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The Synthesis of 4-Hydroxyfuro[2′,3′:7, 8]coumarins and 5*H*-Benzofuro[3,2-*c*]furo[2,3-*h*][1]benzopyran-5-one*[1]

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4-Hydroxyfuro[2′,3′:7,8]coumarin (16) and its 3-phenyl (10) and 3-(2-methoxyphenyl) (11) derivatives were prepared from the corresponding 4-hydroxy-5-benzofuranyl ketones (15, 8a and 8b) by the action of ethyl carbonate and sodium. The furocoumarin 11 thus obtained was converted to 5*H*-benzofuro[3,2-*c*]furo[2,3-*h*][1]benzopyran-5-one (18), a compound having a new pentacyclic ring system, by the demethyl-cyclization with pyridine hydrochloride, hydroiodic acid or aluminum chloride. The attempted preparation of these compounds through their dihydro compounds is also described; 2,3-dihydro-4-hydroxybenzofuran (1) was acylated with phenylacetic acid, with 2-methoxyphenylacetic acid or with 2,4,5-trimethoxyphenylacetic acid by the action of polyphosphoric acid to give a mixture of the 5- and 7-acylated compounds (3 and 2), and the formers were converted to the corresponding 4″,5″-dihydrofuro[2″,3″:7,8]isoflavones (6), 4″,5″-dihydro-2-methylfuro-[2″,3″:7,8]isoflavones (4) and 4′,5′-dihydro-4-hydroxyfuro[2′,3′:7,8]coumarins (7). The 2,3-dihydro-4-hydroxy-5-benzofuranyl benzyl ketone (3a) and the dihydrofuroisoflavones (4a and 4b) were also obtained by the catalytic reduction of the corresponding furo-compounds.

In previous papers, one of the authors and others reported the synthesis of furo[2″,3″ : 7,8]isoflavones,[1] 4-hydroxycoumarins,[2] and benzofuro[3′,2′:3,4]coumarins.[3] Now in this paper, the preparation of closely related 4-hydroxyfuro[2′,3′:7,8]coumarins (10, 11, 16, 17 and 19) and 5*H*-benzofuro[3,2-*c*]-furo[2,3-*h*][1]benzopyran-5-one (18) and the attempted preparation of them through their dihydro compounds will be reported. The synthesis of isomeric 4-hydroxyfuro[3′,2′ : 6,7]coumarins[4] and 6*H*-benzofuro[3,2-*c*]furo[3,2-*g*][1]-benzopyran-6-one derivative (erosnin),[4b] having linearly fused furan ring, has recently been reported by Fukui and Nakayama and others, and that of dimethylfuro-derivatives of 4-hydroxy-3-phenylcoumarin by the thermal condensation of dimethylhydroxybenzofurans with ethyl phenylmalonate has been reported by Royer *et al.*[5]

In the case of isomeric compounds, 2,3-dihydro-6-hydroxybenzofuran was acylated to give the 5-acyl compounds,[6] which were converted to the corresponding dihydrofuro-4-hydroxycoumarins[4,7] and -isoflavones[8] which were further dehydrogenated to the furo-compounds, as the direct acylation of hydroxybenzofurans to give the *o*-hydroxyketones, the convenient starting materials for 4-hydroxycoumarins and isoflavones, was not successful although the acetylation of 2-substituted[9] or 2,3-dimethyl[10] 6-hydroxy- or 6-methoxy-benzofurans gave the 5-acyl compounds. But the dehydrogenation to give 4-hydroxyfurocoumarins was accomplished only in some cases with difficulty or indirectly.[4] Accordingly, the furocoumarins were also prepared[4a,b] by the pyrone ring formation on hydroxybenzofuranyl ketones which were obtained by alkaline degradation of furoisoflavones or by hydrolysis followed by

*1 A part of this was presented at the 20th Annual Meeting of the Chemical Society of Japan, Tokyo, March, 1967.

1) T. Matsumoto, Y. Kawase, M. Nanbu and K. Fukui, This Bulletin, **31**, 688 (1958); K. Fukui and Y. Kawase, *ibid.*, **31**, 693 (1958); Y. Kawase, K. Ogawa, S. Miyoshi and K. Fukui, *ibid.*, **33**, 1240 (1960).

2) Y. Kawase, *Experientia*, **14**, 435 (1958); This Bulletin, **31**, 440 (1958); **32**, 9, 11 (1959); **35**, 1869 (1962).

3) Y. Kawase, *ibid.*, **32**, 690 (1959); **35**, 573 (1962).

4) a) K. Fukui and M. Nakayama, *Nippon Kagaku Zasshi* (*J. Chem. Soc. Japan, Pure Chem. Sect.*), **85**, 444 (1964).
b) K. Fukui and M. Nakayama, *Tetrahedron Letters*, **1965**, 2559. c) A. Vialard-Goudon and N. Blanchecatte, *Compt. Rend.*, **263**, 255 (1966).

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

6) J. S. H. Davies, P. A. McCrea, W. L. Norris and G. R. Ramage, *J. Chem. Soc.*, **1950**, 3206.

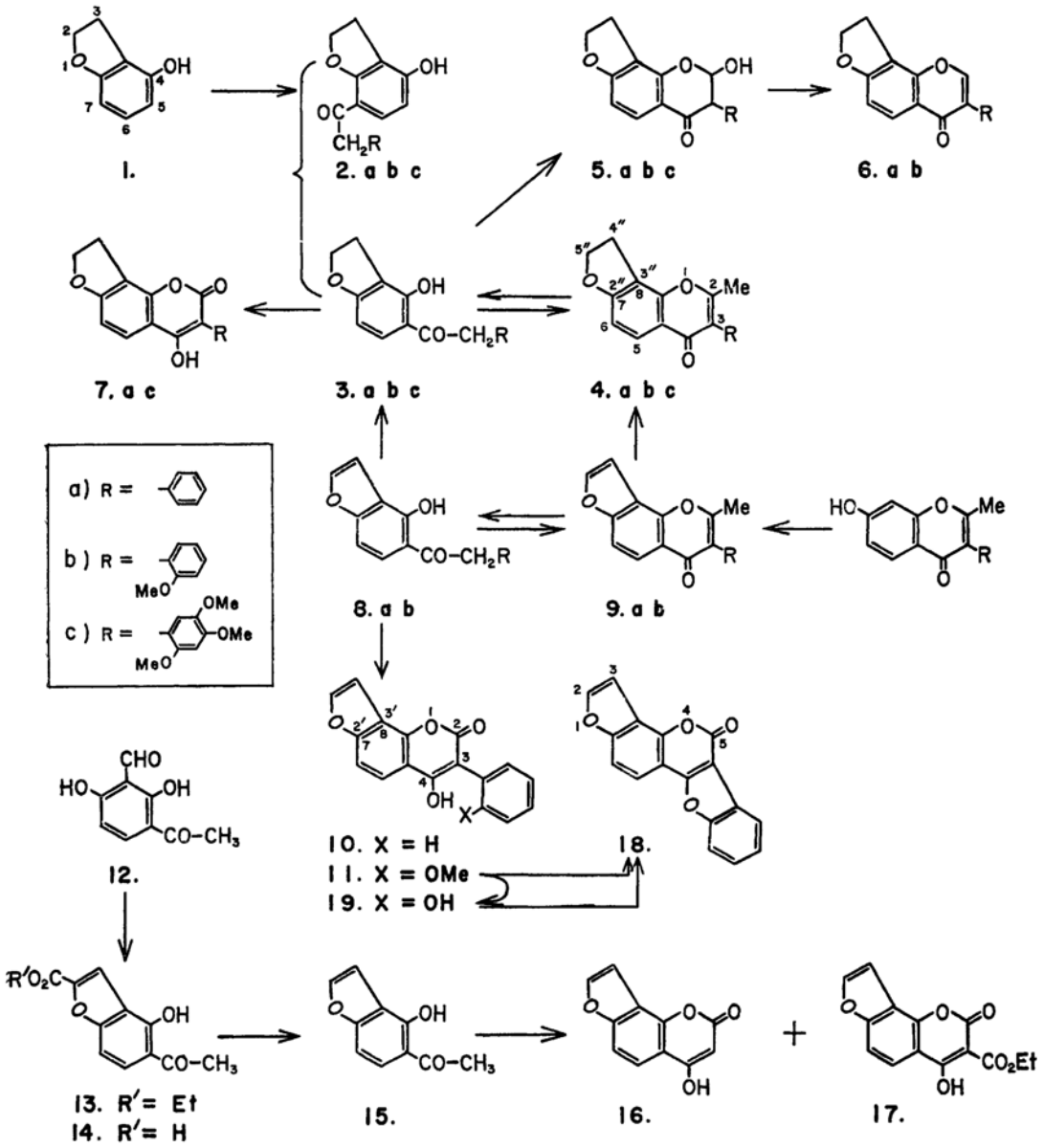
7) E. C. Horning and D. B. Reisner, *J. Am. Chem. Soc.*, **72**, 1514 (1950).

8) S. K. Pavanaram, L. R. Row and T. R. Seshadri, *J. Sci. Ind. Res.* (*India*), **15B**, 495 (1956); S. K. Pavanaram and L. R. Row, *Current Science* (*India*), **26**, 145 (1957); K. Fukui and M. Nakayama, *Experientia*, **19**, 621 (1963); **20**, 668 (1964); K. Fukui, M. Nakayama, A. Tanaka and S. Sasatani, This Bulletin, **38**, 845 (1965); A. S. R. Anjaneyulu, C. S. Krishna and L. R. Row, *Tetrahedron*, **21**, 2677 (1965).

9) P. K. Ramachandran, A. T. Tefteller, G. O. Paulson, T. Cheng, C. T. Lin and W. J. Horton, *J. Org. Chem.*, **28**, 398 (1963); J. Oda H. Fukami and M. Nakajima, *Agr. Biol. Chem.*, **30**, 59 (1966).

10) R. Royer, E. Bisagni, A.-M. Laval-Jeantet and J.-P. Marquet, *Bull. Soc. Chim. France*, **1965**, 2607.

Chart



decarboxylation of acetyl-methoxybenzofuran-2-carboxylate.

Concerning the acylation of 2,3-dihydro-4-hydroxybenzofuran, Seetharamiah[11] reported the acylation of it according to the Hoesch reaction to give the 7-acyl compound while Miyano and Matsui[12] reported the analogous reaction of 2-alkyl compounds to give a mixture of the 5- and 7-acyl compounds, and Dyke *et al.*[13] reported the analogous reaction of 2-isopropyl derivative and the further convertion to the furoisoflavone through its dihydro-compound. On the other hand, Seshadri *et al.*[14] prepared 4″,5″-dihydro-4″-methylfuro[2″,3″ : 7,8]-isoflavone through another route and converted it to the furoisoflavone.

First, in the present experiments the acylation of

11) A. Seetharamiah, *J. Chem. Soc.*, **1948**, 894.
12) M. Miyano and M. Matsui, *Proc. Japan Acad.*, **35**, 175 (1959); *Chem. Ber.*, **92**, 2487 (1959); **93**, 54 (1960); M. Miyano, A. Kobayashi and M. Matsui, *Bull. Agr. Chem. Soc. Japan*, **24**, 540 (1960).
13) S. F. Dyke, W. D. Ollis and M. Sainsburg, *J. Chem. Soc.* (*c*), **1966**, 748.
14) P. S. Sarin, J. M. Sehgal and T. R. Seshadri, *J. Sci. Ind. Res.* (*India*), **16B**, 61, 206 (1957).

2,3-dihydro-4-hydroxybenzofuran (1) and the convertion of the products to dihydrofuro and then to furo derivatives of 4-hydroxycoumarins and isoflavones were studied. The acylation of 1 with phenylacetic acid, with 2-methoxyphenylacetic acid or with 2,4,5-trimethoxyphenylacetic acid by the action of polyphosphoric acid (PPA) furnished a mixture of the 5- and 7-acylated compounds (3a, b, c and 2a, b, c). The acylation by the Hoesch reaction with phenylacetonitrile furnished as well the ketones 2a and 3a, but with 2-methoxyphenylacetonitrile in poorer yield.

The 5-acyl compounds (3a, b, c), separated from the alkali-soluble isomeric 7-acyl compounds (2a,b,c), were converted to the corresponding 4″,5″-dihydro-2-methylfuro[2″,3″7,8]isoflavones (4a, b, c) by the action of acetic anhydride and sodium acetate, and the alkaline degradation of 4a furnished the starting ketone 3a. The ketone 3a and the dihydrofuroisoflavones 4a and 4b were also obtained by the catalytic reduction of the corresponding benzofuranyl ketone[1] (8) and furoisoflavones[1] (9a, b), respectively.

These experiments, their analyses, their infrared and ultraviolet spectra and the analogous acylation described before furnished the proof for the structures of the ketones (2a, b, c and 3a, b, c) and the isoflavones (4a, b, c).

The ketones (3a, b, c) were also converted to 4″,-5″-dihydro-2-hydroxyfuro [2″, 3″ : 7,8] isoflavanones (5a, b, c) by the action of ethyl formate and sodium, two (5a and 5b) among which were readily dehydrated to dihydrofuroisoflavones (6a and 6b). 4′,5′-Dihydro-4-hydroxyfuro[2′,3′:7,8]coumarins (7a and 7c) were also prepared from the ketones by the general method utilizing ethyl chlorocarbonate.

The attempts to dehydrogenate these compounds to the corresponding furo-compounds were unsuccessful.

Then, the 4-hydroxy-5-benzofuranyl ketones (8a and 8b) were prepared through another route by the alkaline degradation of the corresponding furoisoflavones[1] (9a and 9b), and 4-hydroxyfuro[2′,3′:7,8]-coumarins (10 and 11) were synthesized from these ketones by the general method utilizing ethyl carbonate and sodium. 4-Hydroxy-5-benzofuranyl methyl ketone[15] (15) was prepared, in the present experiments, from 2,4-dihydroxy-3-formylphenyl methyl ketone[16] (12) by the action of ethyl bromomalonate and potassium carbonate followed by the hydrolysis of the produced ester (13) and the decarboxylation of the acid (14). The action of ethyl carbonate and sodium on this ketone (15) furnished analogously 4-hydroxyfuro[2′,3′;7,8]coumarin (16) accompanied by a small amount of its 3-ethoxycarbonyl derivative (17); the formation of the latter seems to be the result of double ethoxycarbonylation of the ketone. The structures of these compounds were considered from their analyses and their infrared and ultraviolet spectra.

The 4-hydroxy-3-(2-methoxyphenyl)furocoumarin (11) thus obtained was converted to benzofuro-furobenzopyranone. The reported methods for the synthesis of 6*H*-benzofuro[3,2-c][1]benzopyran-6-ones are (a) by the demethyl-cyclization of 4-hydroxy-3-(2-methoxyphenyl)coumarins,[17] (b) by the hydrolytic cyclization of methoxy derivatives of α-benzoylacetonitrile,[3,18] (c) by the oxidative coupling of 4-hydroxycoumarins with catechol[19] and (d) by the oxidation of flavylium salts.[20] The isomeric 6*H*-benzofuro[3,2-*c*]furo[3,2-*g*][1]benzopyran-6-one derivative (erosnin) was synthesized by the method (c)[4] and the dihydrofuro analogues of it were synthesized by the methods (a),[21] (b),[22] and (c).[21]

In the present experiments, the method (a) was applied to the hydroxyfurocoumarin 11; the action of pyridine hydrochloride or hydroiodic acid on 11 furnished 5*H*-benzofuro[3,2-*c*]furo[2,3-*h*][1]benzopyran-5-one (18), a compound having a new pentacyclic ring system, and the action of aluminum chloride in nitrobenzene caused only the demethylation of the methoxy group to give 4-hydroxy-3-(2-hydroxyphenyl)furocoumarin (19), which was further converted to 18 by heating it with methanolic hydrogen chloride. The structures of these compounds were verified from their analyses and their infrared and ultraviolet spectra.

In the infrared spectra, the dihydrofuroisoflavones (4a, b, c and 6a, b) have their ν_{CO} at 1650—1635 cm^{-1}, characteristic for chromones, while dihydrofuro- (7a and 7c) and furocoumarins (10, 11, 16, 17 and 19) have their broad ν_{OH} at 3100—2950 cm^{-1} and their ν_{CO} at 1710—1660 cm^{-1}, characteristic for hydroxy-coumarins. Benzofuro-furobenzopyranone (18) has its ν_{CO} at somewhat higher wave number region, 1760 cm^{-1}. These data are comparable to those of the isomeric compounds having linearly fused furan ring.[4]

The ultraviolet absorption spectra were measured in ethanol and it proved that the dihydrofuroisoflavones (4a and 6a) have almost similar shape of absorption curves with that of the furo-compounds,[1] having high peaks at 245—250 mμ and low peaks at 305 mμ (Fig. 1), and the 3-(methoxyphenyl)

15) C. B. Rao, G. Subramayam and V. Venkateswarlu, *J. Org. Chem.*, **24**, 683 (1959).
16) K. Nakazawa, *J. Pharm. Soc. Japan*, **59**, 297 (1939).
17) W. J. Bowyer, A. Robertson and W. Whalley, *J. Chem. Soc.*, **1957**, 542; T.R. Govindachari, K. Nagarajan and P. C. Parthasarathy, *ibid.*, **1957**, 548; O. H. Emerson and E. M. Bickoff, *J. Am. Chem. Soc.*, **80**, 4381 (1958).
18) J. N. Chatterjea and S. K. Roy, *J. Indian Chem. Soc.*, **34**, 98 (1957); J. N. Chatterjea, *ibid.*, **36**, 256 (1959).
19) H. Wanzlick, R. Gritzky and H. Heidepriem, *Chem. Ber.*, **96**, 305 (1963).
20) L. Jurd, *Tetrahedron Letters*, **1963**, 1151; *J. Org. Chem.*, **29**, 3036 (1964).
21) K. Fukui *et al.*, Symposium on the Chemistry of Natural Products, Kyoto, Oct., 1965.
22) J. N. Chatterjea and N. Prasad, *Chem. Ber.*, **97**, 1252 (1964).

analogues (4b and 4c) have broader absorption at 220—240 mμ and higher peaks of the 300 mμ region (Fig. 2). Furocoumarins (16 and 17) have high peaks at about 235 mμ and lower ones at 290—300 mμ, and the 3-aryl derivatives (10, 11 and 19) have additional peaks at 217 mμ and broader absorption at 280—330 mμ, while the dihydrofurocoumarins (7a and 7c) have no peaks in the 210—270 mμ region and have higher peaks at about 320 mμ (Figs. 3 and 4). The benzofuro-furobenzopyranone (18) has high peak at 238 mμ and broader absorption at 280—345 mμ having four peaks (Fig. 4). These relations of the ultraviolet spectra are

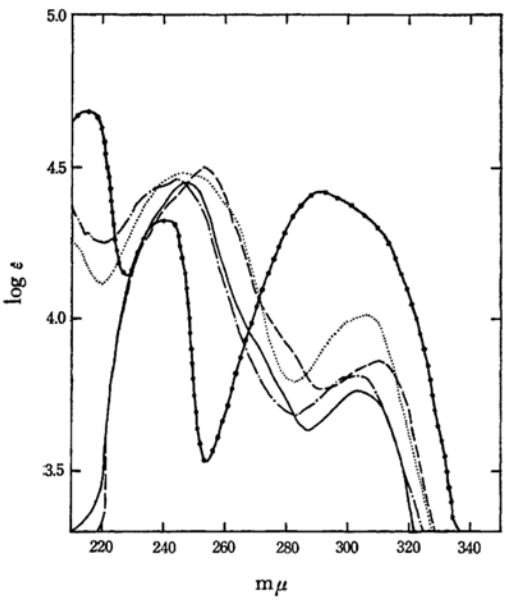


Fig. 1. The UV spectra of furo- and dihydrofuroisoflavones and dihydro-2-hydroxyfuroisoflavanone:
—— 9a*, ---- furoisoflavone* ·—· 4a, ····· 6a, •—• 5a (* from Ref. 1)

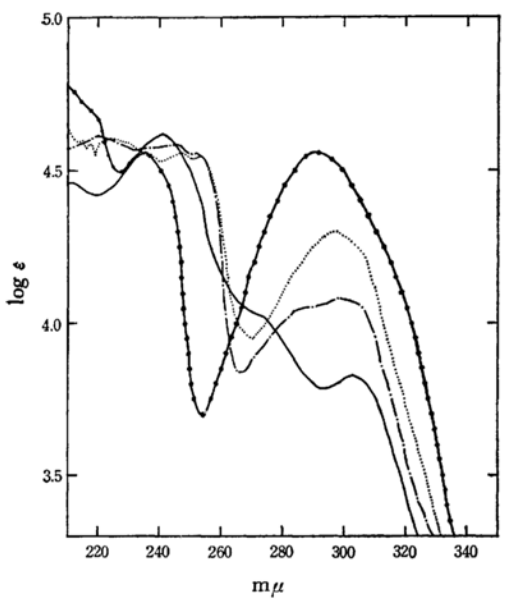


Fig. 2. The UV spectra of furo- and dihydrofuroisoflavones and dihydro-2-hydroxyfuroisoflavanone:
—— 9b, ·—· 4b, ····· 4c, •—• 5c

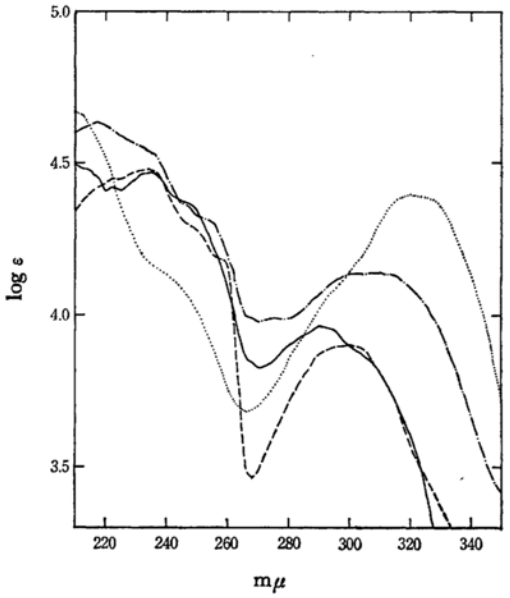


Fig. 3. The UV spectra of furo- and dihydrofurocoumarins:
—— 16, ---- 17, ·—· 10, ····· 7a

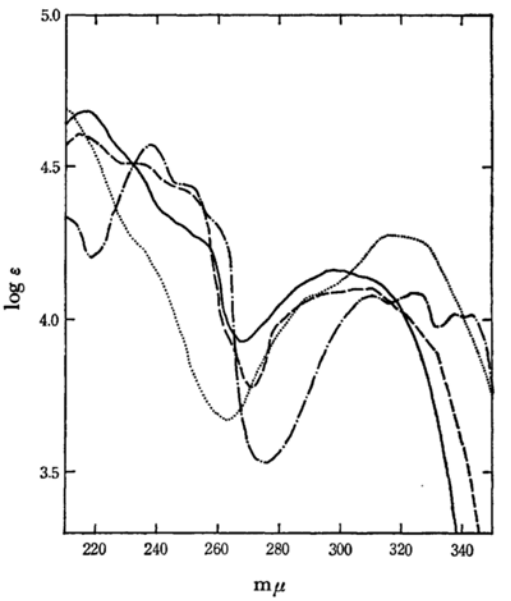


Fig. 4. The UV spectra of furo- and dihydrofurocoumarins and benzofuro-furobenzopyranone:
—— 11, ---- 19, ····· 7c, ·—· 18

TABLE 1. THE ACID-CATALIZED ACYLATION OF COMPOUND 1

Compd.	Acylating agent	Procedure[a], temp. × time	Product composition yield, % 2	3
a	Phenylacetic acid	A, 100°×30′	22	25
a	Phenylacetonitrile	B	24	31
b	2-Methoxyphenylacetic acid	A, 80°×30′	34	28.5
c	2,4,5-Trimethoxyphenylacetic acid	A, 80°×30′	31	28

a) A: PPA, B: Hoesch procedure.

comparable to those of the isomers,[4] except that the absorption band in the 300 mμ region of the isomers appears at the wave length longer by 20 mμ than that of the others.

In conclusion, it seems that the influence of furan ring appears fairly clearly in the absorption of 230—270 mμ region in the case of furocoumarins, but not so clearly in the case of furoisoflavones, probably as coumarins have not or have only weak absorption in that region[23] while isoflavones themselves have already strong absorption in that region,[24] which and that due to furan ring overlap each other.

Experimental*2

Materials. The compound 1 was prepared[11] by the catalytic reduction of the furo-compound and the ketone 8a and furoisoflavones 9a and 9b were prepared according to the Ref. 1. The compound 12 was prepared[16] by the formylation of ethyl resorcylate.

The Preparation of 2,3-Dihydro-4-hydroxy-5-benzofuranyl Ketones and Isomers. *a) By the Acylation of 2,3-Dihydro-4-hydroxybenzofuran* (1) *by Means of Carboxylic Acid and Polyphosphoric Acid (PPA)* (*Table 1*). A mixture of 1 (1 g), phenylacetic acid (1 g, 1 mol equivalent) and PPA (n=1.5, 25 g) was heated at 100°C for 30 min with stirring. The cooled mixture was poured into ice-water and was extracted with ether. The ethereal solution was washed with aqueous sodium bicarbonate, and then was extracted with 5% aqueous sodium hydroxide. The product obtained from the ethereal layer was crystallized from ethanol to give 2,3-dihydro-4-hydroxy-5-benzofuranyl benzyl ketone (3a), having a positive ferric chloride color reaction in ethanol.

The alkaline extract was acidified and extracted with ether. The product obtained from the ethereal solution was crystallized from methanol to give the isomeric 2,3-dihydro-4-hydroxy-7-benzofuranyl benzyl ketone (2a), having a negative ferric chloride color reaction in ethanol.

Similarly, 2,3-dihydro-4-hydroxy-5-benzofuranyl 2-methoxybenzyl ketone (3b) and 2,3-dihydroxy-4-hydroxy-5-benzofuranyl 2,4,5-trimethoxybenzyl ketone (3c) and the isomeric 2,3-dihydro-4-hydroxy-7-benzofuranyl 2-methoxybenzyl ketone (2b) and 2,3-dihydro-4-hydroxy-7-benzofuranyl 2,4,5-trimethoxybenzyl ketone (2c) were also obtained by this method.

b) By the Acylation of 1 by Means of the Hoesch Reaction. (*Table 1.*) Anhydrous powdered zinc chloride (2.5 g) was added to a solution of 1 (1 g) and phenylacetonitrile (1 g, 1 mol equivalent) in anhydrous ether (30 m*l*), and the mixture was saturated with dry hydrogen chloride with stirring and cooling, and then was left 2 days. The upper ethereal layer was decanted off and the residual viscous lower layer was heated on a water-bath for 1 hr with the addition of dilute hydrochloric acid. The cooled mixture was extracted with ether and the ethereal solution was treated similarly as described in the procedure a) to give the ketones 3a and 2a.

c) By the Hydrogenation of Benzofuranyl Ketone (8a). A mixture of 4-hydroxy-5-benzofuranyl benzyl ketone(8a)[1] (0.5 g), palladium carbon (25%, 0.5 g) and ethyl acetate (100 m*l*) was shaken with hydrogen at atmospheric pressure and room temperature until one mole equivalent

TABLE 2. THE SYNTHESIS OF DIHYDROFURO-ISOFLAVONES, -ISOFLAVANONES, -COUMARINS AND FURO-COUMARINS

Compd.	Starting compd. (g)	Procedure[a]	Yield %
4a	3a (0.3)	A	61
4a	9a (0.5)	B	80
4b	3b (0.7)	A	26
4b	9b (0.5)	B	20
4c	3c (0.5)	A	b)
5a	3a (0.6)	C	30
5c[c]	3c (1)	C	28.5
6a	5a (0.5)	D	66
6b[d]	3b (0.3)	C	16
7a	3a (0.3)	E	60.5
7c	3c (0.4)	E	49
10	8a (0.9)	F	80.5
11	8b (1)	F	64
16[e]	15 (2.6)	F	59

a) A: Acetic anhydride and sodium acetate, B: Hydrogenation of furo-compounds, C: Ethyl formate and sodium, D: Reflux in acetic acid, E: Ethyl chlorocarbonate and potassium carbonate, F: Ethyl carbonate and sodium.
b) A small amount.
c) This was not dehydrated by the procedure D.
d) This was obtained directly from 3b.
e) A small amount of 17 was also obtained.

23) J. F. Garden, H. F. Hayes and R. H. Thomson, *J. Chem. Soc.*, **1956**, 3315; C. Mentzer and P. Vercier, *Monatsh.*, **88**, 264 (1957); K. Fukui and M. Nakayama, *Nippon Kagaku Zasshi* (*J. Chem. Soc. Japan, Pure Chem. Sect.*), **85**, 790 (1964).

24) L. Jurd, "The Chemistry of Flavonoid Compounds," ed. by T. A. Geissman, MacMillan, New York, N.Y. (1962), p. 147.

*2 All melting points are uncorrected, infrared spectra were measured by the KBr method and ultraviolet spectra were measured in ethanol. The detailed data are summarized in the tables and figures.

TABLE 3. THE PHYSICAL CONSTANTS 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%
Dihydrobenzofuranyl Ketones								
2a	170—171 (M)	3150	1635—1575	$C_{16}H_{14}O_3$	75.38	5.39	75.57	5.55
2b	215—216 (E)	3375	1640—1590	$C_{17}H_{16}O_4$	72.03	5.72	71.82	5.63
2c	173—174 (M)	3360	1660	$C_{19}H_{20}O_6$	66.02	6.02	66.27	5.85
3a	81.5— 82.5 (E)		1640	$C_{16}H_{14}O_3$	75.63	5.38	75.57	5.55
3b	110—110.5 (P)		1635	$C_{17}H_{16}O_4$	72.57	5.53	71.82	5.63
3c	142—143 (E)		1640	$C_{19}H_{20}O_6$	66.09	5.85	66.27	5.85
Benzofuranyl Ketones								
8b	120—120.5 (E)		1630—1605	$C_{17}H_{14}O_4$	72.44	5.23	72.33	5.00
14	272—273 (D)	3100	1705, 1620	$C_{11}H_8O_5$	59.75	3.44	60.00	3.66
Dihydrofuroisoflavones								
4a	196—197 (E)		1635	$C_{18}H_{14}O_3$	77.82	4.52	77.68	5.07
4b	158—158.5 (E)		1635	$C_{19}H_{16}O_4$	74.12	5.25	74.01	5.23
4c	238—239 (E)		1635	$C_{21}H_{20}O_6$	68.25	5.68	68.47	5.47
6a	135—135.5 (E)		1640	$C_{17}H_{12}O_3$	77.26	4.58	77.19	4.73
6b	165.5—166.5 (E)		1650	$C_{18}H_{14}O_4$	73.51	5.16	73.46	4.80
Dihydrofuroisoflavanones								
5a	159—160 (dec) (A)	3150	1650	$C_{17}H_{14}O_4$	72.63	5.11	72.33	5.00
5c	181—182 (E)	3450	1670	$C_{20}H_{20}O_7$	64.18	5.56	64.51	5.41
Dihydrofurocoumarins								
7a	233.5—235 (E)	3100	1660	$C_{17}H_{12}O_4$	72.27	4.30	72.85	4.32
7c	263—265 (E)	3100	1680	$C_{20}H_{18}O_7$	64.84	4.97	64.86	4.90
Furocoumarins								
10	268—269 (E)	3000	1663	$C_{17}H_{10}O_4$	73.11	3.61	73.38	3.62
11	185—186.5 (E)	3250	1705	$C_{18}H_{12}O_5$	70.17	4.07	70.13	3.92
16	268—269[b] (M)	2950	1710	$C_{11}H_6O_4 \cdot H_2O$	60.60	3.18	60.00	3.66
17	163—164 (E)	3350	1735	$C_{14}H_{10}O_6$	61.70	3.33	61.32	3.68
19	274—276 (dec) (E)	3070	1675	$C_{17}H_{10}O_5$	69.21	3.52	69.39	3.43
Benzofuro-furocoumarin								
18	264—265 (E)		1762	$C_{17}H_8O_4$	73.56	3.11	73.91	2.92

a) A: Ethyl acetate, D: Dilute ethanol, E: Ethanol, M: Methanol, P: Petroleum ether.
b) The anhydride: mp 273—274°C. Found C, 65.05; H, 3.10%. Calcd for $C_{11}H_6O_4$: C, 65.35; H, 2.99%.

TABLE 4. THE UV SPECTRA OF DIHYDROFURO-ISOFLAVONES, -ISOFLAVANONES, -COUMARINS, FUROCOUMARINS AND BENZOFURO-FUROCOUMARIN

Compd.	λ_{max}^{EtOH} mμ[a] (log ε)
4a	244(4.96), 304(3.81)
4b	220(4.61), 245(4.58), 254[s](4.55), 285[s](4.04), 298(4.08)
4c	215(4.60), 218(4.59), 225(4.60), 248(4.56), 254(4.54), 298(4.30)
5a	215(4.39), 240(4.03), 292(4.12)
5c	235(4.27), 290(4.26)
6a	246(4.48), 306(4.01)
7a	243[s](4.10), 321(4.39)
7c	290[s](4.07), 318(4.28)
10	217(4.68), 235[s](4.53), 256[s](4.30), 300[s](4.14), 310(4.14)
11	217(4.68), 255[s](4.26), 298(4.16), 310[s](4.13)
16	235(4.47), 248[s](4.36), 290(3.97)
17	222[s](4.45), 234(4.78), 259[s](4.18), 290[s](3.87), 300(3.90)
18	238(4.57), 250[s](4.44), 311(4.08), 326(4.09), 335(4.02), 342(4.02)
19	215(4.61), 235[s](4.51), 250[s](4.44), 278[s](3.97), 295[s](4.08), 310(4.10)

a) s: Shoulder

of hydrogen was absorped (about 8 hr). Then, the catalyst was filtered and the solvent was distilled off, and the residual product was crystallized to give the ketone 3a, 0.4 g.

d) By the Alkaline Degradation of Dihydrofuroisoflavone (4a). A mixture of dihydrofuroisoflavone 4a (0.5 g) and ethanolic (not methanolic) potassium hydroxide (1 g in 30 m*l* ethanol) was refluxed for 3 hr, then was diluted with water and acidified. The crystalline product formed was collected and recrystallized to give the ketone 3a, 0.3 g.

The Preparation of Dihydrofuroisoflavones (Table 2). *a) By the Action of Acetic Anhydride and Sodium Acetate on the Ketones (3).* A mixture of the ketone 3a (0.3 g), anhydrous sodium acetate (0.3 g) and acetic anhydride (10 m*l*) was refluxed for 12 hr and the cooled mixture was poured into ice-water and left overnight. The crystalline product formed was collected and recrystallized from ethanol to give 4″,5″-dihydro-2-methylfuro[2″, 3″: 7,8]isoflavone (4a).

Similarly, 4″,5″-dihydro-2′-methoxy-2-methylfuro-[2″,3″:7,8]isoflavone (4b) and 4″,5″-dihydro-2-methyl-2′,4′,5′-trimethoxyfuro[2″,3″: 7,8]isoflavone (4c) were also obtained by this method.

b) By the Hydrogenation of Furoisoflavones (9). A mixture of 2-methylfuroisoflavone 9a (0.5 g), palladium carbon (25%, 0.5 g) and ethyl acetate (30 m*l*) was shaken with hydrogen and was treated similarly as described for the ketone 8a to give the dihydrofuroisoflavone 4a.

Similarly, 4b was also obtained by this method through purification by chromatography with alumina and ethyl acetate as a solvent.

c) By the Action of Ethyl Formate and Sodium on the Ketones (3) through Dihydrofuroisoflavanone (5). Small pieces of metallic sodium (0.7 g) were added to cooled (−10°C) ethyl formate (10 m*l*), and to this suspension was added a solution of 3a (0.6 g) in ethyl formate (10 m*l*) with stirring and cooling at 0—2°C over a period of 40 min, then the mixture was stirred for 3 hr at room temperature and left overnight. Methanol was added to destroy the excess sodium, ice-water was added and the excess ethyl formate was removed under diminished pressure. The residual solution was acidified and extracted with ether, and the product obtained from the ethereal solution was crystallized from ethyl acetate to give 4″,5″-dihydro-2-hydroxyfuro[2″,3″:7,8]isoflavanone (5a). The shape of UV spectrum is quite different from that of isoflavones.

Similarly, 4″,5″-dihydro-2-hydroxy-2′,4′,5′-trimethoxyfuro[2″,3″:7,8]isoflavanone (5c) was also obtained by this method from the ketone 3c. In the case of the ketone 3b, the crude product obtained seemed from its spectrum to be a mixture of the hydroxyisoflavanone and isoflavone, therefore, it was purified by chromatography with alumina and ethyl acetate as a solvent to give the pure 4″,5″-dihydro-2′-methoxyfuro[2″,3″:7,8]-isoflavone (6b), but the corresponding hydroxyisoflavanone (5b) was not obtained in a pure form.

To convert the hydroxyisoflavanone (5a) to the isoflavone, 0.5 g of it was heated with acetic acid (30 m*l*) on a water-bath for 1 hr. The cooled mixture was diluted with water and the crystalline product formed was collected and recrystallized from ethanol to give 4″,5″-dihydrofuro[2″,3″:7,8]isoflavone (6a). The hydroxyisoflavanone 5c was not dehydrated by this procedure.

The Preparation of Benzofuranyl Ketones. *4-Hydroxy-5-benzofuranyl 2-Methoxybenzyl Ketone (8b).* A mixture of furoisoflavone 9b (1.7 g), aqueous potassium hydroxide (50%, 8 g) and ethanol (100 m*l*) was refluxed for 4 hr, then most of the ethanol was distilled off. The residual solution was diluted with water and acidified to give the crystalline product. Recystallization from ethanol furnished 8b, 1.2 g (77%).

5-Acetyl-4-hydroxybenzofuran-2-carboxylic Acid (14). A mixture of 2,4-dihydroxy-3-formylphenyl methyl ketone[16] (12) (27 g), ethyl bromomalonate (28 m*l*), anhydrous potassium carbonate (80 g) and methyl ethyl ketone (1.2 *l*) was refluxed for 8 hr. The cooled mixture was filtered and the solvent was distilled off and then the residual product was crystallized from dilute acetone to give crude ethyl 5-acetyl-4-hydroxy-benzofuran-2-carboxylate (13), mp 134.5—136°C, ν_{max} cm^{-1}: 1710, 1625 (CO). This ester 13 was heated with aqueous potassium hydroxide (10%, 150 m*l*) on a water-bath for 1 hr. The cooled solution was filtered and acidified to give the crystalline acid. Recrystallization from dilute ethanol gave pure 14, 11.5 g (37% from 12).

4-Hydroxy-5-benzofuranyl Methyl Ketone (15). A mixture of the acid 14 (13.5 g), copper powder (13.5 g) and quinoline (380 m*l*) was refluxed gently for 1 hr under a stream of nitrogen. The cooled mixture was filtered and acidified with dilute hydrochloric acid and then extracted with ether. The ethereal solution was washed with aqueous sodium bicarbonate and then extracted with aqueous sodium hydroxide. The product obtained by acidifying the alkaline solution was crystallized from petroleum benzine to give the ketone 15, mp 84—85°C (lit[15] mp 86—87°C), yield 5.6 g (47%), ν_{max} cm^{-1}: 1630 (CO). (Found: C, 68.44; H, 4.27%).

The Preparation of Dihydrofuro- and Furocoumarins (Table 2). *a) By the Action of Ethyl Chlorocarbonate and Potassium Carbonate on the Ketones (3).* A mixture of the ketone 3a (0.3 g), ethyl chlorocarbonate (0.9 g), anhydrous potassium carbonate (2.5 g) and acetone (30 m*l*) was refluxed for 4 hr. The cooled mixture was diluted with water and acidified. The precipitates formed were collected and heated with aqueous sodium hydroxide (1 N, 50 m*l*) for 1 hr on a water-bath. The resulting solution was diluted with water and acidified to give the crystalline product. Recrystallization from ethanol gave 4′,5′-dihydro-4-hydroxy-3-phenylfuro [2′,3′,: 7,8]coumarin (7a).

Similarly,4′,5′-dihydro-4-hydroxy-3-(2,4,5-trimethoxyphenyl)furo[2′,3′:7,8]coumarin (7c) was also obtained by this procedure.

b) By the Action of Ethyl Carbonate and Sodium on the Ketones (8 and 15). Small pieces of metallic sodium (1.1 g) were added to a solution of the ketone 8a (0.9 g) in ethyl carbonate (25 m*l*), and the mixture was heated gradually to 100°C. The mixture was heated at that temperature for 1 hr, then methanol was added to the cooled mixture to destroy the excess sodium. The resulting mixture was diluted with water, washed with ether and then was acidified to give the crystalline product. Recrystallization from ethanol gave 4-hydroxy-3-phenylfuro[2′,3′: 7,8]coumarin (10).

Similarly, 4-hydroxy-3-(2-methoxyphenyl)furo[2′,3′: 7,8]coumarin (11) was also prepared by this procedure.

In the case of the ketone 15, the crude product was recrystallized from methanol or ethanol to give 4-hydroxyfuro[2′,3′: 7,8]coumarin (16), mp 268—269°C, having one molecule of water of crystallization. The water of crystallization was removed by drying over phosphorus

pentoxide at 120—130°C in vacuum. From the mother solution of crystallization, a small amount of ethyl 4-hydroxyfuro[2′,3′:7,8]coumarin-3-carboxylate (17) was obtained.

The Preparation of 5*H*-Benzofuro[3,2-*c*]furo-[2,3-*h*][1]benzopyran-5-one (18). *a) By the Action of Pyridine Hydrochloride on 11.* A mixture of 11 (0.35 g) and anhydrous pyridine hydrochloride (2 g) was refluxed gently for 40 min. The cooled mixture was acidified with dilute hydrochloric acid, and the crystalline product formed was collected and recrystallized from ethyl acetate and then from ethanol. Yield 0.08 g.

b) By the Action of Hydroiodic Acid on 11. The furocoumarin 11 (0.4 g) was added to a mixture of hydroiodic acid (10 m*l*), acetic acid (5 m*l*) and acetic anhydride (4 m*l*), and the mixture was refluxed gently under a stream of nitrogen for about 15 min. The cooled mixture was poured into ice-water (100 m*l*) containing a small amount of sodium bisulfite. The crystalline product formed was collected and recrystallized from ethanol then from acetone to give a small amount of 18.

c) By the Action of Aluminum Chloride on 11 through 4-Hydroxy-3-(2-hydroxyphenyl)furo[2′,3′:7,8]coumarin (19). Powdered anhydrous aluminum chloride (0.9 g) was added to a solution of the furocumarin 11 (0.6 g) in nitrobenzene (50 m*l*), and the mixture was heated on a water-bath for 1 hr. The cooled mixture was poured into ice-water containing a small amount of hydrochloric acid, the nitrobenzene was removed by steam-distillation, and the residual mixture was extracted with ethyl acetate. The ethyl acetate solution was extracted with 5% aqueous sodium hydroxide. The product obtained by acidifying the alkaline solution was crystallized from ethanol to give 19, 0.3 g.

A mixture of this furocoumarin 19 (25 mg) and methanol (100 m*l*) saturated with hydrogen chloride was refluxed for 7 hr, then the methanol was distilled off and the residue was diluted with water. The crystalline product formed was collected and recrystallized to give 18, 12 mg.

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