SYNTHESIS AND PROPERTIES OF HETEROCYCLIC ANALOGS OF ISOFLAVONES

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The condensation of cyanomethyl derivatives of furan and benzofuran with di- and trihydric phenols has given the corresponding 2,4-dihydroxy- and 2,4,6-trihydroxy-α-heterylacetophenones. The latter have been converted by reaction with acid anhydride, ethoxalyl chloride, and trifluoroacetic anhydride into 3-heterylchromones with methyl, trifluoromethyl, and ethoxycarbonyl groups in position 2.

It is known that flavones and isoflavones possess physiological activity [1]: some of them stimulate the activity of the cardiac muscle and others exhibit vitamin-P or antitumoral activity, and yet others are growth stimulators or regulators of the activity of the nervous system. Benzofuran analogs of isoflavones of types A and B ($R^1 = CH_3$; $R^2 = H$; R^3 = Alk or Het) have recently been obtained [2, 3]. In an investigation of the physiological activity of these compounds, it was found that some of them possess a considerable antitumoral activity in in vitro experiments. Consequently, it was of interest to synthesize for the investigation of their physiological activity compounds in which the benzofuran nucleus is attached to chromone through the β position (C) and also some chromones with furan (D) and benzofuran (A, B) nuclei in position 3.

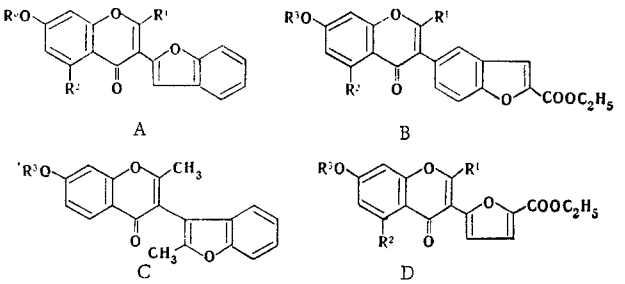

TABLE 1. 2-Methyl-3-(2-methylbenzofuran-3-yl)-7-R^3O-chromones (C)

Compound	R^3	mp, °C	Empirical formula	Found, %		Calc., %		R_f	Yield, %
				C	H	C	H		
II	$COCH_3$	122,5	$C_{21}H_{16}O_5$	72,8	4,9	72,4	4,7	0,77	99
III	H	273	$C_{19}H_{14}O_4$	74,3	4,7	74,5	4,6	0,51	98
XXVI	CH_3	128	$C_{20}H_{16}O_4$	75,0	5,0	75,0	5,0	0,78	69
XXVII	C_2H_5	137	$C_{21}H_{18}O_4$	75,5	5,7	75,4	5,4	0,78	51
XXVIII	C_3H_7	168	$C_{22}H_{20}O_4$	75,8	6,1	75,7	5,8	0,78	86
XXIX	C_4H_9	169,5	$C_{23}H_{22}O_4$	75,9	6,4	76,2	6,1	0,79	86
XXX	$C_6H_5CH_2$	166,5	$C_{25}H_{20}O_4$	79,1	5,1	78,8	5,1	0,70	77
XXXI	p-$O_2NC_6H_4CH_2$	234	$C_{26}H_{19}NO_6$	70,6	4,5	70,7	4,3	0,73	91
XXXII	$CH_2COOC_2H_5$	159	$C_{23}H_{20}O_6$	70,5	5,4	70,4	5,1	0,77	79

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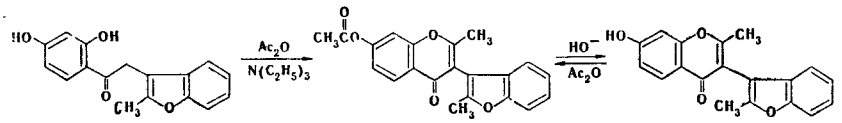
TABLE 2. 2-R^1-3-Heteryl-5-R^2-7-R^3O-chromones (A, B, D)

Compound	General formula	R^1	R^2	R^3	mp, °C	Empirical formula	Found, %		Calc., %		R_f	Yield, %
							C	H	C	H		
VII	D	CH_3	H	$COCH_3$	158	$C_{19}H_{16}O_7$	63,9	4,7	64,0	4,5	0,77	98
VIII	D	CH_3	CH_3	$COCH_3$	167	$C_{20}H_{18}O_7$	64,6	5,1	64,9	4,9	0,70	88
IX	D	CH_3	H	H	228,5	$C_{17}H_{14}O_6$	64,8	4,5	65,0	4,5	0,55	90
X	D	CH_3	CH_3	H	225	$C_{18}H_{16}O_6$	66,1	5,3	65,9	4,9	0,47	96
XI	D	CF_3	OH	H	184	$C_{17}H_{11}F_3O_7$	52,9	3,1	53,1	2,9	0,51	98
XII	D	CF_3	CH_3	H	240	$C_{18}H_{13}F_3O_6$	56,7	3,3	56,6	3,4	0,54	98
XIII	D	$COOC_2H_5$	H	H	163,5	$C_{19}H_{16}O_8$	61,1	4,2	61,3	4,3	0,46	96
XIV	D	$COOC_2H_5$	OH	H	201,5	$C_{19}H_{16}O_9$	58,4	4,4	58,8	4,1	0,50	94
XV	D	$COOC_2H_5$	CH_3	H	168	$C_{20}H_{18}O_8$	62,6	5,1	62,2	4,7	0,52	57
XIX	B	$COOC_2H_5$	OH	H	228	$C_{23}H_{18}O_9$	63,5	4,4	63,0	4,1	0,63	81
XX	B	CH_3	OH	H	250 (разл.)	$C_{21}H_{16}O_7$	65,9	4,4	66,3	4,2		87
XXI	B	CF_3	OH	H	222	$C_{21}H_{13}F_3O_7$	F 12,9		F 13,1		0,65	81
XXII	B	CF_3	CH_3	H	250	$C_{22}H_{15}F_3O_6$	F 13,0		F 13,2		0,69	91
XXIII	A	$COOC_2H_5$	OH	H	204	$C_{20}H_{14}O_7$	65,8	4,2	65,6	3,9	0,62	99
XXIV	A	CF_3	OH	H	211	$C_{18}H_9F_3O_5$	F 15,4		F 15,8		0,58	99
XXV	A	CF_3	H	H	281	$C_{18}H_9F_3O_4$	F 16,1		F 16,5		0,53	97
XXXIII	D	$COOC_2H_5$	OH	C_2H_5	143	$C_{21}H_{20}O_8$	62,8	5,3	63,0	5,0	0,77	94
XXXIV	D	$COOC_2H_5$	CH_3	$C_6H_5CH_2$	123	$C_{27}H_{24}O_8$	67,8	5,3	68,1	5,1	0,78	98
XXXV	B	CF_3	OC_2H_5	C_2H_5	195,5	$C_{25}H_{21}F_3O_7$	60,7	4,2	61,2	4,3	0,80	74
XXXVI	B	CF_3	CH_3	C_2H_5	166	$C_{24}H_{19}F_3O_6$	62,7	4,3	62,6	4,2	0,80	74
XXXVII	B	CF_3	$OCH_2C_6H_5$	$C_6H_5CH_2$	212	$C_{35}H_{25}F_3O_7$	F 9,5		F 9,3		0,81	81
XXXVIII	A	CF_3	OH	C_2H_5	142	$C_{20}H_{13}F_3O_5$	62,0	3,7	61,5	3,4	0,78	68
XXXIX	A	$COOC_2H_5$	OC_2H_5	C_2H_5	174	$C_{24}H_{22}O_7$	67,7	4,9	68,2	5,2	0,78	79
XL	A	CF_3	H	C_2H_5	125	$C_{20}H_{13}F_3O_4$	63,9	3,8	64,2	3,5		56

The starting material for the synthesis of compounds of type C (Table 1) was 3-cyanomethyl-2-methylbenzofuran, obtained from coumarin via coumarilic acid [4], benzofuran [5], 2-chloromethylbenzofuran [2], 2-methylbenzofuran [6], and 3-chloromethyl-2-methylbenzofuran [7]. The condensation of 3-cyanomethyl-2-methylbenzofuran with resorcinol in absolute ether in the presence of zinc chloride and dry hydrogen chloride formed 2,4-dihydroxy-α-(2-methylbenzofuran-3-yl)acetophenone (I). The IR spectrum of compound (I) confirms its structure.

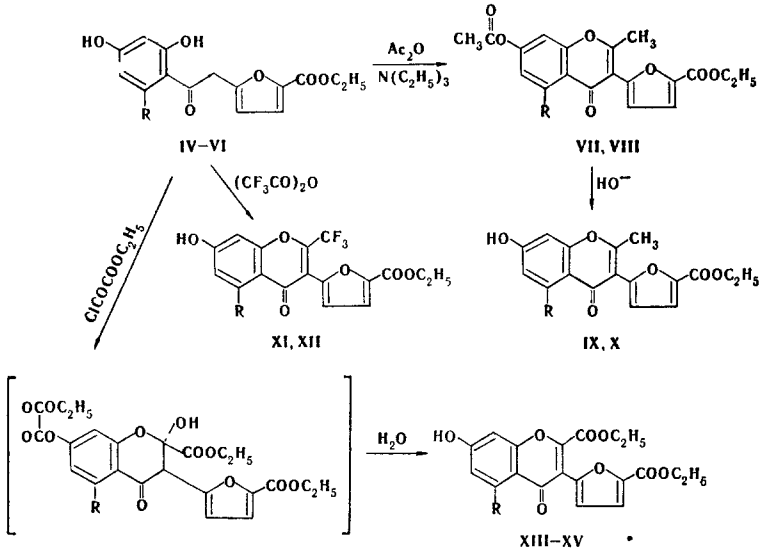
The reaction of compound (I) with acetic anhydride in the presence of triethylamine [8] formed the acetyl derivative of a 7-hydroxychromone (II), from which the 7-hydroxychromone (III) was obtained by heating with dilute alkali.



I II III

The treatment of (III) with acetic anhydride in pyridine in the cold led to the re-formation of compound (II).

The condensation of 2-cyanomethyl-5-ethoxycarbonylfuran [9] with resorcinol, phloroglucinol, and orcinol (3,5-dihydroxytoluene) under the conditions of the Hoesch reaction gave the corresponding acetophenones (IV-VI), which were the starting materials for compounds of type D (Table 2).

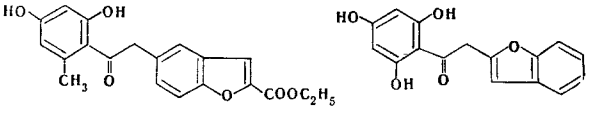


IV–VI VII, VIII XI, XII IX, X XIII–XV

IV, VII, IX, XIII R = H; V, XI, XIV R = OH; VI, VIII, X, XII, XV R = CH_3

The structure of compound (VI) was confirmed by PMR spectroscopy. Its PMR spectrum showed the signals of protons at: 9.57 and 10.05 ppm (OH), 6.36 and 7.13 ppm (3-H and 4-H of a furan ring), and 6.11 and 6.18 ppm (aromatic protons of a phenol ring).

The Hoesch reaction of 5-cyanomethyl-2-ethoxycarbonylbenzofuran [3] with orcinol formed a ketone (XVI), the structure of which was also shown by its PMR spectrum. The following signals were found: 9.5 and 10.0 ppm (OH) and 6.06 and 6.22 ppm (aromatic protons of a phenol ring).



XVI XVII

TABLE 3. Results of Tests on Antitumoral Activity

Type of compound	R^1	R^2	R^3	Diameter of zone, mm
C	—	—	H	20
D	$COOC_2H_5$	H	H	30
D	$COOC_2H_5$	CH_3	H	20
D	$COOC_2H_5$	OH	H	10
D	CF_3	CH_3	H	30
D	CH_3	CH_3	H	35
D	CF_3	OH	H	50
A	H	H	H	65
A	CH_3	H	H	60
A	CF_3	H	H	10
A	CF_3	OH	H	60
A	CH_3	H	$COCH_3$	55
A	CH_3	H	CH_3	50
B	CH_3	H	H	50
B	CH_3	H	CH_3	35
B	CF_3	OH	H	20

TABLE 4. IR Spectra of the 3-Heterylchromones (A-D) and the Ketones (VI, XVI)

Comp.	$\nu_{C=O}$ of a chromone	ν_{COOR}	$\nu_{C=C}$ of a chromone	$\nu_{C=C}$ of a furan	δ_{CH} of a 1,2,4-trisubstituted benzene ring	δ_{CH} of a 1,2-disubstituted benzene ring	ν_{CH_3}	ν_{OH}
II	1645 s	1770 s	1580 s	1625 s	830 w 855 w	755 s		
III	1645 s		1585 s	1615 m	868 w	760 m	2920 w 2950 w	3285 s
VI	1625 s	1700 s			840 w 860 w	770 m*		3250 m
X	1650 s	1730 s	1585 s		825 w 865 w	770 m*	2930 w 2980 w	3250 s
XII	1670 s	1730 s	1585 s	1610 s	850 w 885 w	752 m*		3300 s
XIV	1660 s	1750 s	1600 s		830 m 850 w	770 m*	2940 w 2990 w	3215 s
XV	1650 s	1740 s	1580 s	1605 s	835 m 870 w	770 m*	2940 w 2990 w	3310 s
XVI	1635 s	1710 s						3322 s
XXIII	1670 s	1725 s	1595 s	1630 s	835 w 890 m	765 s	2850 w 2930 w	3450 s
XXIV	1655 s		1585 s	1630 s	850 m 885 m	755 s		3310 s
XXVI	1630 s		1580 m		840 m	760 s		
XXVII	1635 s		1580 m		850 m 890 w	755 m		
XXIX	1630 s		1580 m		845 s	765 s		
XXX	1635 s	1750 s	1575 m		840m	755 s	2925 w 2960 w	
XXXV	1668 s	1715 s	1580 s	1620 s	820 w 850 w		2930 w 2985 m	
XXXVIII	1660 s		1585 s	1612 m			2850 w 2925 w	3350 m
XXXIX	1660 s	1740 s		1615 s	845 m 888 m	760 s		
XL	1670 s		1585 m	1622 s				

*δ for a 2,5-disubstituted furan ring.

It was noted that when 2-cyanomethylbenzofuran [2] was condensed with phloroglucinol, not one but two compounds were formed, the yields of which depended on the amount of catalyst used in the reaction. At a ratio of 0.3 mole of zinc chloride to 1 mole of nitrile, the main reaction product was compound (XVII) with mp 203°C, forming a colored compound with a solution of ferric chloride. The IR spectrum of compound (XVII) confirmed its structure. When 0.6 mole of zinc chloride was used per mole of nitrile, the main reaction product proved to be a compound with mp 189-190°C (XVIII), crystallizing in the form of colorless needles from aqueous acetone, and giving no color reaction with ferric chloride. The structure of compound (XVIII) is being determined at the present time.

The ketones (XVI) and (XVII), and also α-(2-ethoxycarbonylbenzofuran-5-yl)-2,4,6-trihydroxyacetophenone [3] and α-(benzofuran-2-yl)-2,4-dihydroxyacetophenone [2] were converted into the chromones (XIX)-(XXV) (types B and A; R^3 = H, Table 2) by reaction with trifluoroacetic anhydride or ethoxalyl chloride in pyridine at 0°C [3].

In order to obtain derivatives with respect to the hydroxy group in position 7, we studied the alkylation of the chromones obtained with halogen derivatives of the aliphatic series, benzyl bromide, and ethyl bromoacetate. Alkylation was performed in acetone solution in the presence of potassium carbonate. In the alkylation of 5,7-dihydroxychromones, the formation of both 7-alkoxy and 5,7-dialkoxy derivatives may be expected. A comparison of the PMR spectra of the alkyl derivatives and of 5,7-dihydroxychromone enabled the degree of alkylation of the chromones with two hydroxy groups to be estimated. In the PMR spectrum of compound (XXIV) the signals of the protons of hydroxy groups were found at 11.32 ppm (7-OH) and 12.00 ppm (5-OH). The absence of these signals from the PMR spectra of compounds (XXXV), (XXXVII), and (XXXIX) shows their full alkylation, while the presence of a signal at 11.96 ppm for compound (XXXVIII) shows monoalkylation.

The chromones and their derivatives form colorless crystalline substances with high melting points readily soluble in the majority of organic solvents and sparingly soluble in water.

The antitumoral activity of the heteroanalogs of the isoflavones obtained was tested in in vitro experiments by the serial-dilution and the agar-diffusion method [10, 11]. The initial test culture was Staph. aureus UF_3. The activity of the compound tested was read from the diameter of the zone of the absence of growth of Staph. aureus UF_3. For the quantitative evaluation of activity, 10 γ/ml of an individual substance was taken as the unit of action. Information on the activities of the chromones tested is given in Table 3.

EXPERIMENTAL

The purity of the individual compounds and the course of the reactions were monitored by chromatography in a thin layer of Merck silica gel G. Chloroform–methanol (9:1) was used as eluent. Almost all the substances possessed a blue fluorescence in UV light, and in iodine vapor they acquired a light-brown coloration. The IR spectra of the compounds were measured on a UR-10 spectrometer in tablets of potassium bromide (Table 4). The assignment of the absorption bands was made for the chromone [12], furan, and benzofuran [13] nuclei. The PMR spectra were taken on a ZKR-60 instrument with a working frequency of 60 MHz using 0.25 molar solutions in dimethyl sulfoxide at 25°C with TMS as internal standard.

3-Cyanomethyl-2-methylbenzofuran. With stirring, 20 g (0.12 mole) of 3-chloromethyl-2-methylbenzofuran [7] in 10 ml of dimethylformamide was added to a solution of 8.1 g (0.16 mole) of sodium cyanide in 50 ml of dimethylformamide, the mixture was heated at 45-50°C for 6 h, and the precipitate was filtered off and washed with toluene. The solvent was distilled off in vacuum, and the residue was fractionated at 123-124°C (0.5 mm). Colorless viscous liquid crystallizing on standing in the refrigerator in the form of large prisms. Yield 16.1 g (86%). According to the literature [7], bp 115-118°C (0.3 mm), yield 75%.

2,4-Dihydroxy-α-(2-methylbenzofuran-3-yl)acetophenone (I). To a solution of 1.71 g (10 mmoles) of 3-cyanomethyl-2-methylbenzofuran in 10 ml of absolute ether was added a solution of 1.32 g (12 mmoles) of sublimed resorcinol and 0.68 g (5 mmoles) of fused zinc chloride in 10 ml of ether. Dry hydrogen chloride was passed to saturation into the reaction mixture cooled to 0°C, and then the tightly closed reactor was left at 0°C for 15 h. The ether was decanted from the pink oil that had separated out, the oil was added to 100 ml of hot water, and the mixture was kept for an hour at pH 1 at a temperature of 80-90°C. After cooling, the precipitate that had deposited was filtered off and was washed with water. The yield of (I) was 1.84 g (65%) of colorless plates with mp 237°C (from 60% ethanol). IR spectrum, cm^{-1}: 3290 (ν_{OH}); 1635 ($\nu_{C=O}$); 1605 (ν_{OH} of a chelate); 1455 (δ_{CH_2}); 2855, 2925 (ν_{CH_2}); 1230, 1250, 1285 (ν_{C-O} of a furan ring); 1370, 1415 (δ_{C-CH_3}); 1170, 1332 (ν_{C-O} and δ_{O-H} planar for a phenolic OH); 1105, 1135 (δ_{C-H} planar for 1,2-disubstituted and 1,2,4-trisubstituted benzene rings); 765 (δ_{C-H} nonplanar for a 1,2-disubstituted benzene ring); 850, 875 (δ_{C-H} nonplanar for a 1,2,4-trisubstituted benzene ring). Found, %: C 72.0; H 5.1. $C_{17}H_{14}O_4$. Calculated, %: C 72.3; H 5.0.

7-Acetoxy-2-methyl-3-(2-methylbenzofuran-3-yl)chromone (II). A mixture of 1.4 g (5 mmoles) of (I), 2.55 g (25 mmoles) of acetic anhydride, and 2.02 g (20 mmoles) of triethylamine was heated at 145°C for 7 h, after which it was poured into 250 ml of water containing 35 mmoles of HCl. The precipitate that deposited was washed repeatedly with water until it was odorless. Yield 1.72 g, needles (from aqueous ethanol).

7-Hydroxy-2-methyl-3-(2-methylbenzofuran-3-yl)chromone (III). To a solution of 1.69 g (4.8 mmoles) of (II) in 20 ml of ethanol heated to the boil was added 4 ml of a 5% solution of caustic soda. After a few seconds, the boiling solution was diluted with 20 ml of water, boiled for a further 5 min, and acidified with dilute hydrochloric acid to pH 2-3. Yield 1.45 g, needles (from aqueous ethanol).

α-[5-Ethoxycarbonylfuran-2-yl]-2,4-dihydroxyacetophenone (IV). With stirring, a rapid current of dry hydrogen chloride was passed for 10 min through a solution of 10.73 g (60 mmoles) of 2-cyanomethyl-5-ethoxycarbonylfuran in 45 ml of absolute benzene cooled to 0°C. Then a solution of 7.92 g (72 mmoles) of sublimed resorcinol and 4.08 g (30 mmoles) of fused zinc chloride in 28 ml of absolute ether was added. Saturation with hydrogen chloride was continued for another 1 h 30 min to 2 h, and the tightly sealed reaction mixture was left overnight at 0°C. After the decantation of the solvent from the yellow oil that had separated out, the latter was twice triturated with dry benzene and was then added to 250 ml of hot water and the mixture was kept at pH 1 and a temperature of 85°C for 15-20 min. The (IV) was separated from the hot solution and well washed with water on the filter. Yield 12.8-13.5 g (73-77%) of needles with mp 162.5°C (from aqueous acetone). Found, %: C 62.1; H 5.05. $C_{15}H_{14}O_6$. Calculated, %: C 62.1; H 4.9.

α-(5-Ethoxycarbonylfuran-2-yl)-2,4,6-trihydroxyacetophenone (V) was obtained similarly to (IV) from 1.8 g (10 mmoles) of 2-cyanomethyl-5-ethoxycarbonylfuran, 1.51 g (12 mmoles) of phloroglucinol, and 0.68 g (5 mmoles) of zinc chloride. Yield 1.6 g (52%), needles with mp 176°C (from aqueous acetone). Found, %: C 59.1; H 4.8. $C_{15}H_{14}O_7$. Calculated, %: C 58.8; H 4.6.

α-(5-Ethoxycarbonylfuran-2-yl)-2,4-dihydroxy-6-methylacetophenone (VI). In a similar manner to the preparation of (IV), 2.7 g (15 mmoles) of 2-cyanomethyl-5-ethoxycarbonylfuran, 2.25 g (18 mmoles) of orcinol, and 1.02 g (7.5 mmoles) of zinc chloride gave 2.7 g of a bright yellow mixture of isomers. After washing with a small amount of cold chloroform, 2.2 g (48%) of (VI) was obtained in the form of a colorless powder. Needles with mp 137°C (from aqueous acetone). Found, %: C 62.8; H 5.5. $C_{16}H_{16}O_6$. Calculated, %: C 63.1; H 5.3.

Compounds (VII) and (VIII) were obtained similarly to compound (II), and (IX) and (X) similarly to compound (III).

3-(5-Ethoxycarbonyl-2-furyl)-5,7-dihydroxy-2-trifluoromethylchromone (XI). To a solution of 0.4 g (1.3 mmole) of (V) in 2.5 ml of absolute pyridine cooled to 0°C was added 0.74 g (3.5 mmoles) of trifluoroacetic anhydride, and the mixture was left at room temperature for 48 h. After this, it was poured into cold water, and the precipitate that deposited was filtered off and washed until odorless. Yield 0.49 g.

Compounds (XII, XXI, XXII, XXIV, and XXV) were obtained in a similar manner to compound (XI).

2-Ethoxycarbonyl-3-(5-ethoxycarbonyl-2-furyl)-7-hydroxychromone (XIII). Dropwise, 0.54 g (4 mmoles) of ethoxalyl chloride was added to a solution of 0.58 g (2 mmoles) of (IV) in 2.5 ml of absolute pyridine cooled to 0°C, and the mixture was kept at room temperature for a day. Then the reaction mixture was poured into ice water (50 ml) containing 1-3 ml of 1 N hydrochloric acid. The oil that separated out changed into a yellow powder on standing. Yield 0.71 g.

Compounds (XIV, XV, XIX, and XXIII) were obtained in a similar manner to compound (XIII).

α-(2-Ethoxycarbonylbenzofuran-5-yl)-2,4-dihydroxy-6-methylacetophenone (XVI) was obtained similarly to (VI) from 2.29 g (10 mmoles) of 5-cyanomethyl-2-ethoxycarbonylbenzofuran in 20 ml of benzene, 1.48 g (12 mmoles) of orcinol, and 0.68 g (5 mmoles) of zinc chloride in 10 ml of ether. The oily product was converted in the solid state after its treatment with carbon tetrachloride containing a few drops of acetone. Yield 2 g (56%) of needles with mp 170°C (from aqueous ethanol). Found, %: C 67.5; H 5.3. $C_{20}H_{18}O_6$. Calculated, %: C 67.8; H 5.1.

α-(Benzofuran-2-yl)-2,4,6-trihydroxyacetophenone (XVII). A solution of 1.57 g (10 mmoles) of 2-cyanomethylbenzofuran, 1.91 g (15 mmoles) of phloroglucinol, and 0.41 g (3 mmoles) of zinc chloride in 18 ml of ether was saturated with dry hydrogen chloride and was left at 0°C for 2-3 h, after which the solvent was decanted from the oil, which was added to 150 ml of water, the resulting mixture being kept at pH 1 and a temperature of 90°C for 1 h 30 min. The precipitate that had deposited was filtered from the hot solution. Yield 1.23 g (43%), plates with mp 203°C (from 30% ethanol). IR spectrum, cm^{-1}: 3330, 3428 (ν_{OH}); 1650 ($\nu_{C=O}$); 1600 (ν_{OH} of a chelate); 1470 (δ_{CH_2}); 2850, 2925 (ν_{CH_2}); 1230, 1260, 1285 (ν_{C-O} of a furan); 755 (δ_{C-H}, nonplanar, for a 1,2-disubstituted benzene ring); 820, 850 (δ_{C-H}, nonplanar, for a 1,2,4-trisubstituted benzene ring). Found, %: C 68.0; H 4.5. $C_{16}H_{12}O_5$. Calculated, %: C 67.6; H 4.3.

3-(2-Ethoxycarbonylbenzofuran-5-yl)-5,7-dihydroxy-2-methylchromone (XX) was obtained in a similar manner to (III) from 0.48 g (1 mmole) of 5,7-diacetoxy-3-(2-ethoxycarbonylbenzofuran-5-yl)-2-methylchromone [3] in 20 ml of ethanol and 1.67 ml of a 5% solution of caustic soda. Yield 0.33 g.

7-Methoxy-2-methyl-3-(2-methylbenzofuran-3-yl)chromone (XXVI). A solution of 0.15 g (0.5 mmole) of (III) and 0.28 g (2 mmoles) of methyl iodide in 30 ml of acetone was boiled with 0.18 g (1.3 mmole) of calcined potassium carbonate for 16 h. After the separation of the precipitate and evaporation of the solvent, the residue was washed with ether. Yield 0.11 g.

Compounds (XXVII-XL) were obtained in a similar manner to (XXVI).

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