The Reaction of Dimethyl Sulphoxide and Acetic Anhydride with 4-Hydroxycoumarin and Dicoumarol

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Dimethyl sulphoxide and acetic anhydride convert 4-hydroxycoumarin (1a) into the acetate but at 120 °C this is further transformed into the ylide 3-dimethylsulphoniochroman-2,4-dionate (2). At 160 °C the reaction affords dicoumarol (3a) and other products derived from this by further reactions. These products are 2,3-dihydro-2-(2-hydroxybenzoyl)-4*H*-furo[3,2-*c*][1]benzopyran-4-one (6a), 2-(2-hydroxybenzoyl)-4*H*-furo[3,2-*c*][1]benzopyran-4-one (11a), 3-(2,3-dihydro-2-hydroxymethyl-3-oxobenzo[*b*]furan-2-ylmethyl)-4-hydroxycoumarin (13), and 2,3-dihydro-2-(2-hydroxybenzoyl)-2-hydroxymethyl-4*H*-furo[3,2-*c*][1]benzopyran-4-one (12a). Compound (6a) is readily dehydrogenated to give compound (11a), which is identical with a known compound obtained by treating dicoumarol with iodine in ethanol. Pyrolysis of compound (12a) affords (6a); pyrolysis of compound (13) affords the spiran (14).

Spectroscopic studies did not establish the structure of compound (6a) unequivocally and the compound failed to give the appropriate positive responses to iron(III) salts and Gibbs' dichlorobenzoquinone-chloroimine reagent because the dihydrofuran system reduced these reagents, the furan (11a) behaving normally. Chemical evidence for structure (6a) depends mainly upon the ability of boron trichloride to regenerate this compound from its methyl ether.

Dimethyl sulphoxide (DMSO) in acetic anhydride converts enols into sulphur ylides, introduces thiomethyl groups into phenols, oxidises alcohols, and induces oxidative rearrangements in certain hydroxyquinones.[1] 4-Hydroxycoumarin (1a) is an enol that can be regarded as a heterocyclic phenol and as having elements of structure in common with hydroxyquinones; consequently, its interaction with the reagent was a matter of interest. We found that it underwent a novel combination of all four types of process.

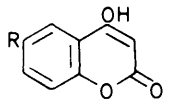
At room temperature, DMSO–acetic anhydride merely converts 4-hydroxycoumarin into 4-acetoxycoumarin. However, at 120 °C a new reaction sets in in which the sulphur ylide (2) is formed, and this is also formed, almost quantitatively, when 4-acetoxycoumarin is heated with DMSO alone. This fact, along with the absence of thiomethylated products or of 3-acetyl-4-hydroxycoumarin from a Fries rearrangement, points to the existence of a particularly favourable mechanism, perhaps the one in Scheme 1, which finds a parallel in the reaction between 4-acetoxycoumarin and pyridine.[2]

If, however, 4-hydroxycoumarin itself is treated with DMSO–acetic anhydride at 160 °C the ylide (2) is accompanied by a new product, $C_{18}H_{12}O_5$. Formally, the molecular composition suggests that two hydroxycoumarin molecules have been combined while the presence of a methylenic band (part of an ABX system) in the ^{1}H n.m.r. spectrum (Table 1) suggests a methylene link and thus a relationship to dicoumarol (39). In turn, this relationship suggests that dicoumarol is an intermediate, the requisite formaldehyde or an equivalent being produced *in situ* or being inserted by some reaction such as that indicated in Scheme 2, involving a Pummerer rearrangement made possible by prior acetylation of DMSO.[1] Accordingly, a reaction conducted by heating DMSO with acetic anhydride for some time and then adding the hydroxycoumarin (1a) at a relatively low temperature (80 °C) gave a good yield of dicoumarol (39) and this, on separate treatment with fresh reagent at a higher temperature, gave the new product, compound A, uncontaminated by the ylide (2).

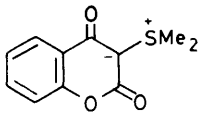
The molecular formula of compound A can be reached from that of dicoumarol (3a) most simply by adding the elements of water and eliminating those of carbon dioxide and 2H atoms; *i.e.*, this suggests hydrolysis, decarboxylation, and oxidation steps in one order or another. Of several structures that might be envisaged on the basis of these considerations, only (4), (5), and (6a) will be discussed, since elimination of the other possibilities is relatively straightforward. A practical difficulty throughout was the tendency of many of the compounds to exist in several crystalline forms with various m.p.s and to undergo transition during their m.p. determination. Moreover, the new compound was unusually difficult to obtain in solutions concentrated enough for satisfactory spectroscopic analysis by the instruments available and the results, as will be seen, were never unambiguous. That compound A has structure (6a) was demonstrated chemically.

The X part of the ABX system mentioned above is at a low field (δ 6.3; Table 1) thus suggesting a $-\underset{|}{C}H-O$ grouping. In structures (4) and (6a) the multiplicity would result from the geometrical relationships of the three protons, in compound (5) from diastereotopicity. The rest of the ^{1}H n.m.r. spectrum of compound A reveals the existence of two very similar aromatic rings with *ortho* oxygen and carbonyl or enol functions, but fails to distinguish clearly between the three sets of possibilities. While the assignments in Table 1 agree with results under comparable conditions for appropriate 2-hydroxybenzoyl derivatives (7) (very similar values have been published already [3]) and for the dihydrofurocoumarin [4] (8), they could easily be arranged to conform with either of the other two structures (4) and (5). Data for relevant derivatives of benzofuran-3(2*H*)-one and chromanone are also available.[3] An attempt to achieve a differentiation by acetylation, which affects only one benzene ring directly in compounds of structure (6), was vitiated by the fact that both benzene rings show marked changes however the detailed assignments are made. Finally, the ^{1}H n.m.r. spectrum exhibits a band at δ 11.7 that is equally well attributed to (hydrogen-bonded) phenolic or enolic hydroxy-groups.

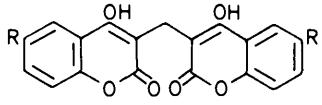
For measuring the ^{13}C n.m.r. spectrum the parent com-



(1) a; R = H
b; R = Me



(2)



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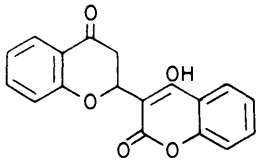
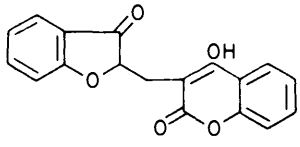
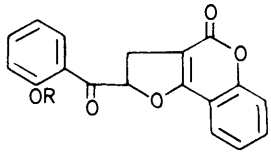


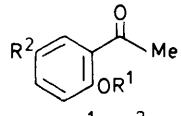
(4)



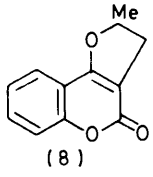
(5)



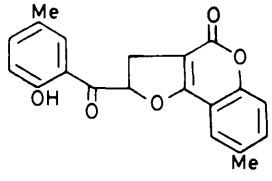
(6) a; R = H
b; R = Ac
c; R = Me



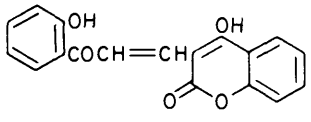
(7) a; $R^1 = R^2 = H$
b; $R^1 = Ac$, $R^2 = H$
c; $R^1 = Me$, $R^2 = H$
d; $R^1 = H$, $R^2 = Me$



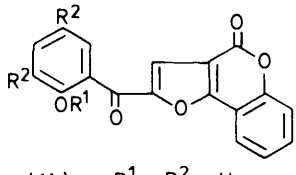
(8)



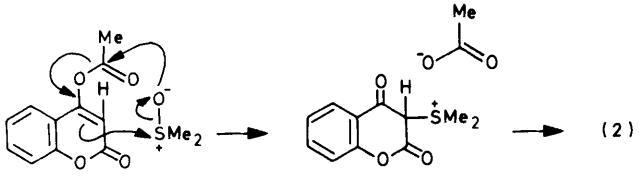
(9)



(10)



(11) a; $R^1 = R^2 = H$
b; $R^1 = Me$, $R^2 = H$
c; $R^1 = H$, $R^2 = I$



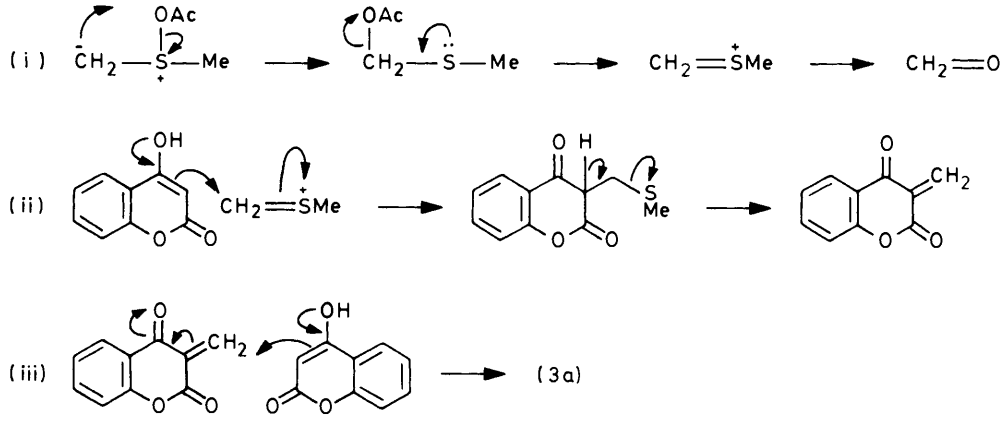
Scheme 1

pound (6a) was barely soluble enough in most solvents, but its derivatives and also the homologue (9) were satisfactory (Table 2). While not excluding structures (4) and (5), the results were again consistent with structure (6a), and the method confirmed the presence of two similar aromatic rings and a grouping $OCHCH_2$. Assignments were facilitated by reference to those made by Cussans and Huckerby [5] for simple 4-hydroxycoumarin derivatives, and to those in a standard atlas for phenolic ketones.[6] However, the method does not distinguish between enol carbon and carboxyl carbon, so that it affords but limited evidence for the presence of a coumarin nucleus. It did establish the presence of a ketonic carbonyl group resonating near δ_C 200 p.p.m., thereby eliminating structures (4) and (5) in their cyclic hemiacetal forms.

The u.v. and i.r. spectra were also in general agreement with all three structures (4), (5), and (6a). The very broad and irregular band shown by coumarins at about $\nu_{max.}$ 1 710 cm^{-1} would mask the ketonic carbonyl absorption in compounds (4) and (5), while enol and other bands could mask the presence of the chelated carbonyl group in compound (6a).

The mass spectrum of the parent compound favoured structure (6a) to some extent by displaying a base peak at *m/z* 121 a.m.u., corresponding to the 2-hydroxybenzoyl fragment; unless one hydrogen atom migrated, the corresponding fragment from compounds (4) or (5) would have been seen at 120 a.m.u. The other very strong peak was at 187 a.m.u., corresponding to the furocoumarin segment. This argument is not strong, however, since if the primary fission occurs by ring opening, then all three structures could yield the identical system (10).

Turning next to chemical characterisation, we found that compound A did not respond to the Gibbs test for a phenol with a free *para* position [7] nor to the ethanolic iron(III) chloride rest for an *ortho*-hydroxy-ketone, but it did respond, though with some difficulty, to Fehling's reagent, which has long been known to be reduced by benzofuran-3(2*H*)-ones containing an enolisable hydrogen atom.[8] These facts seemed to eliminate structure (4) and clearly to favour structure (5) over (6a) so that we were surprised to find that the compound did not dissolve in aqueous sodium hydrogen carbonate, whereas 4-hydroxycoumarin derivatives are normally acidic enough to be freely soluble. It seemed that an insoluble salt might be formed, but none could be isolated; moreover, diazomethane failed to methylate the compound although it methylates solid



Scheme 2

4-hydroxycoumarin and dicoumarol, notwithstanding their very low solubility in diethyl ether.[9]

Compound A is sensitive to alkali and dissolves at once in methanolic sodium hydroxide to give a pale yellow solution from which, however, it cannot be regained by acidification after a few minutes. Coumarins are not normally so sensitive to base, and we have confirmed that 4-hydroxycoumarin can be left in alkaline solution for hours with little loss on acidification. Ethers of 4-hydroxycoumarin would be more easily attacked because they would not be stabilised by salt formation, but no study of the alkaline hydrolysis has been reported, so we have undertaken one as a separate project. These facts do not distinguish in any way between structures (5) and (6a) because benzofuran-3(2*H*)-ones also turn yellow in alcoholic NaOH and are rapidly degraded by alkali if they contain an enolisable hydrogen.[8,10]

Since the new compound seemed somewhat less sensitive to carbonates it was methylated with iodomethane–potassium carbonate. An ether (6c) was obtained, although the product was largely a yellow gum, and therefore it could not be immediately assumed that the ether had been formed without rearrangement. However, boron trichloride is known to be a mild, acidic reagent for the rapid, specific demethylation of methyl ethers *ortho* to a carbonyl group.[11] When the ether (6c) was treated with boron trichloride the parent phenol was regenerated in high yield, thus showing it to be an *ortho*-hydroxy-ketone. In confirmation, 4-methoxycoumarin was shown to be unaffected by boron trichloride (other than by formation of an unstable pyrone salt, immediately decomposed by water), and in the mass spectrum the base peak of the ether (6c) at *m/z* 135 a.m.u. replaced the 2-hydroxybenzoyl fragment ion (121 a.m.u.) of the original phenol. We regard this evidence as unequivocally in favour of structure (6a).

Phenol (6a) may reduce Fehling's reagent because hydrolysis of the furanoid ring liberates an acyloin function or because the methine group of the keto-ether system is itself capable of reduction like that in benzofuran-3(2*H*)-ones.[8] With acetone or *NN*-dimethylformamide (DMF) instead of ethanol solutions (to maximise solubility), iron(III) chloride does produce a purple-brown colour at the instant of mixing, but it fades at once as would be consistent with reduction of the valency state of the metal. It was also noted that the phenol (6a) not only failed to give a positive Gibbs test, but was capable under some conditions of preventing phenol itself from responding, thus indicating that the quinonoid reagent is also being destroyed by reduction.

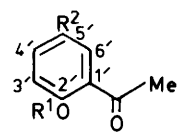
When heated with palladium–charcoal in boiling naphthalene, the phenol (6a) readily gave the furan (11a) with a low-field (two '*ortho*' carbonyl groups) furanoid singlet replacing the original ABX system. Compound (11a) was yellow, in agreement with its chalcone-like constitution, and displayed two benzenoid aromatic proton multiplets at low field, one from the benzoyl group as usual, the other from position 9 on the furocoumarin nucleus, deshielded by the newly aromatised furan ring. Like other furo[3,2-*c*]coumarins,[12] compound (11a) exhibited a lactone $\nu_{C=O}$ band at *ca.* 1 730 cm^{-1} but no chelated carbonyl band could be identified. However, the mass spectrum showed only a single important fragmentation and this resulted in ions with *m/z* 120, 121, and 186 a.m.u., corresponding to 2-hydroxybenzoyl and furocoumarin fragments. Finally, as the compound no longer contained a reducing group, it responded without difficulty to the iron(III) chloride and Gibbs tests.

Checchi, on treatment of 4-hydroxycoumarin or dicoumarol with iodine or tetraiodourotropine in ethanol, obtained a compound which was allocated structure (11a) on limited evidence.[13] Since the m.p. of this compound was relatively low and no yield was reported we repeated the preparation and found that although dicoumarol is attacked only very slowly by iodine in ethanol and the yield is slight, the product is indeed the same as our compound (11a). By modifying the conditions we obtained relatively high yields and found that compound (6a) was also formed and was then dehydrogenated to the product (11a). A base such as hexamine * (urotropine) is required for smooth reaction, but too strong a base (*e.g.* pyridine) also effects aromatic iodination, giving compound (11c). Since the furocoumarin (11a) is one of the minor products of the DMSO–acetic anhydride reaction, we conclude that Checchi's reaction and ours follow essentially the same course.

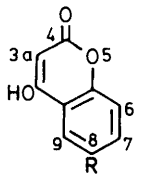
Two other minor products from the DMSO–acetic anhydride reaction were isomers with the composition $C_{19}H_{14}O_6$. The first of these, compound B, was obtained regularly and its ^1H n.m.r. spectrum exhibited two methylenic quartets instead of an ABX system, and it could therefore be formulated as the hydroxymethyl compound (12a) corresponding in a formal sense to the addition of a formaldehyde unit to the phenol (6a). Accordingly, pyrolysis smoothly converted it into compound (6a), possibly *via* the enol formed by the electron movements shown in the structure (12), and all other properties (including the ^{13}C n.m.r. spectrum and mass spectrum) were those expected from the structure given. The

* 1,3,5,7-Tetra-azatricyclo[3.3.1.$1^{3,7}$]decane.

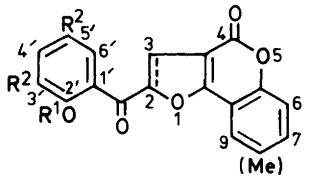
Table 1. ^{1}H N.m.r. spectra (δ; $CDCl_3$; 220 MHz) [a]



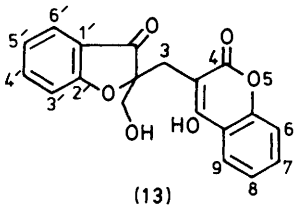
(7)



(1), (3)



(6), (8), (9), (11), (12)



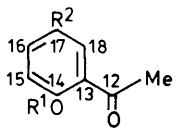
(13)

Positional assignments are as shown, based on the systematic numbering scheme for compounds (6) *etc.*

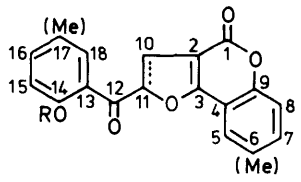
Compound	Position in furobenzopyran-4-one nucleus							Position in 2-hydroxybenzoyl nucleus				Other positions or groups			
	2 [b]	3 [c]		6 [d]	7 [e]	8 [e]	9 [d]	3′ [d]	4′ [e]	5′ [e]	6′ [d]	OH	OMe, OCH_2	OAc	CMe, CH_2
(6a)	6.33	3.54	3.59	7.39	7.59	7.31	7.73	7.07	7.58	7.01	7.74	11.7			
(6b)	6.13	3.47	3.53	7.22	7.61	7.31	7.52	7.21	7.61	7.37	7.84			2.34	
(6c)	6.31	3.19	3.61	7.35	7.56	7.29	7.75	7.02	7.56	7.06	7.91		3.96		
(9)	6.32	3.43	3.62	7.29	7.40		7.47	6.98	7.39		7.54	11.46			2.39 and 23.4
(12a)		3.44	3.69	7.24	7.46	7.22	7.75	6.98	7.46	6.90	8.10	11.85, 3.75br	4.10 and 4.24 [f]		
(13) [g]		3.07	3.19	7.27	7.60	7.31	7.58	7.11	7.57	7.06	7.90		3.84 and 3.96		
(11a) [h]		7.80		7.48	7.59	7.42	8.16	7.08	7.59	7.02	8.05	11.67			
(11c)		7.90		7.35	7.70	7.48	8.06		8.33		8.53	*ca.* 12.0			
(8) [i]	5.75	2.76	3.29	7.36	7.53	7.26	7.63								1.54
(7a)								6.94	7.43	6.86	7.69	12.23			2.57
(7b)								7.08	7.49	7.27	7.79			2.30	2.52
(7c)								6.93	7.41	6.95	7.70		3.85		2.57
(7d)								6.90	7.28		7.49	12.24			2.28 and 2.61
2,3-Dihydrobenzo[*b*]furan-3-one	4.58 [j]							7.05	7.59	7.12	7.64				
(1b) [k]				7.19	7.39		7.61					12.12			2.37
(3b) [k]				7.25	7.39		7.76					11.11			2.42 and 3.81

[a] Rules (⌐¬) link multiplets analysed by double irradiation. Coupling constants (Hz) were not usually determined precisely and represent first-order analysis only. [b] J_{AX} 12, J_{BX} 7. [c] J_{gem} 16. [d] *J* 8, 2. [e] t, *J ca.* 8, 2. [f] Bands sharpened by addition of D_2O. [g] In CD_3OD. [h] At 90 MHz. [i] J_{gem} 12, J_{AX} 14.5, J_{BX} 10, J_{vic} 7. [j] Ring CH_2. [k] With added $(CD_3)_2SO$.

Table 2. ^{13}C N.m.r. spectra (δ/p.p.m.; $CDCl_3$; 25.2 MHz) [a]



(7)



(6a), (8), (9), (12a) and 4-Methoxycoumarin

Positional assignments are as shown, based on the arbitrary numbering scheme for compounds (6) *etc.*

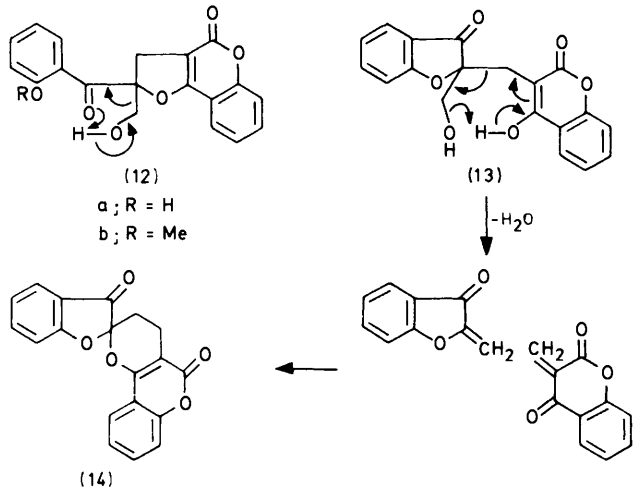
	Compound						
Carbon	(6b)	(9)	(12a)	(8)	4-Methoxy-coumarin	(7a)	(7b)
1	159.7 (s)	161.4	163.6 (s)	160.5 (s)	162.5 (s)		
2	101.5 (s)	101.2	101.8 (s)	101.6 (s)	89.9 (d)		
3	168.7 (s)	166.2	165.1 (s)	166.1 (s)	166.2 (s)		
4	122.6 (d)	122.3	122.5 (d)	122.5 (d)	122.8 (d)		
5	124.0 (d) [b]	135.9	124.1 (d)	123.7 (d)	123.7 (d)		
6	132.4 (d)	133.7	132.6 (d)	132.0 (d)	132.2 (d)		
7	116.7 (d)	116.7	116.7 (d)	116.6 (d)	116.5 (d)		
8	154.7 (s)	153.2	154.6 (s)	154.7 (s)	153.1 (s)		
9	111.9 (s)	111.6	111.8 (s)	112.5 (s)	115.5 (s)		
10	29.9 (t)	31.3	33.6 (t)	33.9 (t)			
11	86.5 (d)	83.5	99.3 (s)	84.0 (d)			
12	193.4 (s)	197.4	201.5 (s)			204.1	197.2 (s)
13	127.3 (s)	115.9	116.8 (s)			118.5	130.5 (s)
14	149.7 (s)	160.0	160.0 (s)			161.5	148.9 (s)
15	124.0 (d) [b]	118.9	118.9 (d) [c]			118.9	123.8 (d)
16	130.3 (d)	138.6	130.8 (d)			129.7	130.1 (d)
17	126.1 (d)	128.6	118.9 (d) [c]			118.3	125.9 (d)
18	134.2 (d)	128.7	137.1 (d)			135.5	133.3 (d)
$MeCO_2$	165.8 (s)						169.2 (s)
$MeCO_2$	21.1 (q)						21.0 (q)
Other CMe		20.6 (q), 20.8 (q)		21.9 (q)		25.4	29.3 (q)
OMe					56.3 (q)		
CH_2OH			66.9 (t)				

[a] Spectra were determined with $SiMe_4$ as internal standard. Multiplicities obtained from SFORD are in parentheses. Values in the last three columns were determined in the present work but compare very closely with earlier reports. [b,c] Very strong peaks believed to indicate coincident resonances.

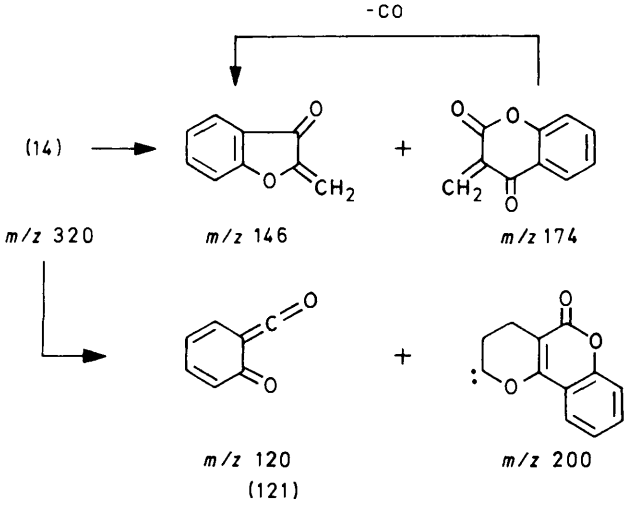
tests with iron(III) chloride and Gibbs' reagent were normal and positive. The solubility in methanol was high and even in benzene it was good, a very sharp contrast with the phenol (6a) notwithstanding the presence of an extra hydroxy-group. The m.p. was also much lower and the only residual special features were the erratic nature of the m.p. and the sensitivity to alkali. It now seems that the reducing ability of the methine group of compound (6a) is confirmed, and that the high m.p. and low solubilities of the phenol (6a) have to be attributed to crystal-lattice phenomena, although models gave us no insight as to their nature.

The other $C_{19}H_{14}O_6$ isomer, compound C, was obtained only once. It also exhibited two methylenic quartets instead of an ABX spin system in its ^1H n.m.r. spectrum. It had a high m.p., was easily soluble in methanol (but not in benzene), gave negative responses to both iron(III) chloride and Gibbs' reagent, and was readily soluble in aqueous sodium hydrogen carbonate. These properties pointed unequivocally to structure (13). When heated just above its m.p. compound C effervesced mainly, we suggest, because of loss of water and formation of two heterocyclic quinone methides that recombine in a characteristic fashion [14] to give the spiran (14) (Scheme 3). The mass spectrum of (14) disclosed a molecular ion at *m/z* 320 ($C_{19}H_{12}O_5$ requires *M*, 320) which underwent two major fragmentations. One of these gave the salicyloyl unit (peaks at *m*/3 120, 121) and a pyranocoumarin carbene nucleus (very strong peak at *m/z* 200); the other appeared to be the expected fission into the parent quinone methides (*m/z* 174 and 146), but the coumarin peak (*m/z* 174) was weak and the benzofuranone one (*m/z* 146) was very strong because, we think, the former moiety loses 28 a.m. units (CO) to generate another fragment ion at *m/z* 146. These relations are shown in Scheme 4.

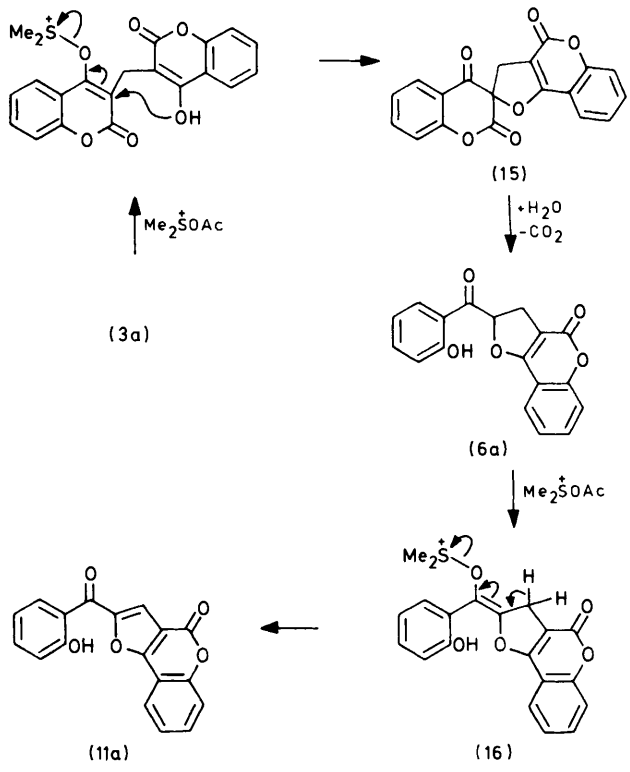
Any explanation of the conversion of dicoumarol (3a) into the phenol (6a) must rationalise both the survival of one hydroxycoumarin nucleus and the resistance to the degradation by the other, coumarins being insensitive to hydrolysis in neutral or weakly acidic media. For this reason we take the first step to be oxidation to the spiran (15), perhaps as suggested in Scheme 5. Similar oxidations have given spirans in the dimedone series,[15] though the oxidising agents were the more usual ones, *viz.* iodine or hexacyanoferrate(III). One coumarin nucleus has now lost the electronic interactions that stabilised the lactone group, so hydrolysis to a 3-keto-acid and decarboxylation should now be easy. Since a second, similar oxidation is not possible in the product (6a) this retains



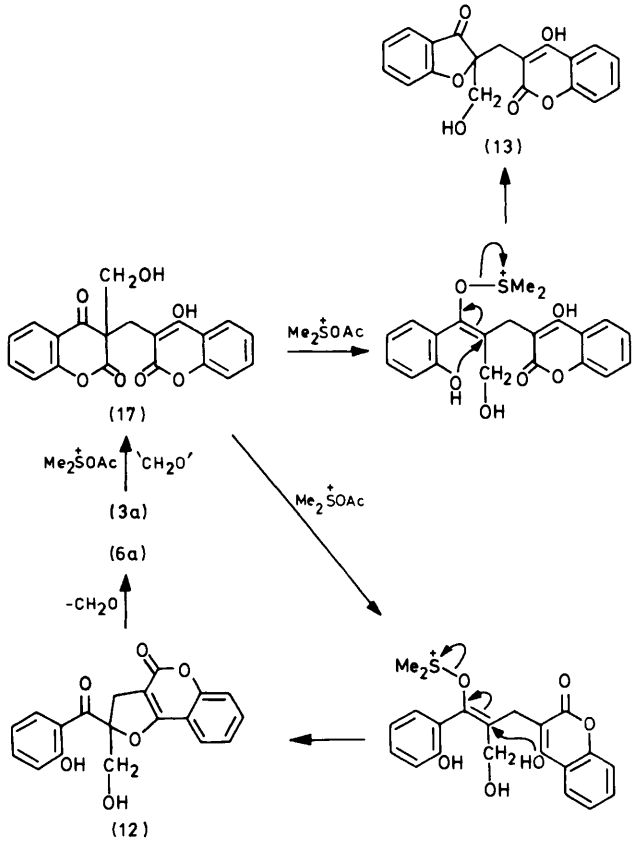
Scheme 3



Scheme 4



Scheme 5



Scheme 6

the second coumarin ring. A second oxidation can be envisaged if the reagent converts (6a) into the enol sulphonium salt (16) (Scheme 5) thus allowing deprotonation to lead to the furocoumarin (11a) which, as noted above, is one of the minor products.

A slightly different origin is proposed for compounds B (12a) and C (13). Having been formed by methylene insertion as in Scheme 2, dicoumarol might suffer a further insertion as in Scheme 6, giving compound (17) and again destabilising one coumarin nucleus. Hydrolysis and decarboxylation now lead to a ketone (enolic derivative shown) in which an equivalent of oxidative phenolic coupling can again occur. In one direction it affords compound B (12a) which is protected against any further oxidative attack, in the other it affords compound C (13) which is not, and is accordingly difficult to obtain in any quantity.

Since the hydroxymethyl compound (12a) loses formaldehyde when heated it might, under appropriate conditions, be the main product, compound (6a) being formed from it as suggested in Scheme 6. Certainly, both compounds (12a) and (6a) are formed early on in high-temperature reactions and then the yield of compound (12a) diminishes as that of compound (6a) increases.

Experimental

U.v. spectra were recorded on a Unicam SP8 100 spectrophotometer, i.r. spectra on a Perkin–Elmer 125 spectrophotometer, and ^{1}H n.m.r. spectra on a Perkin–Elmer R34 spectrometer, with $SiMe_4$ as internal standard. Light petroleum refers to that fraction boiling in the range 60—80 °C.

3-*Dimethylsulphoniochroman*-2,4-*dionate* (2).—A solution of 4-acetoxycoumarin (0.5 g) in DMSO (6 ml) was kept at 120 °C under nitrogen for 5 h. The residue left after removal of solvent under reduced pressure was crystallised from benzene to give the *ylide* (2) as prisms (0.4 g), m.p. 193 °C; $\lambda_{max.}$ (MeOH) 280 nm (log ε 4.02); $\nu_{max.}$ (Nujol) 1 680, 1 620, 1 610, and 1 560 cm^{-1}; δ($CDCl_3$) 6.87 (6 H, SMe_2); *m/z* 222 ($M^{\cdot+}$, 82%) (Found: C, 59.4; H, 4.85. $C_{11}H_{10}O_3S$ requires C, 59.45; H, 4.5%).

Conversion of 4-*Hydroxycoumarin* (1a) *into Dicoumarol* (3a).—DMSO (16 ml) and acetic anhydride (8 ml) were heated together at *ca.* 80 °C for 2 h, then 4-hydroxycoumarin (1a) (10 g) was added to the mixture which was left at room temperature for a week. The solid that separated during this time was filtered off, washed with benzene, and dried and was identified as dicoumarol (3a) (yield 6 g) by direct comparison with an authentic sample.

Conversion of 4-*Hydroxycoumarin* (1a) *into Compounds* (6a), (11a), (12a), *and* (13).—(i) A mixture of DMSO (16 ml), acetic anhydride (8 ml), and 4-hydroxycoumarin (1a) (8 g) was heated as quickly as possible to 170 °C and was kept at that temperature for 6 h. The viscous dark product (which smelled strongly of organic sulphides) was treated with water and the mixture left for 12 h. Chloroform (250 ml) was then added and the organic phase (A) was separated and washed several times with aqueous sodium hydrogen carbonate saturated with carbon dioxide. The aqueous washings were combined and treated with dilute hydrochloric acid to precipitate a solid which was crystallised from methanol to give 3-(2,3-*dihydro*-2-*hydroxymethyl*-3-*oxobenzo*[b]*furan*-2-*ylmethyl*)-4-*hydroxycoumarin* (13) as prisms (0.15 g), m.p. 208—210 °C (decomp.); $\lambda_{max.}$ (MeOH) 246, 281, and 308 nm (log ε 4.05, 3.90, and 3.98); $\nu_{max.}$ (KBr) 3 340br, 1 710, 1 700, and 1 685 (three overlapping bands), 1 605br with several sub-maxima, and 1 570 cm^{-1}; *m/z* 338 (vw; $M^{\cdot+}$), 320 (w), 308, 290, 262, 221, 208, 204, 187, 175, 164, 162, 147, 146, 134 (base), 121, 120, 105, and 104 (Found: C, 67.5; H, 4.3. $C_{19}H_{14}O_6$ requires C, 67.45; H, 4.2%). This compound is readily soluble in aqueous sodium hydrogen carbonate; its solution in methanol gives no characteristic colour with iron(III) chloride and is not turned yellow by the addition of dilute sodium hydroxide at ambient temperature.

The washed chloroform solution (A; see above) was washed again with water and was then dried (Na_2SO_4), concentrated, and diluted with light petroleum. The precipitate that formed was chromatographed on a column of silica gel (360 g) with methanol–chloroform (5 : 95 v/v) as eluant and appropriate fractions were recombined and further purified on thick-layer plates [SiO_2; MeOH–$CHCl_3$ (5 : 95)] to give compound (2) (2.6 g) and 2,3-*dihydro*-2-(2-*hydroxybenzoyl*)-4H-*furo*[3,2-c][1]*benzopyran*-4-*one* (6a) which formed feathery needles, m.p. 212—214 °C (rapid heating) or m.p. *ca.* 224 °C (slow heating) from chloroform–hexane or DMF–methanol; $\lambda_{max.}$ (MeOH) 250, 285, and 310 nm (log ε 4.20, 4.06, and 4.06); $\nu_{max.}$ (Nujol) 1 715, 1 700, 1 675, 1 645, 1 610, 1 600, and 1 567 cm^{-1}; *m/z* 308 ($M^{\cdot+}$), 290, 262, 204, 187, 186, 175, 162, 147, 146, 134, 121 (base), 120, 104, and 102 (Found: C, 70.35; H, 4.0. $C_{18}H_{12}O_5$ requires C, 70.1; H, 3.9%). Compound (6a) is soluble only with difficulty in a wide range of solvents; it is most easily soluble in ketones and in DMF. With aqueous ethanolic sodium hydrogen carbonate the crystals appear to swell and flocculate; they dissolve in 1M-aqueous sodium hydroxide–ethanol to give a yellow solution from which compound (6a) cannot be recovered (except in trace amounts) by neutralisation. When heated the alkaline solution becomes deep yellow and readily reduces Fehling's reagent. A saturated solution of the compound in acetone is transiently coloured by a solution of iron(III) chloride in acetone. The Gibbs test was negative when applied under a wide range of conditions. The compound is stable to acids; a suspension in methanol dissolves when saturated with hydrogen chloride, but the compound is recovered without loss upon dilution with water.

Acetylation of compound (6a) by acetic anhydride with either sodium acetate or sulphuric acid as catalyst gave the same product, which crystallised from methanol containing a little chloroform as either fat prisms or long, silky needles (favoured by separation from warm solvent). The two forms had identical chromatographic properties and gave the same mass- and ^{1}H n.m.r.-spectra; this showed them to be two crystallographic forms of the *acetate* (66%) (Found: C, 68.2; H, 3.95. $C_{20}H_{14}O_6$ requires C, 68.55; H, 4.0%). This compound does not exhibit a characteristic m.p.; both forms melt between 177 and 204 °C with major melting at *ca.* 190 °C. A change of crystalline form is often seen on heating. At the same time a heavy distillate forms on the cover glass if the hot-stage technique is employed; many related compounds tend to behave in this way, but the acetate is the most extreme example. The i.r. spectrum of the needles showed $\nu_{max.}$ [Nujol] 1 745, 1 706, 1 650, 1 605, and 1 590 cm^{-1}.

(ii) A reaction conducted as in (i) above but at 160 °C for 2 h gave, after work-up in the same way, compound (2) (3.3 g), compound (13) (0.2 g), and compound (6a) (0.3 g).

(iii) A solution of 4-hydroxycoumarin (1a) (5 g) in DMSO–acetic anhydride (2 : 1 v/v; 15 ml) was heated quickly to 170 °C and was kept at that temperature for 6 h. Addition of water (100 ml) then caused an oil to separate out slowly. The oil was removed and was covered with diethyl ether; a solid gradually separated out and was identified as the phenol (6a) (1 g). The rest of the oily fraction was chromatographed on silica (100 g) using benzene with increasing amounts of ethyl acetate as eluant; the earlier fractions gave the furocoumarin (11a) (0.15 g), identified by companion with an authentic sample (see below), and the later fractions gave a second crop of the phenol (6a) (1 g) and then the diol (12a) (1.2 g) (see below).

(iv) A mixture of DMSO (20 ml), acetic anhydride (10 ml), and 4-hydroxycoumarin (1a) (10 g) was kept at 160 °C for 2 h and was then mixed with water and extracted with diethyl ether. Work-up of the precipitate afforded the phenol (6a). Chromatography of the diethyl ether-soluble material gave more of this compound (combined yield 2 g) together with a product (4 g) that was found to crystallise slowly from benzene–hexane to give 2,3-*dihydro*-2-(2-*hydroxybenzoyl*)-2-*hydroxymethyl*-4H-*furo*[3,2-c][1]*benzopyran*-4-*one* (12a) as thick prisms (4 g), m.p. 143—145 °C (slow heating induced melting over the range 137—154 °C); $\lambda_{max.}$ (MeOH) 263, 290, and 310 nm (log ε 4.00, 3.91, and 3.96); $\nu_{max.}$ (Nujol) 3 400br, 1 720, 1 650, 1 630, and 1 570 cm^{-1}; *m/z* 338 ($M^{\cdot+}$), 320, 308, 290, 187 (72), 147, 146 (97), 134 (35), and 121 (100%) (Found: C, 67.7; H, 4.3. $C_{19}H_{14}O_6$ requires C, 67.45; H, 4.2%). This compound is readily soluble in alcohols and acetone, though only sparingly so in other solvents. It develops a brown-purple colour when treated with ethanolic iron(III) chloride. It is insoluble in aqueous sodium carbonate saturated with carbon dioxide, but will dissolve in the usual bench reagent (pH *ca.* 10), or in dilute sodium hydroxide, to give a pale-

yellow solution. At pH 10 in very dilute aqueous sodium hydrogen carbonate the compound gives a positive Gibbs test with 2,6-dichlorobenzoquinone chloroimine, the colour being greenish blue at first and gradually becoming navy blue.

Methylation of this dihydrofurobenzopyranone (2.5 g) with iodomethane (5 ml) and potassium carbonate (2 g) in acetone was slow and gave a gummy product which was purified (silica column; benzene eluant) and then crystallised from benzene–hexane to afford 2,3-*dihydro*-2-*hydroxymethyl*-2-(2-*methoxybenzoyl*)-4H-*furo*[3,2-c][1]*benzopyran*-4-*one* (12b) (0.7 g), m.p. 169—172 °C; $\lambda_{max.}$ (MeOH) 290 and 310 nm (log ε 4.01 and 4.01); $\nu_{max.}$ (Nujol) 3 480br, 1 715br, 1 640, and 1 605 cm^{-1}; δ($CDCl_3$; 90 MHz) 3.22 and 3.60 (each 1 H, both d, *J* 17 Hz, together 3-H_2), 3.47 (3 H, s, OMe), 3.94 and 4.32 (each 1 H, both d, *J* 11 Hz, together CH_2OH), 6.81 (1 H, d, *J* 8 Hz, 3′-H), 7.01 (1 H, dd, *J* 8, 8 Hz, 5′-H), and 7.4 (total 6 H, m, 6 × ArH); *m/z* 352 ($M^{\cdot+}$), 322 (100), 187 (99), 186 (72), 136 (99), and 135 (98%) (Found: C, 68.4; H, 5.9. $C_{20}H_{16}O_6$ requires C, 68.2; H, 5.7%).

Reaction of Dicoumarol (3a) *and DMSO.*—A mixture of dicoumarol (3a) (25 g), DMSO (250 ml) and acetic anhydride (125 ml) was kept at 80 °C for 24 h. Addition of water then precipitated compound (6a) (15 g) which was filtered off. The filtrate was extracted with diethyl ether. The extract was washed with water and was then subjected to chromatography on silica gel with light petroleum as eluant. Several fractions were obtained but only the yellow one gave identifiable material on work-up. The product was the furocoumarin (11a) (0.4 g), identical with a specimen prepared as follows.

Dehydrogenation of compound (6a).—Compound (6a) (100 mg) was heated with palladium–charcoal (10%; 50 mg) in boiling naphthalene (5 g) for 5 h. The solution was then cooled, diluted with benzene (10 ml), filtered and passed through a short column of silica gel to remove naphthalene. The product was crystallised from benzene–hexane to give 2-(2-hydroxybenzoyl)-4*H*-furo[3,2-*c*][1]benzopyran-4-one (11a) as long, pale-yellow prisms (72 mg), m.p. 183—184 °C (lit.,[13] 177—179 °C); $\lambda_{max.}$ (MeOH) 274 and 335 nm (log ε 4.16 and 4.32); $\nu_{max.}$ (Nujol) 1 740, 1 620, and 1 590 cm^{-1}; *m/z* 306 ($M^{\cdot+}$) (82), 186 (100), 158 (30), 121 (91), and 120 (53%) (Found: C, 70.4; H, 3.15. Calc. for $C_{18}H_{10}O_5$: C, 70.5; H, 3.15%). This compound gives a dark red colour with ethanolic iron(III) chloride and a green-blue colour with Gibbs' reagent at pH 10. It gives a deep yellow solution in 2M-ethanolic sodium hydroxide.

The *methyl ether* (11b) was obtained on treatment of the phenol (11a) with iodomethane and potassium carbonate in boiling acetone and was crystallised from methanol as faint yellow prisms, m.p. 151—153 °C; $\nu_{max.}$ ($CHCl_3$) 1 745, 1 650, 1 630, and 1 600 cm^{-1}; δ(F_3CCO_2H) 4.0 (3 H, s, OMe), 7.87 (1 H, s, 3-H), *ca.* 7.3 and *ca.* 7.7 (total 8 H, m, 8 ArH) (Found: M^+, 320.0640. $C_{19}H_{12}O_5$ requires *M*, 320.0685).

The same compound (0.18 g; m.p. and mixed m.p. 151—153 °C) was formed when the methyl ether (6c) (see below) (0.2 g) was heated in boiling naphthalene (10 g) for 10 h with palladium–charcoal (10%; 0.1 g).

Pyrolyses.—(i) *Compound* (12a). Compound (12a) (20 mg) was heated in boiling naphthalene (1 g) for 5 h and the mixture was then diluted with benzene and the naphthalene was removed as in the foregoing experiment. The product was purified from methanol to give compound (6a) (12 mg), identified by its m.p., mixed m.p., and i.r. spectrum.

(ii) *Compound* (13). Compound (13) (33 mg) was heated under vacuum (0.1 mmHg) until it melted at *ca.* 220 °C; as it did so an effervescence was observed, together with a yellowish residual gum and a sublimate somewhat contaminated by the gum. Resublimation of this crude sublimate gave a product which was recrystallised from a small volume of dichloromethane–methanol. The first crop of crystals consisted of a small quantity of squat prisms (*ca.* 1 mg) that sublimed at ordinary pressure at *ca.* 250 °C to give shining prisms, m.p. 285 °C (Found: M^+, 336.0618. Calc. for $C_{19}H_{12}O_6$: *M*, 336.0634). This substance has not been identified.

The mother liquors were evaporated to dryness and the residue was crystallised from methanol, a slight amount of insoluble material being removed by filtration. The product, 3,4-*dihydro*-2H,5H-*pyrano*[3,2-c][1]*benzopyran*-2-*spiro*-2′-2′,3′-*dihydrobenzo*[b]*furan*-3,5′-*dione* (14), formed long, shining prisms (8 mg), m.p. 218—220 °C [with changes in crystal form and distillation near the m.p. very similar to the behaviour observed in compound (6a); however a mixture with compound (6a) depresses the m.p. of compound (14) by *ca.* 40 °C]; $\nu_{max.}$ (KBr) 1 730 (lactone C=O), 1 715 (benzofuranone C=O), and 1 642, 1 615, and 1 608 cm^{-1} (ene and aromatic); δ($CDCl_3$) 2.27 (2 H, m, 3-H_2) and 2.93 (2 H, m, 4-H_2); *m/z* 320 (M^+), 200 ($C_{12}H_8O_3$), 174 ($C_{10}H_6O_3$), 146 ($C_9H_6O_2$), and 120 ($C_7H_4O_2$).

Methylation of Compound (6a).—(i) Treatment of compound (6a) (0.5 g) with iodomethane (4 ml) and potassium carbonate (1 g) in boiling acetone during 1 h gave a product which, isolated in the usual way, formed a yellow gum that partly crystallised from methanol to give the *methyl ether* (6c) as long, shining prisms (0.3 g) m.p. 168—169 °C; $\lambda_{max.}$ (MeOH) 250, 290, and 310 nm (log ε 4.07, 4.00, and 4.09); $\nu_{max.}$ (Nujol) 1 710br, 1 670, 1 650, and 1 590 cm^{-1}; *m/z* 322 ($M^{\cdot+}$) (8), 187 (80), and 135 (100%) (Found: C, 71.1; H, 4.7. $C_{19}H_{14}O_5$ requires C, 70.8; H, 4.3%). The ether (6c) was insoluble in cold ethanolic sodium hydroxide, but gave a yellow solution upon warming.

A solution of compound (6c) (20 mg) in dichloromethane (5 ml) was treated with an excess of boron trichloride in the same solvent (1 : 4 v/v; 0.5 ml) at room temperature. The solution immediately became deep yellow and after 5 min it was washed several times with water and dried (Na_2SO_4). After work-up in the usual way the product was crystallised from methanol to give the parent phenol (6a) as long prisms (17 mg) m.p. *ca.* 224 °C, identified spectroscopically.

(ii) A suspension of the phenol (6a) in dichloromethane was treated with an ethereal solution of diazomethane (dried over KOH) added in small portions during 3 h, *i.e.* until solution was complete. Removal of the solvents under reduced pressure left a gum which crystallised when in contact with methanol; recrystallisation (MeOH) of this product provided the phenol (6a). The mother liquors continued to provide further crops of compound (6a). Finally, the solvent was completely removed under reduced pressure and the residue was examined spectroscopically. The i.r. spectrum showed bands absent from the phenol (6a), but the ^1H n.m.r. spectrum showed that no methoxy-protons were present. This fraction was not examined further.

(iii) A suspension of the phenol (6a) in methanol was subjected to a stream of hydrogen chloride gas. The phenol dissolved, but removal of volatile materials and recrystallisation of the residue provided only a *ca.* quantitative recovery of the phenol. When the solution was heated for 15 min before work-up the result was the same.

Reactions with Iodine and Hexamine.—(i) Following Checchi,[13] we treated compound (6a) (1.0 g) with iodine (1 g) in refluxing ethanol (200 ml) for 6 h. T.l.c. indicated no reaction had occurred.

(ii) Following of Checchi,[13] we heated dicoumarol (3a) (1 g) in ethanol (200 ml) with iodine (1 g) for 6 h. The mixture was

allowed to cool whereafter unchanged dicoumarol was filtered off. The filtrate was concentrated until it deposited a yellow solid which was crystallised from ethanol to give the furocoumarin (11a) as yellow prisms (<0.05 g), m.p. 183—184 °C, identical with samples prepared previously (see above).

(iii) Dicoumarol (3a) (1 g), iodine (1 g), and hexamine (1 g, 2 mol equiv.) were heated in refluxing ethanol (180 ml) for 1.5 h. Removal of the solvent left a residue which was extracted with dichloromethane and the extract was washed with aqueous sodium thiosulphate. Column chromatography of the extract on silica with diethyl ether–hexane (1 : 4 v/v) as eluant gave first, the furocoumarin (11a) (0.26 g), and then, with diethyl ether–hexane (1 : 1 v/v) as eluant, compound (6a) (0.18 g).

(iv) Compound (6a) (0.3 g) was heated in ethanol (70 ml) under reflux with iodine (0.3 g) and hexamine (0.3 g) for 1.5 h. Chromatographic separation of the products was conducted as described in (iii) above to give the furocoumarin (11a) (0.21 g) together with some starting material. This method worked well on a larger scale (6 g) and was adopted for routine preparative purposes, the reaction time being extended to 4 h.

(v) A solution of compound (6a) (0.11 g) in DMF (5 ml) was mixed with one of iodine (0.2 g) in the same solvent (5 ml) containing pyridine (2 ml) and the mixture was kept for 40 min before being warmed briefly to 60 °C and then being added rapidly to methanol (25 ml) containing enough aqueous sodium thiosulphate to react with any remaining iodine. The yellow precipitate was collected by filtration and was crystallised from DMF containing a little methanol to give 2-(2-*hydroxy*-3,5-*di-iodobenzoyl*)-4H-*furo*[3,2-c][1]*benzopyran*-4-*one* (11c) as bright yellow prisms (0.12 g), m.p. 245 °C (Found: M^+, 557.8462. $C_{18}H_8I_2O_5$ requires M, 557.8464). The chief mass-spectral fragmentation gave fragment ions at m/z 372 (100%) (di-iodobenzoyl moiety) and m/z 185 (80%) (furocoumarin moiety), the latter ion collapsing to a salicyloyl fragment ion at m/z 121 (23%).

(*With I. W. Easton*) 2,3-*Dihydro*-2-(2-*hydroxy*-5-*methylbenzoyl*)-8-*methyl*-4H-*furo*[3,2-c][1]*benzopyran*-4-*one* (9).—A mixture of 6,6′-dimethyldicoumarol [3,3′-methylenebis-(4-hydroxy-6-methylcoumarin)] (3b) (2 g), DMSO (10 ml), and acetic anhydride (5 ml) was kept at 80 °C for 24 h and was then cooled to 40 °C and diluted with water (10 ml). The precipitate was collected, washed with ethanol, and recrystallised from ethanol to give the *dihydrofurobenzopyranone* (9) as feathery crystals (1.1 g), m.p. 225 °C; $\nu_{max.}$ (Nujol) 1 720, 1 710, and 1 655 cm^{-1} (Found: C, 71.5; H, 4.7. $C_{20}H_{16}O_5$ requires C, 71.4; H, 4.8%). In addition to a molecular ion at m/z 336, the compound exhibited major mass spectral peaks at 318, 201, 176, 160, 148, and 135 a.m.u.

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Received 9*th July* 1982; *Paper* 2/1156