The Acylation of *bz*-Hydroxy- and *bz*-Methoxy-2,3-dimethylbenzofurans and the Synthesis of Furobenzopyranone Derivatives[1]

Yoshiyuki KAWASE, Seiji YAMAGUCHI, Nobuo OKI, and Fumiko OKUMURA

Department of Chemistry, Faculty of Literature and Science, Toyama University, Gofuku, Toyama

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The action of acetic acid, phenylacetic acid, or β-phenylpropionic acid and polyphosphoric acid on 5-, 7-, and 6-hydroxy-2,3-dimethylbenzofurans afforded 6-acyl-5-hydroxy-, 6-acyl-7-hydroxy-, and 5-acyl-6-hydroxybenzofurans, some of which were also obtained by the Friedel-Crafts acylation of the corresponding methoxybenzofurans. The hydroxyketones thus obtained were converted to dimethylfuro derivatives of 4-hydroxycoumarins and isoflavones, and 3-benzyl-4-hydroxyfurocoumarins were also prepared by the thermal condensation of the hydroxybenzofurans and diethyl benzylmalonate.

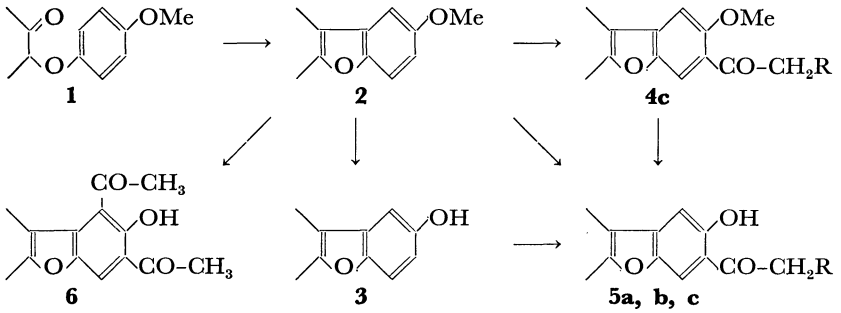
The formylation and acetylation of *bz*-methoxy-2,3-dimethylbenzofurans have been reported by Royer *et al.*,[2] while the acetylation and phenylacetylation of 4- and 6-methoxy- and -hydroxybenzofurans have been reported by one of the present authors.[3] The acyl compounds obtained have been converted to dimethylfuro derivatives of coumarins, chromones, flavones, and isoflavones.[2-4]

In connection with this, the acetylation, phenylacetylation, and β-phenylpropionylation of 5-, 7-, and 6-hydroxy- (**3**, **9**, **15**) and -methoxy-2,3-dimethylbenzofurans (**2**, **8**, and **14**) were carried out in the present experiments; also, dimethylfuro derivatives of 4-hydroxycoumarins (**17**, **18**, and **19**) and of isoflavones (**20**, **21**, **22**, and **23**) were prepared from the acyl compounds in order to test the pharmacological activities.

The starting compounds, *bz*-methoxy-2,3-dimethylbenzofurans (**2**, **8**, and **14**), were prepared in good yields in the present experiments by the cyclodehydration of aryloxybutanones (**1**, **7**, and **12**) with polyphosphoric acid. The reagent seemed to be excellent in the case of 3-(*m*-methoxyphenoxy)-2-butanone[5] (**12**), as the 6-methoxybenzofuran (**14**) was obtained in the pure state.[6] For the preparation of the 6- or 4-hydroxybenzofuran, the cyclization of 3-(*m*-acetoxyphenoxy)-2-butanone (**13**) by sulfuric acid was attempted in order to obtain the 6-hydroxybenzofuran (**15**) in a low yield.

The action of acetic acid, phenylacetic acid, or β-phenylpropionic acid on the 5- and 7-hydroxy-2,3-dimethylbenzofurans[7] (**3** and **9**) in the presence of polyphosphoric acid afforded the corresponding 6-acyl compounds (**5a**, **5b**, **5c**, **11a**, **11b**, and **11c**), while the analogous β-phenylpropionylation of the 6-hydroxybenzofuran[8] (**15**) afforded the 5-(β-phenylpropionyl) compound (**16**) (Charts 1—3).

The 6-acyl-5-hydroxy compounds (**5a** and **5b**) were also obtained by the Friedel-Crafts acylation of the methoxybenzofuran (**2**) in carbon disulfide at the reflux temperature, while the β-phenylpropionylation under those conditions afforded the 6-acyl-5-methoxybenzofuran (**4c**), which was then dimethylated to **5c** by heating it with aluminum chloride in nitrobenzene (Chart 1). Royer *et al.*[2] have obtained the 6-acetyl-5-methoxybenzofuran (**4a**) by the Friedel-Crafts acetylation of the 5-methoxybenzofuran (**2**) at room temperature and then changed it to the hydroxyketone (**5a**) by demethylation. The Friedel-Crafts β-phenylpropionylation of the 7-methoxybenzofuran (**8**) afforded mainly the 4-acyl-7-methoxybenzofuran (**10c**), accompanied by a small amount of the 6-acyl-7-hydroxy compound (**11c**) (Chart 2) analogously



1 **2** **4c** **6** **3** **5a, b, c**

For all Chart: a) R=H, b) R=Ph, c) R=CH_2Ph

Chart 1

1) The major part of this work was presented at the 23rd Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1970.

2) R. Royer, E. Bisagni, A.-M. Laval-Jeantet, and J.-P. Marquet, *Bull. Soc. Chem. Fr.*, **1965**, 2607.

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

4) Y. Kawase, M. Nanbu, F. Miyoshi, and H. Kawamura, *ibid.*, **41**, 2683 (1968).

5) Preliminary report: Y. Kawase, *Chem. Ind.* (London), **1970**, 687.

6) The reported cyclization by sulfuric acid or other reagents afforded a mixture of the 6- and 4-methoxybenzofurans (Ref. 7 and 8); their ratio was determined to be 97 : 3 in the case of sulfuric acid by estimating the areas of the peaks corresponding to each of the 3-methyl protons in the NMR spectrum (Ref. 5).

7) R. Royer, E. Bisagni, C. Hudry, A. Cheutin, and M.-L. Desvoye, *Bull. Soc. Chim. Fr.*, **1963**, 1003.

8) E. Bisagni and R. Royer, *ibid.*, **1962**, 925.

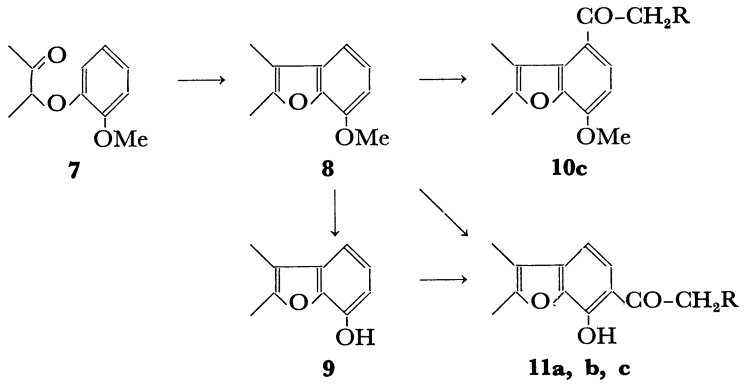


Chart 2

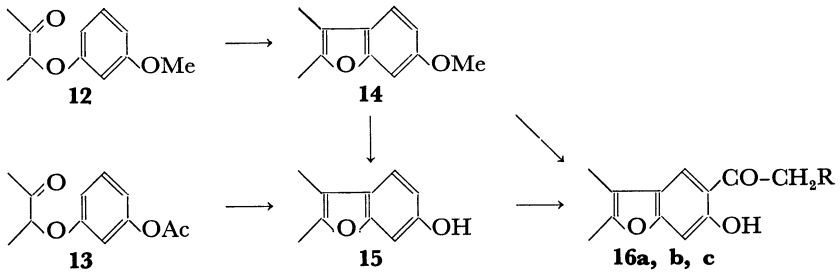


Chart 3

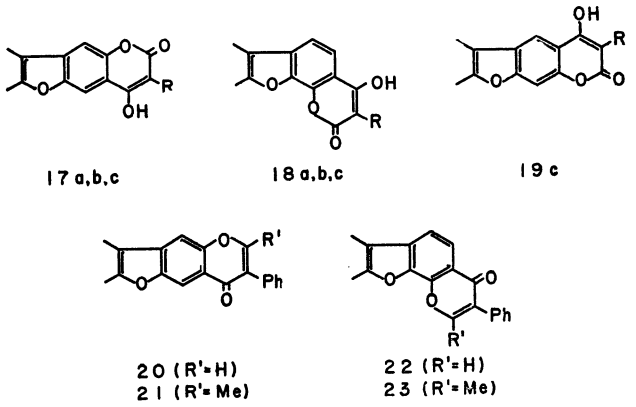


Chart 4

to what has been reported in the case of the acetylation.[2] The analogous β- phenylpropionylation of the 6-methoxybenzofuran (**14**) aforded also the 5-acyl-6-hydroxybenzofuran (**16c**), similarly as has been reported in the cases of the acetylation and phenylacetylation.[3] The Friedel-Crafts acetylation of **2** with a double amount of the reagents afforded the diacetyl compound (**6**), analogously to the cases of 5-methylbenzofuran[9] and 7-methoxybenzofuran.[2]

The positions of the acyl groups in the acylation product were determined by NMR spectroscopy; the methoxyketone (**4c**) and hydroxyketones (**5a**, **5b**, **5c**, and **16c**) have two singlets corresponding to two aromatic para protons, while the methoxyketone (**10c**) and hydroxyketones (**11a**, **11b**, and **11c**) have two doublets of J=8 Hz corresponding to two aromatic ortho protons (Table 3).

The hydroxyketones (**5a**, **5b**, **5c**, **11a**, **11b**, **11c**, and **16c**) thus obtained were converted to dimethylfuro derivatives of 4-hydroxycoumarins (**17a**, **17b**, **17c**, **18a**, **18b**, **18c**, and **19c**) by the action of diethyl carbonate and sodium,[4] and to dimethylfuro derivatives of isoflavones (**20**, **21**, **22**, and **23**) by the action of ethyl orthoformate and piperidine in pyridine or acetic anhydride and sodium acetate.[3] The furocoumarins (**17c**, **18c**, and **19c**) were also prepared by the thermal condensation of the hydroxybenzofurans (**3**, **9**, and **15**) with diethyl benzylmalonate, analogously as has been reported in the cases of 3-phenylfurocoumarins[10] (**17b**, **18b**, and **19b**) (Chart 4).

Experimental

All the melting points and boiling points are uncorrected. The IR spectra were measured as KBr disks on a Hitachi EPI-S spectrophotometer, the UV spectra were measured on a Hitachi 139 spectrophotometer, the NMR spectra were measured on a JEOL JNM-C-60H (60 MHz) spectrometer, and the mass spectra were measured on a JEOL JMS-OlS spectrometer. The detailed data are summarized in Tables 1—4.

The Preparation of Methoxybenzofurans. A mixture of 3-(*p*-methoxyphenoxy)-2-butanone[7] (**1**) (3 g) and polyphosphoric acid (n=2.5, 60 g) was heated at 100°C for 1 hr, after which the cooled mixture was poured into ice water. The mixture was extracted with ether, and the residual product from the ethereal solution was distilled to give methoxybenzofuran (**2**), bp 143—147°C/21 mmHg (lit,[7] bp 133—134°C/11 mmHg); 1.5 g (55%). Similarly, **8** and

9) R. Royer, Y. Kawase, M. Hubert-Habart, L. René, and A. Cheutin, *Bull. Soc. Chim. Fr.*, **1966**, 211.

10) J. -P. Lechartier, P. Demerseman, A. Cheutin, and R. Royer, *ibid.*, **1966**, 1716.

Table 1. Summarized data of reactions

Starting compd.	Reagent	Prod.	Mp °C(solv[a]) or bp °C/mmHg	Yield %
	Preparation of Aryloxybutanone			
b)	Cl-butanone	**13**	145—150/7	72.5
	Preparation of Methoxy- and Hydroxybenzofurans			
1	PPA[c]	**2**	143—147/21[d]	55
7	PPA	**8**	143—147/25[e]	59
12	PPA	**14**	141—144/21[f]	81
13	H_2SO_4	**15**	105—107 (Et)[g]	17
	Preparation of Methoxy- and Hydroxyketones			
2	$PhCH_2CH_2COCl - AlCl_3$	**4c**	105—108 (Et)	60
2	$AcCl - AlCl_3$	**5a**	140—141 (Et)[h]	81
3	AcOH - PPA	**5a**	140—141 (Et)[h]	39
2	$PhCH_2COCl - AlCl_3$	**5b**	134—135 (Et)	58
3	$PhCH_2CO_2H$ - PPA	**5b**	134—135 (Et)	15
3	$PhCH_2CH_2CO_2H$ - PPA	**5c**	139—140.5 (Et)	31.5
4c	$AlCl_3$	**5c**	139—140.5 (Et)	34
2	$AcCl - AlCl_3$	**6**	150.5—151 (Et)	67
8	$PhCH_2CH_2COCl - AlCl_3$	**10c**[i]	64—66 (Me)	42
		11c	98—98.5 (Me)	6
9	AcOH - PPA	**11a**	127—129.5 (Et)[j]	41
9	$PhCH_2CO_2H$ - PPA	**11b**	159.5—161.5 (Et)	48.5
9	$PhCH_2CH_2CO_2H$ - PPA	**11c**	98—98.5 (Et)	36
14	$PhCH_2CH_2COCl - AlCl_3$	**16c**[k]	100—101 (Et)	2
15	$PhCH_2CH_2CO_2H$ - PPA	**16c**	100—101 (Et)	8
	Preparation of Furocoumarins			
5a	$CO(OEt)_2 - Na$	**17a**	308 (Et)	67.5
5b	$CO(OEt)_2 - Na$	**17b**	284—285 (Et)[l]	72.5
3	$PhCH_2CH(CO_2Et)_2$	**17c**	285—286 (Et)	55
5c	$CO(OEt)_2 - Na$	**17c**	285—286 (Et)	30
11a	$CO(OEt)_2 - Na$	**18a**	310 (Et)	29.5
11b	$CO(OEt)_2 - Na$	**18b**	283—284 (Et)[m]	52
9	$PhCH_2CH(CO_2Et)_2$	**18c**	283.5—285 (Et)	42
11c	$CO(OEt)_2 - Na$	**18c**	283.5—285 (Et)	21
15	$PhCH_2CH(CO_2Et)_2$	**19c**	269—270 (Et)	8
16c	$CO(OEt)_2 - Na$	**19c**	269—270 (Et)	74
	Preparation of Furoisoflavones			
5a	$CH(OEt)_3$	**20**	233—234 (Et)	97
5a	Ac_2O - AcONa	**21**	150.5—151.5 (Et)	28
11a	$CH(OEt)_3$	**22**	216—217 (Et)	85
11a	Ac_2O - AcONa	**23**	198—201 (Et)	61

a) Et: ethanol, Me: methanol. b) *m*-Acetoxyphenol. c) Polyphosphoric acid. d) Lit. bp 133—134°C/11 mmHg (Ref. 7). e) Lit. bp 136°C/12 mmHg, mp 38.5°C (Ref. 7). f) Lit. bp 128—129°C/9 mmHg (Ref. 7). g) Lit. mp 107.5—108°C (Ref. 8). h) Lit. mp 141°C (Ref. 2). i) The crude product was crystallized from methanol to give **11c**, and **10c** was obtained from the mother solution. j) Lit. mp 130°C (Ref. 2). k) The crude product was distilled to give fraction a, bp 134—140°C/20 mmHg, and fraction b, bp 150—170°C/20 mmHg. The fraction b was crystallized to give **16c**, and the fraction a was purified by chromatography on silica gel, with cyclohexane and then benzene as the solvent, to give the recovery **14** (total 39%) and indanone (total 68%). l) Lit. mp 187°C (Ref. 10). m) Lit. mp 287°C (Ref. 10).

14 were also prepared by this procedure.

The Preparation of Hydroxybenzofurans. Hydroxybenzofurans (**3**, **9**, and **15**) were prepared by the demethylation of the methoxybenzofurans (**2**, **8**, and **14**) by following the methods of Refs. 7 and 8. Compound **15** was also prepared by the cyclization of **13** as follows:

*The Preparation of 3-(m-Acetoxyphenoxy)-2-butanone (**13**).* A mixture of *m*-acetoxyphenol (28 g), 3-chloro-2-butanone (20.5 g), acetone (150 m*l*), and anhydrous potassiun carbonate (70 g) was refluxed for 8 hr; the mixture was treated with water and then extracted with ether. The residual product from the ethereal solution was distilled to give **13**, bp 145—150°C/7 mmHg; 29.6 g (72.5%).

*The Cyclization of **13**.* Concentrated sulfuric acid (20 m*l*) was stirred into **13** (13.5 g) with cooling below 15°C, after which the mixture was kept at 15°C for 1 hr. The resulting mixture was poured into ice water and extracted with ether. The residual product from the ethereal solution was crystallized from cyclohexane to give **15**, mp 105—107°C (lit,[7] mp 107.5—108°C); 1.7 g (17%).

TABLE 2. THE IR SPECTRA AND ANALYSIS OF NEW COMPOUNDS

Compd.	ν_{CO}^{KBr}	Formula	Found C%	Found H%	Calcd C%	Calcd H%	$m/e(M^+)$
			Aryloxybutanone				
13	1775 1729	$C_{12}H_{14}O_4$	64.82	6.45	64.85	6.35	
			Methoxy- and Hydroxy-ketones				
4	1664	$C_{20}H_{20}O_3$	77.68	6.49	77.90	6.54	308
5b	1655	$C_{18}H_{16}O_3$	77.00	5.70	77.12	5.75	280
5c	1658	$C_{19}H_{18}O_3$	77.51	6.12	77.53	6.16	294
6	1671 1626	$C_{14}H_{14}O_4$	68.21	5.44	68.28	5.73	246
10c	1674	$C_{20}H_{20}O_3$	77.85	6.51	77.90	6.54	308
11b	1664	$C_{18}H_{16}O_3$	76.96	5.74	77.12	5.75	280
11c	1658	$C_{19}H_{18}O_3$	77.75	6.30	77.53	6.16	294
16c	1632	$C_{19}H_{18}O_3$	77.69	6.21	77.53	6.16	294
			Furocoumarins				
17a	1692	$C_{13}H_{10}O_4$	68.02	4.39	67.82	4.38	230
17c	1670	$C_{20}H_{16}O_4$	75.10	4.80	74.99	5.03	320
18a	1678	$C_{13}H_{10}O_4$	67.51	4.38	67.82	4.38	230
18c	1672	$C_{20}H_{16}O_4$	75.21	4.83	74.99	5.03	320
19c	1650	$C_{20}H_{16}O_4$	74.95	5.12	74.99	5.03	320
			Furoisoflavones				
20	1625	$C_{19}H_{14}O_3$	78.60	4.82	78.60	4.85	290
21	1637	$C_{20}H_{16}O_3$	78.79	5.19	78.93	5.30	304
22	1637	$C_{19}H_{14}O_3$	78.56	4.80	78.60	4.85	290
23	1635	$C_{20}H_{16}O_3$	78.73	5.35	78.93	5.30	304

TABLE 3. THE NMR SPECTRA[a)]

Compd.	Ph-H of benzofuran[b)]	Ph-H	2-Me	3-Me
	Methoxybenzofurans			
2			2.32	2.08
8			2.35	2.10
14			2.24	2.00
c)			2.24	2.24
	Methoxy- and Hydroxyketones			
4c	7H 7.60 4H 6.67	7.12	2.30	2.05
5a	7H 7.54 4H 6.76		2.36	2.08
5b	7H 7.61 4H 6.75	7.25	2.32	2.04
5c[d)]	7H 7.60 4H 6.85	7.26	2.34	2.06
6[d)]	7.70		2.37	1.97
10c	5H 7.31(d) 6H 6.48(d) J=8 Hz	7.14	2.35	2.10
11a[d)]	5H 7.49(d) 4H 6.88(d) J=8 Hz		2.41	2.12
11b	5H 7.52(d) 4H 6.73(d) J=8 Hz	7.24	2.43	2.12
11c	5H 7.39(d) 4H 6.70(d) J=8 Hz	7.17	2.38	2.08
16a	4H 7.40 7H 6.68		2.28	2.03
16b[d)]	4H 7.82 7H 6.91	7.34	2.33	2.11
16c	4H 7.48 7H 6.75	7.18	2.28	2.05

a) δ-Values in CCl_4 (about 5% solution), with TMS as the internal standard. b) d: Doublet. c) 2,3-Dimethyl-4-methoxybenzofuran. d) In $CDCl_3$.

The Acylation of the Hydroxybenzofuran with Carboxlyic Acid and Polyphosphoric Acid (PPA). A mixture of **3**[7] (2.4 g), acetic acid (1 g), and PPA (n=1.5, 45 g) was heated at 100°C for 1 hr. The cooled mixture was poured into ice water and then extracted with chloroform. The residual product from the chloroform solution was crystallized from ethanol to give **5a**, mp 140—141°C (lit,[2] mp 141°C); 1.3 g (39%). Similarly, the acetyl, phenylacetyl, and β-phenylpropionyl compounds (**11a**, **5b**, **11b**, **5c**, **11c**, and **16c**) were also prepared by this procedure.

The Friedel-Crafts Acylation of the Methoxybenzofurans. Powdered aluminum chloride (9.7 g) was added, with stirring and cooling, to a solution of **2**[7] (5 g) and acetyl chloride (2.5 g) in carbon disulfide (50 m*l*); the mixture was stirred

Table 4. The UV spectra

Compd.	λ_{max}^{EtOH} mμ[a] (log ε)
	Methoxybenzofurans
2	214(4.33), 255(4.02), 292.5(3.68), 301(3.62)
8	217(4.41), 251(4.09), 285(3.01)
14	217(4.24), 249(4.06), 256(4.06), 292(3.72)
b)	215.5(4.34), 258(4.08), 276[s](3.55), 287(3.45)
	Hydroxybenzofurans
3	216(5.36), 255(5.13), 295(4.73)
9	216(4.36), 250(4.12), 255.5(4.12), 286(3.16)
15	216(5.36), 248(5.09), 255(5.08), 293(4.76)
c)	218(5.35), 252(5.03), 281(4.44), 289(4.41)
	Hydroxyketones
5a	230(4.20), 316(4.30)
5b	213.5(4.18), 231(4.22), 318(4.33)
11a	239(4.33), 296(4.16), 336(3.96)
11b	211(4.38), 239(4.32), 301(4.17), 341(4.01)
16a	240(4.56), 267(3.97), 360(3.55)
16b	240(4.55), 360(3.57)
d)	243(4.49), 265.5(3.98), 280.5(3.82), 345(3.51)
e)	211.5(4.16), 244(4.50), 253(4.47), 283(3.95), 348(3.56)
	Furocoumarins
17a	214(4.50), 323(4.49), 338(4.28)
17b	216(4.55), 332(4.42), 342[s](4.40)
17c	216(4.52), 328.5(4.33), 340(4.25)
18a	212(4.40), 239.5(4.45), 245.5(4.44), 265[s](3.98), 285[s](3.92), 296(4.04), 323.5(4.06)
18b	215.5(4.45), 236.5(4.38), 250[s](4.33), 302[s](4.00), 332(4.22)
18c	217(4.49), 249(4.36), 300.5(4.03), 326(4.11)
19c	216(4.47), 246(4.46), 253(4.40), 301(4.14), 320(4.11), 331[s](4.08)
	Furoisoflavones
20	253(4.43), 315(4.25)
21	240(4.43), 312(4.28)
22	261(4.59), 311(4.03)
23	257(4.57), 309(4.08)

a) s: Shoulder. b) 2,3-Dimethyl-4-methoxybenzofuran. c) 2,3-Dimethyl-4-hydroxybenzofuran. d) 2,3-Dimethyl-4-hydroxy-5-benzofuranyl methyl ketone. e) 2,3-Dimethyl-4-hydroxy-5-benzofuranyl benzyl ketone.

at room temperature for 2 hr and then at the reflux temperature for 1 hr. The cooled mixture was poured into ice water containing hydrochloric acid and extracted with chloroform. The chloroform solution was washed with an aqueous sodium hydroxide solution, and the residual product from the chloroform solution was crystallized from ethanol to give **5a**, mp 140—141°C, identical with the sample described above. Yield, 4.7 g (81%). Similarly, **5b** was obtained by the action of phenylacetyl chloride, while the methoxyketone (**4c**) was obtained in the case of β-phenylpropionyl chloride. The β-phenylpropionylation of **8** afforded a small amount of **11c** and a fairly large amount of the methoxyketone (**10c**), while that of **14** afforded a small amount of **16c** and fairly large amounts of the recovered **14** and indanone. The diacetylation of **2** afforded the hydroxydiketone (**6**).

*The Demethylation of the Methoxyketone (**4c**).* A mixture of **4c** (1.4 g), nitrobenzene (40 m*l*), and powdered aluminum chloride (0.9 g) was heated at 100°C for 1 hr. The cooled mixture was poured into dilute hydrochloric acid, and the nitrobenzene was removed by steam distillation. The residual precipitates obtained were crystallized from ethanol to give **5c**, mp 139—140.5°C, identical with the sample described above. Yield, 0.46 g (34%).

The Preparation of Furocoumarins. *a) From the Hydroxyketones*: Small pieces of sodium (1.1 g) was added to a mixture of **5a** (1.1 g) and diethyl carbonate (40 m*l*), after which the mixture was heated at 110—120°C for 30 min. The cooled mixture was treated with a small amount of methanol and with water, and was then extracted with ether. The aqueous layer was acidified, and the crystalline precipitates thus formed were recrystallized from ethanol to give 6*H*-8-hydroxy-2,3-dimethylfuro[2,3-*g*][1]benzopyran-6-one (**17a**), mp 308°C (dec.); 0.8 g (67.5%). Similarly, 7-phenyl and 7-benzyl derivatives (**17b** and **17c**) of **17a**, 8*H*-6-hydroxy-2,3-dimethylfuro[3,2-*h*][1]benzopyran-8-one (**18a**) and its derivatives (**18b** and **18c**), and 7*H*-6-benzyl-5-hydroxy-2,3-dimethylfuro[3,2-*g*][1]benzopyran-7-one (**19c**) were also prepared by this procedure.

b) From the Hydroxybenzofurans: A mixture of **3** (0.5 g) and diethyl benzylmalonate (2.5 g) was refluxed for 8 hr. The cooled mixture was washed with ether, and the residual solid was crystallized from ethanol to give **17c**, mp 285—286°C, identical with the sample described above. Yield, 0.54 g (55%). Similarly, **18c** and **19c** were also prepared by this procedure.

The Preparation of Furoisoflavones. *a) By the Action of Ethyl Orthoformate*: A mixture of the hydroxyketone **5b** (0.4 g), ethyl orthoformate (4 g), piperidine (1 drop), and pyridine (16 m*l*) was refluxed for 8 hr, after which the cooled mixture was poured into dilute hydrochloric acid to form crystalline precipitates, which were then recrystallized from ethanol to give 8*H*-2,3-dimethyl-7-phenylfuro[2,3-*g*][1]benzopyran-8-one (**20**), mp 233—234°C; 0.4 g (97%). Similarly, 6*H*-2,3-dimethyl-7-phenylfuro[3,2-*h*][1]benzopyran-6-one (**22**) was also prepared by this procedure.

b) By the Action of Ac_2O-AcONa: A mixture of **5b** (0.5 g), anhydrous sodium acetate (2 g), and acetic anhydride (10 m*l*) was refluxed for 12 hr, the cooled mixture was then poured into water to form crystalline precipitates, which were recrystallized from ethanol to give the 6-methylderivative (**21**) of **20**, mp 150.5—151.5°C; 0.15 g (28%). Similarly, the 8-methyl derivative (**23**) of **22** was also prepared by this procedure.

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