3-[5-(2-ETHOXYCARBONYL)BENZOFURYL]CHROMONES

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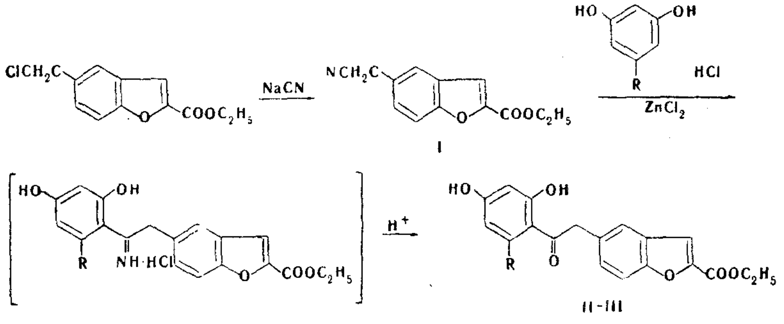
The previously undescribed 3-(5-benzofuryl)chromones and their derivatives were obtained, and their UV and IR spectra were measured.

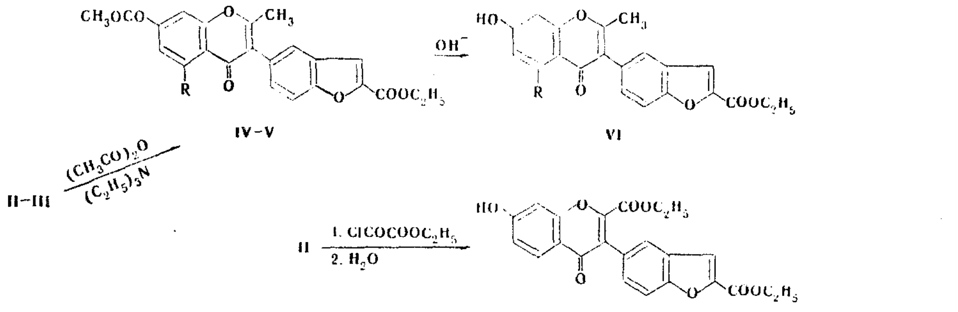
Continuing our syntheses of heterylchromones [1], we have obtained chromones that contain a benzofuran ring in the 3 position.

The starting compound for the synthesis of these compounds was 5-chloromethyl-2-ethoxycarbonylbenzofuran [2]. On reaction with sodium cyanide in dimethylformamide the latter was converted to the corresponding nitrile (I), the condensation of which with resorcinol and phloroglucinol gave benzofurylacetophenones II and III:



II R = H; III R = OH

Compounds II and III were closed to the corresponding chromones (VI and VII) by methods in [3, 4]:



IV R = H; V R = OCOCH$_3$

In order to obtain substances with new pharmacological properties [5, 6], VI and VII were alkylated with alkyl halides, ethyl bromoacetate, and chloromethyl derivatives of furan [7] and benzofuran [2] (Table 1).

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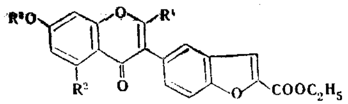
TABLE 1



Compound	R¹	R²	R³	mp, °C	$\varepsilon \cdot 10^4$	λ_{max}, nm	Empirical formula	Found, %		Calc., %		R_f	Color in UV light	Yield, %
								C	H	C	H			
IV	CH_3	H	CH_3CO	141	2,15	275	$C_{23}H_{18}O_7$	68,0	4,3	68,0	4,5	0,81	Azure	92
V	CH_3	$OCOCH_3$	CH_3CO	200	3,18	273	$C_{25}H_{20}O_9$	65,1	4,5	64,7	4,3	0,83	Azure	68
VI	CH_3	H	H	197,5	2,09	278	$C_{21}H_{16}O_6$	69,2	4,8	69,2	4,4	0,69	Azure	Quantitative
VII	$COOC_2H_5$	H	H	237,5	2,90	275	$C_{23}H_{18}O_8$	65,5	4,8	65,1	4,3	0,73	Orange	92
VIII	CH_3	H	CH_3	152	3,23	280	$C_{22}H_{18}O_6$	69,9	4,8	69,8	4,8	0,80	Azure	95
IX	CH_3	H	C_2H_5	155,5	3,12	280	$C_{23}H_{20}O_6$	70,6	5,5	70,4	5,1			95
X	CH_3	H	C_4H_9	136	2,74	280	$C_{25}H_{24}O_6$	71,2	5,8	71,4	5,8	0,71	Azure	70
XI	CH_3	H	CH_2CN	158	2,18	276	$C_{23}H_{17}NO_6$	69,0	4,4	68,5	4,2	0,82	Azure	65
XII	CH_3	H	$CH_2COOC_2H_5$	153	2,08	275	$C_{25}H_{20}O_8$	66,7	5,0	66,7	4,9	0,91	Yellow	79
XIII	CH_3	H	A*	192,5	4,20	260	$C_{28}H_{22}O_9$	66,8	4,6	66,9	4,4	0,79	Yellow	50
XIV	CH_3	H	B*	184	3,04	278	$C_{33}H_{26}O_9$	70,0	4,9	70,0	4,6	0,82	Yellow	76
XV	$COOC_2H_5$	H	CH_3	171,5	2,68	270	$C_{24}H_{20}O_8$	66,5	4,9	66,0	4,6	0,84	Dark-blue	93
XVI	$COOC_2H_5$	H	C_2H_5	147	2,33	270	$C_{25}H_{22}O_8$	66,3	5,3	66,7	4,9	0,72	Dark-blue	71
XVII	$COOC_2H_5$	H	$CH_2COOC_2H_5$	141,5	2,14	270	$C_{27}H_{24}O_{10}$	63,7	4,9	63,8	4,8	0,82	Dark-blue	84
XVIII	CH_3	H	C_3H_7	132	2,25	280	$C_{24}H_{22}O_6$	70,6	5,5	70,9	5,5			45

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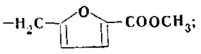
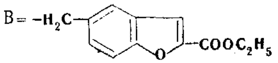
* A = ; B = 

TABLE 2. Frequencies of the IR Spectra of 3-Benzofurylchromone Derivatives

Compound	$\nu_{C=O}$ Chromone	Ester $\nu_{C=O}$	Ester ν_{C-O}	$\nu_{C=C}$ Chromone	Furan $\nu_{C=C}$	Furan ν_{C-O}	Out-of-plane δ_{CH} for the 1,2,4-trisubstituted benzene ring	δ_{C-CH_3}		ν_{CH_3}
								as	*s*	
IV	1640 s	1738 s		1570 s	1625 s		810 m, 865 w	1445 s	1372 m	
		1765 s								
V	1635 s	1722 s		1585 s			840 m, 370 w	1440 s	1375 m	
		1775 s								
VI	1630 s	1720 s	1297 s	1585 s		1270 m	860 s, 890 m	1465 m	1375 m	
VII	1640 s	1730 s	1300 m	1585 s		1245 m	850 m, 890 w	1470 m	1370 m	
						1270 m				
VIII	1638 s	1730 s	1300 s	1580 s	1615 s		840 s, 880 m	1445 s	1373 m	2985 m, 2930 w
IX	1635 s	1730 s	1300 s	1580 m	1605 m		810 m, 880 w			2870 w, 2940 m
X	1635 s	1740 s		1570 s	1615 s		810 m, 900 w	1445 s	1375 w	
XIII	1635 s	1740 s		1575 m			830 m, 900 w	1445 m	1375 m	
XIV	1635 s	1730 s		1580 s	1615 s		810 m, 885 w	1445 m	1375 w	
		1740 s								
XV	1635 s	1730 s	1300 s	1575 s	1610 s		846 m, 890 w			
		1740 s								
XVI	1650 s	1725 s		1580 s	1630 s		820 m, 890 w	1445 s	1370 m	
		1735 s								
XVII	1650 s	1705 m	1300 s	1580 s	1630 s		850 m, 890 w	1445 m	1370 w	
		1730 s	1200 s							
		1765 s								
XVIII	1635 s	1730 s	1293 s	1575 s			820 m, 890 w			2930 w, 2970 w
XIX	1630 s	1720 s		1580 s			840 m, 890 w	1460 s	1370 m	

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* Abbreviations: s is strong, m is medium, and w is weak.

The IR spectra of KBr pellets of II-XIX were recorded with a UR-10 spectrophotometer, and data on them are presented in Table 2. The absorption bands were assigned for the chromone [8] and benzofuran [9] rings.

EXPERIMENTAL

The homogeneity of the compounds obtained was verified by chromatography on plates in a thin layer of Merck silica gel G with elution by chloroform–methanol (85 : 15). The substances were detected from their fluorescence in UV light or in iodine vapors.

2-Ethoxycarbonyl-5-cyanomethylbenzofuran (I). A solution of 24 g (0.1 mole) of 2-ethoxycarbonyl-5-chloromethylbenzofuran in 30 ml of dimethylformamide was added with stirring to a solution of 7.5 g (0.15 mole) of sodium cyanide in 40 ml of dimethylformamide, and the mixture was held at 30° for 6 h. The precipitate was then removed by filtration and washed thoroughly with benzene. The filtrate was shaken with 50 g of aluminum oxide for 10 min. The aluminum oxide was separated, the solvent was removed by distillation, and the residue was fractionated in vacuo at 173-174° (0.2 mm). The colorless viscous liquid crystallized on standing to give 19 g (83%) of a product with bp 174° (0.2 mm) and mp 81° (from alcohol). Found: N 6.2%. $C_{13}H_{11}NO_3$. Calculated: N 6.1%.

α-(2-Ethoxycarbonyl-5-benzofuryl)-2,4-dihydroxyacetophenone (II). Dry hydrogen chloride was bubbled with stirring and cooling to 0° into a solution of 2.29 g (10 mmole) of II in 20 ml of absolute benzene for 25 min, after which 0.65 g (5 mmole) of fused zinc chloride and 1.32 g (12 mmole) of sublimed resorcinol in 10 ml of absolute ether were added, and dry hydrogen chloride was bubbled through the mixture until it was saturated. The reactor was then sealed tightly and allowed to stand at 0° for 24 h. The solvent was decanted from the liberated rose-colored oil, and the oil was triturated twice with dry benzene. The residue was introduced into 100 ml of hot water, and the mixture was held at 80-90° and pH 1 for 1 h. The mixture was then cooled, and the precipitate was removed by filtration and washed with water to give 2.46 g (72%) of colorless plates or needles with mp 170° (from 50% alcohol). Found: C 67.1; H 5.0%. $C_{19}H_{16}O_6$. Calculated: C 67.1; H 4.7%.

α-(2-Ethoxycarbonyl-5-benzofuryl)-2,4,6-trihydroxyacetophenone (III). This compound [2.21 g (62%)] was similarly obtained from 1.51 g (12 mmole) of phloroglucinol and 2.29 g (10 mmole) of I and had mp 245° (dec., from aqueous alcohol). Found: C 64.6; H 4.7%. $C_{19}H_{16}O_7$. Calculated: C 64.6; H 4.5%.

2-Methyl-3-(2-ethoxycarbonyl-5-benzofuryl)-7-acetoxychromone (IV). A mixture of 1 g (2.9 mmole) of II, 1.21 g (12 mmole) of triethylamine, and 1.55 g (15 mmole) of acetic anhydride was held at 145-150° for 7 h. The mixture was then poured into 100 ml of cold water containing 7 mole of hydrochloric acid per mole of acetophenone used. The resulting precipitate was washed repeatedly with water until the odor of triethylamine and acetic anhydride was absent to give 1.1 g of product.

2-Methyl-3-(2-ethoxycarbonyl-5-benzofuryl)-5,7-diacetoxychromone (V). This compound was similarly obtained.

2-Methyl-3-(2-ethoxycarbonyl-5-benzofuryl)-7-hydroxychromone (VI). A total of 8 ml of 5% sodium hydroxide solution was added to a boiling solution of 4 g (10 mmole) of IV in 40 ml of alcohol, and the mixture was refluxed for a few seconds. It was then diluted with water to twice its original volume, refluxed for 5 min, and neutralized to pH 3 with dilute hydrochloric acid. The colorless precipitate was crystallized from alcohol to give 3.6 g of product.

2-Ethoxycarbonyl-3-(2-ethoxycarbonyl-5-benzofuryl)-7-hydroxychromone (VII). A 3-g (22 mmole) sample of ethoxalyl chloride was added to a cooled (to 0°) solution of 3.7 g (11 mmole) of II in 6 ml of absolute pyridine, and the mixture was allowed to stand at room temperature for 48 h. It was then poured over ice, and the resulting yellow oil began to solidify on repeated washing with water to give 4 g of a finely crystalline powder (from aqueous acetone).

2-Methyl-3-(2-ethoxycarbonyl-5-benzofuryl)-7-ethoxycarbonylmethoxychromone (XII). A mixture of 0.5 g (1.37 mmole) of VII, 0.92 g (5.5 mmole) of ethyl bromoacetate, and 0.42 g (3.4 mmole) of calcined potassium carbonate in 60 ml of absolute acetone was stirred and refluxed for 6 h. It was then filtered, and the solvent was removed by distillation. The residue was washed with ether to give 0.48 g of colorless plates.

Compounds VIII-XI and XIII-XVII were similarly obtained.

2-Methyl-3-(2-ethoxycarbonyl-5-benzofuryl)-7-propoxychromone (XVIII). A mixture of 0.5 g (1.37 mmole) of VI, 0.61 g (5.5 mmole) of propyl iodide, and 0.42 g (3.4 mmole) of potassium carbonate in 60 ml of absolute acetone was refluxed for 34 h. The insoluble material was removed by filtration, the solvent was removed by distillation, and the residue was washed with ether to give 0.25 g of product.

This reaction also yielded the potassium salt of XIX, which was insoluble in acetone. Dilute hydrochloric acid was added dropwise to a hot suspension of this salt in alcohol until all of the solid had dissolved. The resulting solution was diluted with water, and the precipitate was removed by filtration to give 0.18 g (35%) of a product with mp 198° and λ_{max} 278 nm. Found: C 69.5; H 5.0%. $C_{22}H_{18}O_6$. Calculated: C 69.8; H 4.8%.

Bands at 3395 cm^{-1} (ν_{OH}), 1712 cm^{-1} (ester $\nu_{C=O}$), 1630 cm^{-1} (ketone $\nu_{C=O}$), 1605 cm^{-1} (furan $\nu_{C=C}$), 1300 cm^{-1} (ester ν_{C-O}), 1445 cm^{-1} (δ_{CH_2}), 2850 cm^{-1} (ν_{CH_2}), and several other bands were observed in the IR spectrum of II. Similar absorption bands (ν_{OH} 3310, $\nu_{C=O}$ 1710, 1645, $\nu_{C=C}$ 1610, δ_{CH_2} 1462 cm^{-1}, etc.) were observed in the IR spectrum of III.

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