols,[4]



(I)



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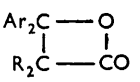


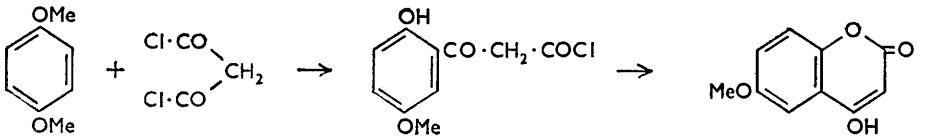
(III)

Walker and his associates prepared over thirty compounds which were regarded as indanediones on the basis of their analyses and molecular weights, coupled with the fact that they did not behave as lactones. Re-investigation of part of this work in connection with an attempted synthesis of 4 : 7-dimethoxyindanedione, has now shown that these compounds are actually coumarins.

Walker *et al.*[3] could obtain no useful result from condensations with quinol dimethyl ether but in our hands reaction with malonyl chloride (or bromide) readily gave a product (A), $C_{10}H_8O_4$, corresponding to a hydroxymethoxyindanedione (I; R = H, R′ = OH, R″ = OMe). (Partial demethylation had previously been observed in reactions with

[1] Freund and Fleischer, *Annalen*, 1910, **373**, 291; 1913, **399**, 182; 1914, **402**, 51; 1916, **411**, 14; 1918, **414**, 1; 1921, **422**, 231.
[2] Black, Shaw, and Walker, *J.*, 1931, 272.
[3] Walker, Suthers, Roe, and Shaw, *J.*, 1931, 514.
[4] Robinson, Suthers, and Walker, *Biochem. J.*, 1932, **26**, 1890.

resorcinol dimethyl ether.[2]) However, its infrared spectrum showed that it could not be an indanedione and further investigation established the coumarin structure (IV) which was confirmed by an alternative synthesis.[5] The formation of coumarins by this reaction,



(IV)

which must include partial demethylation as shown above, was previously observed by Freund and Fleischer [6] who found that diethylmalonyl chloride and quinol dimethyl ether gave the expected indanediones (I; R = Et, R′ = R″ = OMe, and R = Et, R′ = OH, R″ = OMe) but the major product was a coumarin derivative. Black, Shaw, and Walker [2] refer to this work but overlooked that point. Two homologues of the coumarin (IV) were obtained in low yield by interaction of methyl- and ethyl-malonyl chlorides respectively with quinol dimethyl ether.

We therefore repeated one of the experiments of Walker *et al.* in each group, *i.e.*, one with resorcinol dimethyl ether and one with methyl *p*-tolyl ether. The product from methyl *p*-tolyl ether and malonyl chloride had the properties described. Its ultraviolet absorption curve is almost identical with that of 4-hydroxycoumarin, and an alternative synthesis by Boyd and Robertson's method established the structure 4-hydroxy-6-methylcoumarin. Similarly, the product from resorcinol dimethyl ether and ethylmalonyl chloride had the ultraviolet and infrared spectra of a 4-hydroxycoumarin; and the compound [2] obtained from methylmalonyl chloride had m. p. 225—226° which corresponds to that (227°) of 4-hydroxy-7-methoxy-3-methylcoumarin.[7]

By condensation of resorcinol dimethyl ether and malonyl chloride Black, Shaw, and Walker [2] obtained a product, m. p. 217°, which they considered to be a hydroxy-methoxyindanedione. We have been unable to repeat this work and several variations of the experimental procedure did not affect the result. In our hands the major product was di-(2 : 4-dimethoxybenzoyl)methane (II; R = H, R′ = R″ = OMe), m. p. 133°, accompanied by a trimethyl ether, m. p. 118—120°. The structure of the tetramethoxydibenzoylmethane was established by alkaline hydrolysis to 2 : 4-dimethoxybenzoic acid and 2 : 4-dimethoxyacetophenone and by the infrared spectrum which showed the chelated carbonyl and hydroxyl absorption of the enolic form. The preferential formation of a dibenzoylmethane in the reaction of malonyl chloride with resorcinol dimethyl ether must be a consequence of the reactivity of the latter at $C_{(4)}$, coupling of two molecules proceeding more rapidly than demethylation, the necessary preliminary for coumarin formation. It may be noted that Freund and Fleischer [6] could not isolate a pure product from the reaction of diethylmalonyl chloride with resorcinol dimethyl ether. The formation of an indanedione from this ether is highly improbable as it involves cyclisation at $C_{(5)}$, a most unreactive position [cf. cyclisation of γ-(2 : 4-dimethoxyphenyl)butyric acid, which yields only *ca.* 5% of the corresponding tetralone [8]].

The ultraviolet absorption maxima of the 4-hydroxycoumarins are listed in the Table. The absorption curve of 4 : 6-dimethoxycoumarin is markedly different from that of 4 : 6-dihydroxycoumarin and the other 4-hydroxycoumarins; not only are the peaks displaced but they are separated by a trough of much lower intensity. This implies that the 4-hydroxycoumarins exist in the keto-form in ethanol solution (but cf. ref. 9). The introduction of an alkyl group has the usual effect of shifting the absorption to longer wavelengths, but a 7-methoxyl group produces a marked change in the absorption pattern,

[5] Badcock, Dean, Robertson, and Whalley, *J.*, 1950, 903.
[6] Freund and Fleischer, *Annalen*, 1915, **409**, 268.
[7] Boyd and Robertson, *J.*, 1948, 174.
[8] Halpern, *Helv. Chim. Acta*, 1952, **35**, 930 (footnote); Davies, King, and Roberts, *J.*, 1955, 2782.
[9] Chmielewska and Ciecierska, *Przemysl Chem.*, 1952, **31**, 253.

Ultraviolet absorption maxima (mμ) *of 4-hydroxycoumarins.*

Coumarin	Ethanol solution					
	$\lambda_{max.}$	log ε	$\lambda_{max.}$	log ε	$\lambda_{infl.}$	log ε
4-Hydroxy	—	—	290	4·10	301	4·08
4-Hydroxy-6-methoxy	—	—	300	4·17	314	4·05
4 : 6-Dihydroxy	—	—	300	4·135	315	3·94
4 : 6-Dimethoxy	—	—	270	4·07	327 (max.)	3·73
3-Ethyl-4-hydroxy-6-methoxy	—	—	307	4·12	322 (max.)	4·12
4-Hydroxy-6-methoxy-3-methyl	—	—	306	4·17	320 (max.)	4·14
4-Hydroxy-6-methyl	—	—	293	4·12	304	4·07
4-Hydroxy-7-methoxy	245	4·07	304	4·23	—	—
3-Ethyl-4-hydroxy-7-methoxy	249	4·03	314	4·28	—	—
4-Hydroxy-7-methoxy-3-methyl	247	4·05	313	4·25	—	—

consistent with its position *para* to the unsaturated side chain. The infrared spectra of these compounds will be reported in a separate communication.

Experimental

4-Hydroxy-6-methoxycoumarin.—(*a*) Finely powdered anhydrous aluminium chloride (13·5 g.) was added, in portions, during 20 min., to a mixture of quinol dimethyl ether (7 g.) and malonyl chloride (7 g.) in dry carbon disulphide (50 ml.). The mixture was set aside for 24 hr. and then refluxed in a water-bath for 2 hr. After removal of the solvent, the complex was decomposed with water (100 ml.) and concentrated hydrochloric acid (50 ml.), warmed to 80°, and cooled, and the precipitate collected. The product, after dissolution in 10% aqueous sodium hydroxide (100 ml.) and reprecipitation with dilute hydrochloric acid, separated from aqueous acetic acid as needles, m. p. 270° (3 g., 30%) (Found : C, 62·35; H, 4·2. Calc. for $C_{10}H_8O_4$: C, 62·5; H, 4·35%). Refluxing the hydroxymethoxycoumarin in methyl sulphate–acetone–potassium carbonate for 2 hr. gave the *dimethyl ether* as needles, m. p. 138° [from light petroleum (b. p. 100—120°)], also obtained by treatment of 4 : 6-dihydroxycoumarin with diazomethane (Found : C, 64·2; H, 4·55. $C_{11}H_{10}O_4$ requires C, 64·1; H, 4·85%). 4-Hydroxy-6-methoxycoumarin was demethylated by brief treatment in fused aluminium chloride–sodium chloride at 180°. 4 : 6-*Dihydroxycoumarin* crystallised from aqueous acetic acid in plates, m. p. 290° (45%) (Found : C, 60·55; H, 3·6. $C_9H_6O_4$ requires C, 60·7; H, 3·4%). The *diacetate* formed crystals, m. p. 226°, from aqueous acetic acid (Found : C, 59·55; H, 3·6. $C_{13}H_{10}O_6$ requires C, 59·55; H, 3·8%).

(*b*) A mixture of 2-hydroxy-5-methoxyacetophenone (0·9 g.), diethyl carbonate (30 ml.), and pulverised sodium (0·9 g.) was set aside overnight at room temperature, then warmed on a steam-bath for 1½ hr., cooled, and worked up as described by Badcock *et al.*[5] The coumarin formed needles, m. p. 270° (from glacial acetic acid) (1 g.), identical with those obtained in (*a*) above. The m. p. 170° quoted in ref. 5 is a misprint.

Hydrolyses.—(*a*) A solution of 4-hydroxy-6-methoxycoumarin (0·5 g.) in 30% aqueous potassium hydroxide (50 ml.) was refluxed for 2 hr., cooled, acidified, and extracted with ether, to give 2-hydroxy-5-methoxybenzoic acid which crystallised from light petroleum (b. p. 100—120°) in needles, m. p. and mixed m. p. 144° (35%). Methylation gave 2 : 5-dimethoxybenzoic acid, m. p. and mixed m. p. 80°. Concentration of the mother-liquor after separation of the acid, m. p. 144°, yielded 2-hydroxy-5-methoxyacetophenone as yellow needles, m. p. and mixed m. p. 52° (60%); demethylation with hydrobromic acid gave 2 : 5-dihydroxyacetophenone m. p. and mixed m. p. 204°.

(*b*) By the above procedure, 4 : 6-dihydroxycoumarin gave 2 : 5-dihydroxyacetophenone and 2 : 5-dihydroxybenzoic acid, needles, m. p. 206° (from ethyl acetate–light petroleum). This acid was also obtained by demethylation of its mono- and di-methyl ether (above) using (i) aluminium chloride–sodium chloride and (ii) hydrobromic acid.

(*c*) In the same way hydrolysis of 4 : 6-dimethoxycoumarin (0·3 g.) yielded 2-hydroxy-5-methoxyacetophenone (0·18 g.) and 2-hydroxy-5-methoxybenzoic acid (75 mg.).

4-Hydroxy-6-methoxy-3-methylcoumarin.—This coumarin, prepared from methylmalonyl chloride and quinol dimethyl ether, crystallised from aqueous methanol as plates, m. p. 222° (4%) (Found : C, 63·75; H, 4·65. $C_{11}H_{10}O_4$ requires C, 64·0; H, 4·85%).

3-Ethyl-4-hydroxy-6-methoxycoumarin.—This was obtained from quinol dimethyl ether and ethylmalonyl chloride as plates, m. p. 187° (8%) (Found : C, 65·15; H, 5·45. $C_{12}H_{12}O_4$

requires C, 65·4; H, 5·45%). The *acetate* formed needles (from aqueous acetic acid), m. p. 78° (Found: C, 63·9; H, 5·35. $C_{14}H_{14}O_5$ requires C, 64·1; H, 5·35%).

3-Ethyl-4-hydroxy-7-methoxycoumarin.—This was obtained from resorcinol dimethyl ether and ethylmalonyl chloride by following the procedure of Black, Shaw, and Walker,[2] and formed fawn-coloured cubes, m. p. 192° from methanol (Found: C, 65·3; H, 5·4; OMe, 13·0. $C_{12}H_{12}O_4$ requires C, 65·5; H, 5·5; OMe, 14·1%). The *acetate* crystallised from water in needles, m. p. 99° (Found: C, 64·4; H, 5·3. $C_{14}H_{14}O_5$ requires C, 64·15; H, 5·4%). The *methyl ether* formed needles, m. p. 70°, from methanol (Found: C, 66·7; H, 6·0. $C_{13}H_{14}O_4$ requires C, 66·7; H, 6·0%).

4-Hydroxy-6-methylcoumarin.—(*a*) Methyl *p*-tolyl ether and malonyl chloride in nitrobenzene were treated with anhydrous aluminium chloride according to Walker *et al.*[3] The coumarin crystallised from methanol in needles, m. p. 258°. The acetate formed prismatic needles, m. p. 149°, from methanol.

(*b*) 2-Acetyl-4-methylphenol (1·0 g.), ethyl carbonate (30 ml.), and pulverised sodium (0·75 g.) were heated on a steam-bath for ¾ hr. and worked up as before. The coumarin formed needles m. p. 258°, identical with those obtained in (*a*).

Di-(2 : 4-dimethoxybenzoyl)methane.—Anhydrous aluminium chloride (13·5 g.) was added gradually to a stirred solution of resorcinol dimethyl ether (7 g.) and malonyl chloride (7 g.) in dry nitrobenzene (60 ml.), the temperature being allowed to rise. The mixture was then warmed to 60—65° for 30 min., cooled, and treated with ice and hydrochloric acid. After removal of the solvent in steam, the residue was repeatedly extracted with ether, and the extract then shaken with 5% aqueous sodium hydroxide. Evaporation of the dried ether solution left crystalline material (0·6 g.) which separated from methanol in lemon-yellow needles, m. p. 133° (Found: C, 66·0; H, 6·0; OMe, 34·8. $C_{19}H_{20}O_6$ requires C, 66·2; H, 6·25; 4OMe, 36·0%). Light absorption: max. at 206, 245, 273, 308, and 373 mμ (log ε 4·5, 4·09, 4·05, 4·08, and 4·43 respectively) in EtOH. The carbonyl frequency lay at 1605 cm.$^{-1}$, diffuse hydroxyl absorption from 2800 to below 2000 cm.$^{-1}$ in $CHCl_3$. The *product* was soluble in warm aqueous sodium hydroxide and gave a green colour with ferric chloride. Acidification of the sodium hydroxide washings precipitated an oil (2·7 g.) which, after crystallisation from methanol, was chromatographed in chloroform on alumina. Two yellow bands appeared. From the lower one a further small quantity of the tetramethoxy-compound, m. p. 130—131°, was obtained whilst the upper zone gave the *trimethyl ether* which separated from methanol in yellow needles, m. p. 118—120° [Found: C, 64·65; H, 5·7; OMe, 26·7. $C_{15}H_9O_3(OMe)_3$ requires C, 64·45; H, 5·5; 3OMe, 28·1%]. Methylation of the latter with methyl sulphate–acetone–potassium carbonate gave the tetramethoxy-compound as lemon-yellow needles, m. p. and mixed m. p. 133°.

Hydrolysis of Di-(2 : 4-dimethoxybenzoyl)methane.—The tetramethyl ether (1 g.) was refluxed for 2 hr. with 15% aqueous potassium hydroxide (20 ml.). On cooling, the oil which had separated solidified and was collected. Crystallisation from aqueous methanol gave prisms (0·45 g.), m. p. 38—40° alone or mixed with 2 : 4-dimethoxyacetophenone. Acidification of the alkaline filtrate deposited needles (0·43 g.) which on recrystallisation from water had m. p. 108° alone or mixed with 2 : 4-dimethoxybenzoic acid. A similar hydrolysis of the trimethoxydibenzoylmethane also gave 2 : 4-dimethoxyacetophenone together with acidic material, converted by methylation into 2 : 4-dimethoxybenzoic acid.

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