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The Syntheses of Dimethylfuro Derivatives of 4-Hydroxycoumarins and Benzofuro[1]benzopyranones*[1]

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4',5'-Dimethyl-4-hydroxyfuro[2',3':7,8]coumarin (2) and its 3-phenyl, 3-(2-methoxyphenyl), and 3-(2,4,5-trimethoxyphenyl) derivatives (4, 5 and 6), and also their isomers, 4',5'-dimethyl-4-hydroxyfuro[3',2':6,7]coumarins (14, 15, 16 and 17), were prepared by the action of ethyl carbonate or of ethyl chlorocarbonate on the corresponding 2,3-dimethyl-4- or isomeric 6-hydroxy-5-benzofuranyl ketones. Two furocoumarins (2 and 14) were also obtained in poor yields by the condesnation of 2,3-dimethyl-4- or 6-hydroxybenzofuran with malonic acid. The action of hydroiodic acid on the furocoumarins 5 and 6 afforded 2,3-dimethyl-5*H*-benzofuro[3,2-*c*]furo-[2,3-*h*][1]benzopyran-5-one (8) and its 7,8-dihydroxy derivative (9) respectively; 8 was also synthesized by building up the dimethylfuran ring on 3-hydroxy-6*H*-benzofuro[3,2-*c*][1]benzo-pyran-6-one, while 9 was also synthesized by the oxidative coupling of 2 with catechol. On the other hand, the action of pyridine hydrochloride on 5 caused the closure of the furan ring towards the 2-position, giving 1,2-dimethyl-6*H*-benzofuro[2,3-*b*]furo[2,3-*h*][1]benzopyran-6-one (11), which had a new pentacylic ring system; the only demethylated compound (12) was also obtained. The structure of 11 was confirmed by its IR and UV spectra and by the formation of 12 upon its alkaline hydrolysis. The action of aluminum chloride on 5 also gave 12. Analogously, isomeric 1,2-dimethyl-6*H*-benzofuro[3,2-*c*]furo[3,2-*g*][1]benzopyran-6-one (20) and its 8,9-dihydroxy compound (21) were also synthesized.

Several derivatives of benzofuran,[1)] 4-hydroxy-coumarin,[1)] furocoumarins,[1,2)] and benzofuro-coumarin[1,2)] were obtained from natural sources; some of them have biological activities. In the present experiments, some furo-derivatives of 4-hydroxycoumarins and of benzofurocoumarin are synthesized in order to test their pharmacological activities, for convenient starting compounds for the synthesis of these compounds could be obtained readily.[3)] Concerning the synthesis of these compounds, the present authors have reported previously[4)] on the synhesis of 4-hydroxyfuro[2',3':7,8]-coumarins and 5*H*-benzofuro[3,2-*c*]furo-[2,3-*h*][1]-benzopyran-5-one, while the synthesis of isomeric 4-hydroxyfuro[3',2':6,7]coumarins[5-7)] and 6*H*-benzofuro[3,2-*c*]furo[3,2-*g*][1]benzopyran-6-one derivative (erosnin)[6)] has been reported on by Fukui and Nakayama and others, and that of dimethylfuro-derivatives of 4-hydroxy-3-phenylfuro-coumarin has been reported on by Royer *et al.*[8)]

In the present experiments, 4',5'-dimethyl-4-hydroxy-furo[2',3':7,8]coumarins (2—6) and isomeric -furo[3',2':6,7]coumarins (14—17) were synthesized from the corresponding hydroxybenzofuranyl ketones (1 and 13); some of them (2, 5, and 6, and isomeric 14, 16, and 17) were converted to derivatives of 5*H*-benzofuro[3,2-*c*]furo-[2,3-*h*][1]benzopyran-5-one (8 and 9), 6*H*-benzofuro[2,3-*b*]furo[2,3-*h*][1]benzopyran-6-one(11) and 6*H*-benzofuro[3,2-*c*]furo[3,2-*g*] [1] benzopyran-6-one (20 and 21), one (11) of these ring systems forming a new pentacyclic ring system.

4-Hydroxyfurocoumarins had been prepared previously by the action of ethyl carbonate and sodium on hydroxybenzofuranyl ketones[4-6)] and by the dehydrogenation of dihydrofurocoumarins,[5-7)] while the 4',5'-dimethyl-3-phenyl compounds had been prepared by the thermal condensation of dimethyl-hydroxybenzofurans with

*1 A part of this work was presented at the 29th Annual Meeting of the Chemical Society of Japan, Tokyo, March, 1967.

1) F. M. Dean, "Naturally-occurring Oxygen-ring Compounds," Butterworths, London (1963), pp. 135, 176.

2) A. Mustafa, "Furopyrans and Furopyrones," ed. by A. Weissberger, Interscience Publishers, London (1967), pp. 14, 243.

3) Y. Kawase, M. Nanbu and F. Miyoshi, This Bulletin, **41**, 2676 (1968).

4) Y. Kawase, M. Nanbu and H. Yanagihara, *ibid.*, **41**, 1201 (1968).

5) K. Fukui and M. Nakayama, *Nippon Kagaku Zasshi (J. Chem. Soc. Japan, Pure Chem. Sect.)*, **85**, 444 (1964).

6) K. Fukui and M. Nakayama, *Tetrahedron Letters*, **1965**, 2559.

7) A. Vialard-Goudon and N. Blanchcatte, *Compt. Rend.*, **263**, 255 (1966).

8) J.-P. Lechartier, P. Demerseman, A. Cheutin and R. Royer, *Bull. Soc. Chim. France*, **1966**, 1716.

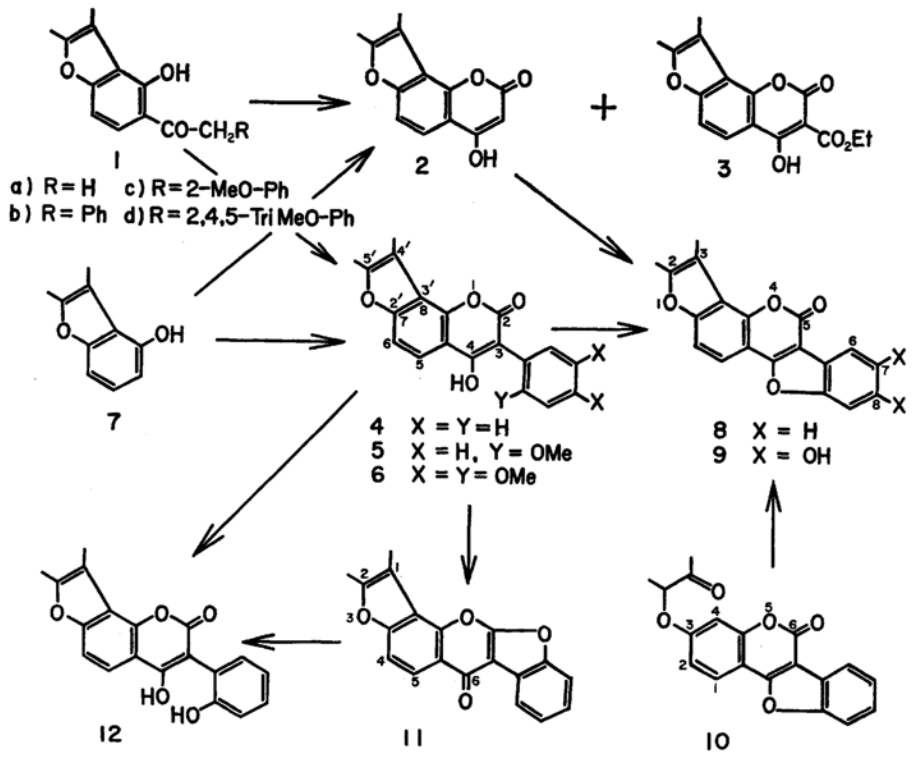

Chart 1

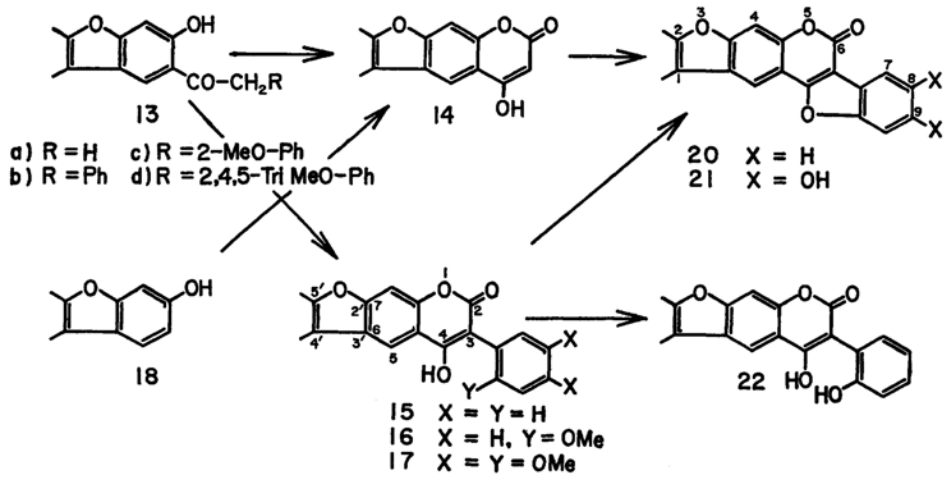

Chart 2

ethyl phenylmalonate.[8] In the present exeriments, 4',5'-dimethyl-4-hydroxyfuro[2',3':7,8]-coumarin (2) and its 3-phenyl, 3-(2-methoxyphenyl), and 3-(2,4,5-trimethoxyphenyl)derivatives (4, 5, and 6) as well as the isomeric 4',5'-dimethyl-4-hydroxyfuro[3',2': 6,7]coumarins (14, 15, 16, and 17) were synthesized in good yields from the corresponding 2,3-dimethyl-4- or -6-hydroxy-5-benzofuranyl ketones (1 or 13), the preparation of which has been reported on in a preceding paper,[3] by the action of ethyl carbonate and sodium[9] or of ethyl chlorocarbonate and potassium carbonate[10] according to the general method for the synthesis of 4-hydroxycoumarins. In the case of 2, a small

9) J. Boyd and A. Robertson, *J. Chem. Soc.*, **1948**, 174.
10) A. H. Gilbert, A. McGookin and A. Robertson, *ibid.*, **1957**, 3740.

amount of its 3-ethoxycarbonyl derivative (3) was also obtained as a by-product, much as in the case of furocoumarin without dimethyl groups;[4] its formation is probably due to the double ethoxycarbonylation of the ketone 1a, followed by cyclization. The 3-phenyl compound (4) thus obtained was identical with the furocoumarin which had been obtained by the above-mentioned thermal condensation of 2,3-dimethyl-4-hydroxybenzofuran (7) with ethyl phenylmalonate[8]; the furocoumarin 15 was an isomer of 4′,5′-dimethyl-4-hydroxy-3-phenylfuro[2′,3′:5,6]coumarin (19), which had been obtained by a similar thermal condensation from 2,3-dimethyl-6-hydroxybenzofuran (18). The condensation of hydroxybenzofurans (7 and 18) with malonic acid to obtain the corresponding 4-hydroxycoumarins directly was also attempted by the action of polyphosphoric acid[11a] or of phosphoryl chloride and zinc chloride,[11b] but such attempts resulted in the formation of furocoumarins (2 and 14) in only poor yields; this is comparable to the unfavorable results of the thermal condensation of the unsubstituted malonic ester with phenols.[12]

Then, the 4-hydroxyfurocoumarins (2, 5, 6 and isomeric 14, 16, 17) thus obtained were converted to benzofuro-furo[1]benzopyranones by procedures analogous to those reported previously. The reported procedures involve the demethyl-cyclization of 4-hydroxy-3-(2-methoxyphenyl)furocoumarins with hydroiodic acid, with pyridine hydrochloride, or with aluminum chloride,[4] or involve the oxidative coupling of 4-hydroxyfurocoumarin with catechol.[6] In the present experiments, the action of hydroiodic acid in acetic acid on the furocoumarins 5 and 6 caused demethyl-cyclization, thus giving 2,3-dimethyl-5*H*-benzofuro-[3,2-*c*]furo[2,3-*h*][1]benzopyran-5-one (8) and its 7,8-dihydroxy derivative (9) respectively. The compound 8 was also obtained by building up the furan ring on 3-hydroxy-6*H*-benzofuro[3,2-*c*]-[1]benzopyran-6-one[13,14] through the action of 3-chlorobutanone-2 and potassium carbonate to give the 3-(α-acetylethoxy) compound (10), which was then cyclized by the action of polyphosphoric acid. The compound 9 was also prepared by the oxidative coupling of the furocoumarin 2 with catechol by means of potassium ferricyanide. On the other hand, the action of pyridine hydrochloride on 5 gave 1,2-dimethyl-6*H*-benzofuro[2,3-*b*][1]-benzopyran-6-one (11), a compound with a new pentacyclic ring system, and a small amount of a merely-demethylated 3-(2-hydroxyphenyl) compound (12), which was also obtained by the action of anhydrous aluminum chloride in nitrobenzene on 5. The compound 11 has ν_{CO} at 1650 cm^{-1}, which is in the region characteristic of that of the chromone type.[3-5,14,15] The pattern of its UV spectrum, showing a strong absorption at about 250 mμ and only a weak absorption at 315 mμ, is different from that of the benzofuro[3,2-*c*][1]-benzopyranones; rather, it is comparable to that of furoisoflavones.[3-5,16] Its alkaline hydrolysis gave the hydroxyfurocoumarin 12. The structure of 11 was assigned on the basis of these observations and was confirmed by comparing it with that of lisetin,[17] a compound recently isolated from a natural source; this compound has a tetracyclic ring system, 11*H*-benzofuro[2,3-*b*][1]benzopyran-11-one, which is also included in the compound 11. The formation of 11 from 5 is probably a result of the closure of the new furan ring at the 2-hydroxy group of the 2-hydroxyisoflavone derivative, a tautomeric form[14,15] of the 4-hydroxycoumarin 12, but the attempted dehydro-cyclization of 12 by refluxing it with methanolic hydrogen chloride was unsuccessful.

Analogously, the isomeric furocoumarins (16 and 17) were converted to 1,2-dimethyl-6*H*-benzofuro[3,2-*c*]furo[3,2-*g*][1]benzopyran-6-one (20) and its 7,8-dihydroxy derivative (21) by the action of hydroiodic acid; 21 was also obtained by the oxidative coupling of 14 with catechol. The action of both aluminum chloride and pyridine hydrochloride on 16 gave the demethylated compound (22).

In the IR spectra, the furocoumarins and benzofuro-furobenzopyranones prepared have the ν_{CO} at 1740—1670 cm^{-1}, which is in the region characteristic for those of the coumarin type,[4-6,14,15,17] except that the ν_{CO} of the compounds 4, 12, 14 and 22 are at 1655—1645 cm^{-1}, which is rather in the region characteristic for those of the chromone type,[3-6,14,15,17] moreover, the wave numbers of these ν_{CO} are in general smaller by about 20 cm^{-1} than those of homologues without dimethyl groups.[4-6]

In the UV spectra, the furocoumarins and benzofuro-furobenzopyranones have two bands, the band I and the band II; the band I is in general at 235—240 mμ, while the band II of the compounds with an angularly-fused furan ring is at 320—330 mμ, which is longer by about 20—25 mμ than those of the isomers. These UV spectra are almost identical with those of the compounds without dimethyl groups.[4-6]

11) a) L. Reichel and G. Proksch, *Naturwissenschaften*, **50**, 520 (1963). The experimental conditions and the yield are not given. b) J. L. Bose, R. C. Shah and V. R. Shah, *Chem. and Ind.*, **1960**, 623; V. R. Shah, J. L. Bose and R. C. Shah, *J. Org. Chem.*, **25**, 677 (1960).
12) G. Urbain and C. Mentzer, *Bull. Soc. Chim. France*, **11**, 171 (1944).
13) T. R. Govindachari, K. Nagarajan and P. C. Parthasarathy, *Tetrahedron*, **15**, 129 (1961).
14) Y. Kawase, This Bulletin, **35**, 573 (1962).
15) Y. Kawase, *Experientia*, **14**, 345 (1958); This Bulletin, **32**, 11 (1959).
16) K. Fukui and Y. Kawase, *ibid.*, **31**, 693 (1958).
17) C. P. Falshaw, W. D. Ollis, J. A. Moore and K. Magnus, *Tetahedron*, **Supplement No. 7**, 333 (1966).

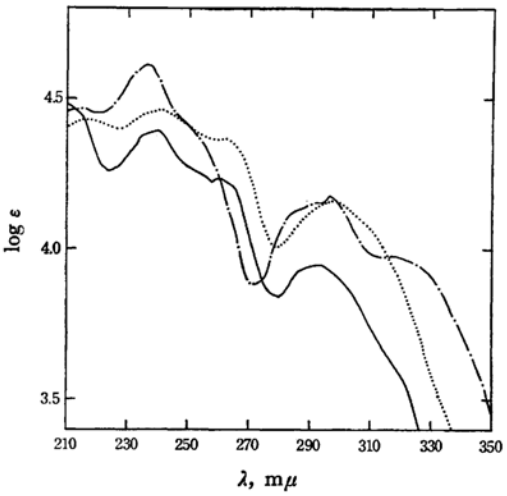

Fig. 1. The UV spectra of furocoumarins: —— 2, ···· 3 and —·—· 14.

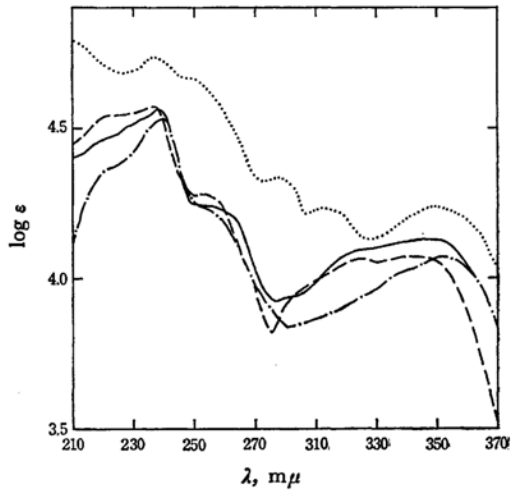

Fig. 3. The UV spectra of furocoumarins: —— 15, ---- 16, ····· 17 and —·—· 22.

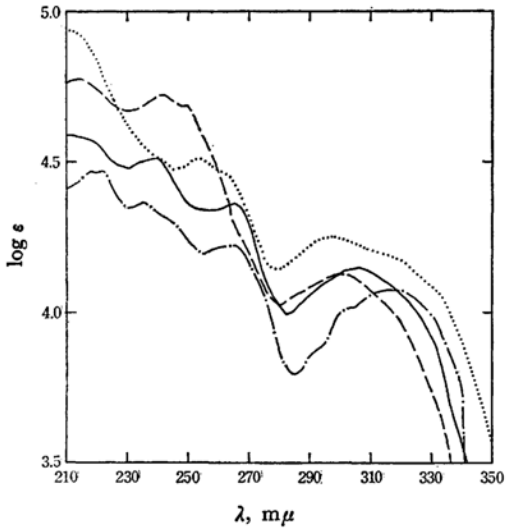

Fig. 2. The UV spectra of furocoumarins: —— 4, ---- 5, ····· 6 and —·—· 12.

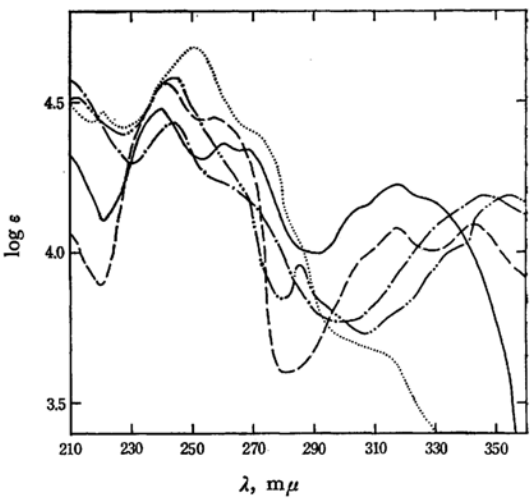

Fig. 4. The UV spectra of benzofuro-furobenzopyranones: —— 8, —·—· 9, ····· 11, ---- 20 and —···— 21.

Experimental*2

Materials. *Benzofuranyl Ketones 1a, b, c, d and Isomeric 13a, b, c, d.* These compounds were prepared by a previously-reported procedure.[3]

Hydroxybenzofurans 7 and 18. These compounds were prepared by the procedure reported by Royer *et al.*[18]

3-Hydroxy-6*H*-benzofuro[3,2-*c*][1]benzopyran-6-one was prepared, in the present experiments, by the action of ethyl chlorocarbonate and potassium carbonate[10] on the 2,4-dihydroxyphenyl 2-methoxybenzyl ketone to give hydroxycoumarin, which was then converted to the compound by demethyl-cyclization as follows:

4,7-Dihydroxy-3-(2-methoxyphenyl)coumarin. A mixture of the 2,4-dihydroxyphenyl 2-methoxybenzyl ketone[19] (10 g), ethyl chlorocarbonate (14 m*l*), acetone (100 m*l*), and anhydrous potassium carbonate (90 g) was refluxed for 3 hr. The cooled mixture was treated with water (1 *l*) and acidified, and the precipitates thus formed were collected and heated with 1 N aqueous sodium hydroxide (500 m*l*) for 1 hr. The resulting solution was acidified, and the precipitates formed were collected and recrystallized from ethanol; yield 6 g (54.5%). (See Tables 3 and 4).

3-Hydroxy-6H-benzofuro[2,3-c][1]benzopyran-6-one. A mixture of the coumarin (4 g), hydroiodic acid (d=1.7,

*2 All melting points are uncorrected; the IR spectra were measured in the form of KBr disks, while the UV spectra were measured in ethanol. The detailed data are summarized in the tables and figures.

18) E. Bisagni and R. Royer, *Bull. Soc. Chim. France*, **1962**, 925.

19) M. Nakajima, H. Fukami, K. Konishi and J. Oda, *Agr. Biol. Chem.*, **27**, 700 (1963).

Table 1. The syntheses of furocoumarins

Compd.	Starting compd.	Procedure[a]	Yield %
2	1a	A	41[b]
2	7	B	1.5
4	1b	A	72
4	1b	C	74
4	1b	D	30.5
5	1c	A	92
6	1d	A	95
12	5	E	66.5
12	5	F	6[c]
12	11	G	76
14	13a	A	72.5
14	18	B	1.5
14	18	H	d)
15	13b	A	82.5
15	13b	C	37
16	13c	A	89
17	13d	A	62
22	16	E	d)
22	16	F	26

a) A: Et_2CO_3+Na, B: Malonic acid+PPA, C: $ClCO_2Et+K_2CO_3$, D: $ClCO_2Et$+pyridine, E: $AlCl_3$, F: Pyridine-HCl, G: KOH, H: Malonic acid+$POCl_3$+$ZnCl_2$.
b) A small amount of 3 was also obtained.
c) The major product was 11.
d) A small amount.

Table 2. The syntheses of benzofuro-furobenzopyranones

Compd.	Starting compd	Procedure[a]	Yield %
8	5	A	22
8	10	B	59.5
9	2	C	49
9	6	A	35
11	5	D	22[b]
20	16	A	44.5
21	14	C	17
21	17	A	39

a) A: HI, B: PPA, C: Catechol+$K_3Fe(CN)_6$, D: Pyridine-HCl.
b) A small amount of 12 was also obtained.

100 m*l*), acetic acid (40 m*l*), and acetic anhydride (35 m*l*) was refluxed gently for 1 hr under a stream of nitrogen. The cooled mixture was poured into ice water containing a small amount of sodium bisulfite, and the precipitates formed were collected and recrystallized from ethanol. Mp 276—277°C (lit mp 285°C[13] or 276—277°C[14]); yield 1.6 g (45%).

The Preparation of Furocoumarins from Benzofuranyl Ketones (Table 1). *a) By the Action of Ethyl Carbonate and Sodium.* Small pieces of metallic sodium (2 g) were added to a solution of 1b (1.4 g) in ethyl carbonate (30 m*l*), and the mixture was heated gradually to 100°C. The mixture was heated at that temperature for 1 hr, and then methanol was added to the cooled mixture to destroy the excessive sodium. The resulting solution was diluted with water, washed with ether, and then acidified. The crystalline product formed was collected and recrystallized from ethanol to give 4′,5′-dimethyl-4-hydroxy-3-phenylfuro[2′,3′:7,8]-coumarin (4); mp 272—273°C (lit.[8] mp 271°C) (Found: C, 74.08; H, 4.34%).

Similarly, 4′,5′-dimethyl-4-hydroxyfuro[2′,3′:7,8]-coumarin (2) and its 3-(2-methoxyphenyl) and 3-(2,4,5-trimethoxyphenyl) derivatives (5 and 6), as well as isomeric 4′,5′-dimethyl-4-hydroxyfuro[3′,2′:6,7]-coumarin (14) and its 3-phenyl, 3-(2-methoxyphenyl), and 3-(2,4,5-trimethoxyphenyl) derivatives (15, 16, and 17), were prepared by this procedure. In the case of 2, a small amount of ethyl 4′,5′-dimethyl-4-hydroxy-furo[2′,3′:7,8]coumarin-3-carboxylate (3) was also obtained from the mother solution of the crystallization of 2.

b) By the Action of Ethyl Chlorocarbonate and Potassium Carbonate. A mixture of 1b (0.5 g), ethyl chlorocarbonate (0.5 g), acetone (15 m*l*), and anhydrous potassium carbonate (3.0 g) was refluxed for 3 hr. The cooled mixture was treated in a manner similar to that described in the case of 4,7-dihydroxy-3-(2-methoxyphenyl)-coumarin to give the furocoumarin 4.

Similarly, the furocoumarin 15 was also synthesized by this procedure.

c) By the Action of Ethyl Chlorocarbonate and Pyridine. Ethyl chlorocarbonate (0.6 g) was added gradually, with stirring and cooling, to a solution of 1b (0.6 g) in pyridine (10 m*l*), after which the mixture was allowed to stand overnight. The resulting mixture was poured into ice water and extracted with ether. The ether solution was washed with dilute hydrochloric acid, and the ether was distilled off. The residual product was heated with 10% aqueous sodium carbonate (40 m*l*) for 2 hr, and the cooled mixture was washed with ether and then acidified. The crystalline product formed was collected and recrystallized from ethanol to give 4.

The Preparation of 4-Hydroxycoumarins and 4-Hydroxyfurocumarins (2 and 14) Directly from Hydroxy-compounds (Table 1). *a) By the Action of Polyphosphoric Acid (PPA).* A mixture of the hydroxybenzofuran 7 (5 g), malonic acid (3.5 g), and PPA (n=2.5, 100 g) was heated at 100°C for 2 hr with stirring. The cooled mixture was poured into ice water and extracted with ethyl acetate. The ethyl acetate solution was extracted with 5% aqueous sodium hydroxide, and the alkaline solution was acidified. The crystalline product thus formed was collected and recrystallized from ethanol to give the hydroxyfuro-coumarin 2; mp 287°C (dec.), yield 0.1 g (1.5%).

Analogously, the furocoumarin 14 was also obtained by this procedure from the hydroxybenzofuran 18, while the reaction of resorcinol or its monomethyl ether and malonic acid gave 4,7-dihydroxycoumarin[11a] or 4-hydroxy-7-methoxycoumarin, mp 264.5°C (dec.) (lit.[20] mp 265°C (dec.)) and mp 252.5°C (dec.) (from ethanol) (lit.[20] mp 256°C (dec.)) respectively, in yields of 5% and 9.5%.

b) By the Action of Phosphoryl Chloride and Zinc Chloride. A mixture of 18 (5 g), malonic acid (3.5 g), anhydrous zinc chloride (12.5 g), and phosphoryl chloride (8.5 m*l*) was heated at 60—70°C for 8 hr

20) A. Sonn, *Ber.*, **50**, 1292 (1917).

TABLE 3. THE MP, IR AND ANALYSIS OF NEW COMPOUNDS

Compd.	Mp °C (solvent)[a]	ν_{OH}^{KBr} cm^{-1}	ν_{CO}^{KBr} cm^{-1}	Formula	Found C%	Found H%	Calcd C%	Calcd H%
			Coumarins					
b)	265—266(A)	3120	1630	$C_{16}H_{12}O_5$	67.60	4.32	67.60	4.03
2	287(dec)(A)	3100	1690	$C_{13}H_{10}O_4$	67.67	4.49	67.82	4.38
3	188(dec)(A)	2600	1740	$C_{16}H_{14}O_6$	63.80	4.85	63.57	4.67
5	244.5—245.5(A)	2950	1670	$C_{20}H_{16}O_5$	71.40	4.78	71.42	4.80
6	245—245.5(A)	3200	1710	$C_{22}H_{20}O_7$	66.58	5.22	66.66	5.09
12	273—274(dec)(B)	3340	1655	$C_{19}H_{14}O_5$	71.01	4.54	70.80	4.38
14	288—290(A)	2550	1650	$C_{13}H_{10}O_4$	67.89	4.48	67.82	4.38
15	256—257(A)	3100	1675	$C_{19}H_{14}O_4$	74.53	4.54	74.45	4.60
16	220—221(A)	2950	1680	$C_{20}H_{16}O_5$	71.13	4.92	71.42	4.80
17	255—256(A)	3450	1705	$C_{22}H_{20}O_7$	66.54	5.08	66.66	5.09
22	267—268(dec)(A)	3000	1645	$C_{19}H_{14}O_5$	70.92	4.58	70.80	4.38
			Benzofuro-benzopyranones					
8	242—243(C)		1740	$C_{19}H_{12}O_4$	74.91	4.15	74.99	3.97
9	>360(B)	3200	1705	$C_{19}H_{12}O_6$	68.04	3.82	67.85	3.60
10	186—187.5(C)		1735	$C_{13}H_{10}O_4$	67.89	4.48	67.82	4.38
11	257.5—258.5(C)		1650	$C_{19}H_{12}O_4$	75.09	4.16	74.99	3.97
20	265.5—267(C)		1740	$C_{19}H_{12}O_4$	74.74	4.02	74.99	3.97
21	>360(B)	3270	1700	$C_{19}H_{12}O_6$	67.56	3.81	67.85	3.60

a) A: ethanol, B: acetone, C: ethyl acetate.
b) 4,7-Dihydroxy-3-(2-methoxyphenyl)coumarin.

TABLE 4. THE UV SPECTRA

Compd.	λ_{max}^{EtOH} mμ[a] (log ε)
	Coumarins
b)	286(4.02), 315(4.32)
2	215[s](4.45), 240(4.40), 260[s](4.23), 294(3.95)
3	217(4.43), 241(4.46), 263[s](4.36), 297(4.16)
4	215[s](4.59), 238(4.51), 265(4.36), 305(4.15)
5	215(4.77), 242(4.72), 250[s](4.68), 265[s](4.30), 300(4.12)
6	211(4.93), 253(4.50), 297.5(4.25), 318[s](4.18)
12	217[s](4.47), 222(4.47), 236(4.37), 262(4.22), 320(4.07)
14	212(4.47), 237(4.61), 250[s](4.41), 296(4.18), 318[s](3.98)
15	238(4.49), 255[s](4.25), 300[s](4.08), 327(4.13)
16	221[s](4.54), 237(4.58), 252[s](4.28), 305(4.07), 320(4.07)
17	235(4.71), 250[s](4.67), 294(4.25), 333(4.24)
22	220[s](4.36), 240(4.53), 255[s](4.23), 331(4.07)
	Benzofuro-benzopyranones
8	240(4.48), 261(4.36), 270(4.34), 318(4.23)
9	244(4.43), 347(4.19)
11	221(4.47), 251(4.68), 315[s](3.65)
20	241(4.56), 258(4.45), 318(4.08), 343(4.09)
21	213[s](4.52), 244(4.58), 286(3.96), 353(4.19)

a) s: shoulder.
b) 4,7-Dihydroxy-3-(2-methoxyphenyl)coumarin.

with stirring. The cooled mixture was poured into ice water, and the precipitates formed were collected and dissolved in aqueous sodium carbonate and then filtered. The filtrate was acidified and extracted with ethyl acetate. The ethyl acetate was distilled off, and the residue was recrystallized from ethanol to give the furocoumarin 14.

The Formation of 3-(2-Hydroxyphenyl)coumarins (12 and 22) (Table 1). *a) By the Action of Aluminum Chloride on Methoxyphenylcoumarins (5 and 16).* Anhydrous aluminum chloride (1.1 g) was added to a solution of 5 (0.5 g) in nitrobenzene (30 m*l*), and the mixture was heated on a water bath for 2 hr. The cooled mixture was poured into ice water containing hydrochloric acid, and then the nitrobenzene was removed by steam-distillation. The residual product was recrystallized from acetone to give 4′,5′-dimethyl-4-hydroxy-3-(2-hydroxyphenyl)furo[2′,3′:7,8]coumarin (12).

Analogously, 4′,5′-dimethyl-4-hydroxy-3-(2-hydroxyphenyl)furo[3′,2′:6,7]coumarin (22) was obtained from 16 by this procedure.

b) By the Action of Pyridine Hydrochloride on 5 and 16. A mixture of 16 (0.4 g) and anhydrous pyridine hydrochloride (2 g) was refluxed for 30 min, after which the cooled mixture was treated with dilute hydrochloric acid. The precipitates formed were collected and recrystallized from ethyl acetate and then from ethanol to give the hydroxycoumarin 22.

In the case of 5, a small amount of the hydroxycoumarin 12 was obtained from the mother solution of the crystallization of the major product (11), the preparation of which will be described bellow.

c) By the Alkaline Hydrolysis of 11. A mixture of 11 (64 mg), 10% aqueous potassium hydroxide (10 m*l*), and methanol (20 m*l*) was refluxed for 2 hr. The cooled mixture was acidified with dilute hydrochloric acid, and the precipitates formed were collected and recrystallized from ethyl acetate to give the hydroxycoumarin 12.

The Preparation of Benzofuro-furo[1]benzopyranones (Table 2). *a) By the Action of Hydroiodic Acid on the Methoxyphenyl-furocoumarins.* A mixture of 5 (0.5 g), hydroiodic acid (d=1.7, 11m*l*), acetic acid (4.5 m*l*), and acetic anhydride (5 m*l*) was refluxed gently for 45 min under a stream of nitrogen. The cooled mixture was treated much as has been described in the case of 3-hydroxybenzofuro-benzopyranone; this gave 2,3-dimethyl-5*H*-benzofuro[3,2-*c*]furo[2,3-*h*]-[1]benzopyran-5-one (8).

Similarly, the 7,8-dihydroxy derivative of 8 (9), 1,2-dimethyl-6*H*-benzofuro[3,2-*c*]furo[3,2-*g*][1]benzopyran-6-one (20), and its 8,9-dihydroxy derivative (21) were also obtained by this procedure.

b) By the Action of Pyridine Hydrochloride on the Furocoumarin 5. A mixture of 5 (0.4 g) and anhydrous pyridine hydrochloride (2 g) was refluxed for 20 min, after which the cooled mixture was treated much as has been described in the case of hydroxycoumarins. The crude product was recrystallized from ethyl acetate to give 1,2-dimethyl-6*H*-benzofuro[2,3-*b*]furo[2,3-*g*][1]-benzopyran-6-one (11); the hydroxycoumarin 12 was also obtained from the mother solution by the method described before.

c) By the Oxidative Coupling of 2 or 14 with Catechol. A solution of potassium ferricyanide (1.2 g) and sodium acetate (1 g) in water (10 m*l*) was added to a solution of 2 (0.3 g) and catechol (0.12 g) in a mixture of acetone (30 m*l*) and water (4.5 m*l*), after which the mixture was allowed to stand at room temperature for 2 hr. The resulting mixture was filtered from the inorganic precipitates formed, the filtrate was treated with formic acid (46%, 3 m*l*), and then the acetone was removed *in vacuo*. The precipitates formed were collected and recrystallized from acetone to give the compound 9.

d) By Building Up the Furan Ring on 3-Hydroxybenzofurobenzopyranone. i) 3-(α-Acetylethoxy)-6H-benzofuro[3,2-c][1]benzopyran-6-one (10): A mixture of 3-hydroxy-6*H*-benzofuro[3,2-*c*][1]benzopyran-6-one (1.3 g), 3-chlorobutanone-2 (0.6 g), the methyl ethyl ketone (50 m*l*), and anhydrous potassium carbonate (2.5 g) was refluxed for 10 hr. The cooled mixture was filtered, the solvent was distilled off, and the residual product was recrystallized from ethyl acetate to give the compound 10; yield 1.2 g (74%).

ii) The Ring Closure of 10: A mixture of 10 (0.5 g) and PPA (n=2.5, 20 g) was heated on a water bath for 2 hr. The cooled mixture was poured into ice water, and the precipitates formed were collected and crystallized from ethyl acetate to give the compound 8 in an impure form; mp 210—230°C, 0.4 g. A part of it (0.1 g) was purified through chromatography, using alumina and benzene as a solvent; the product obtained from the elute was recrystallized from ethyl acetate to give the pure 8.

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