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CHEMISTRY OF MODIFIED FLAVONOIDS. 19.* SYNTHESIS OF PHENOXYL ANALOGS OF ISOFLAVONE

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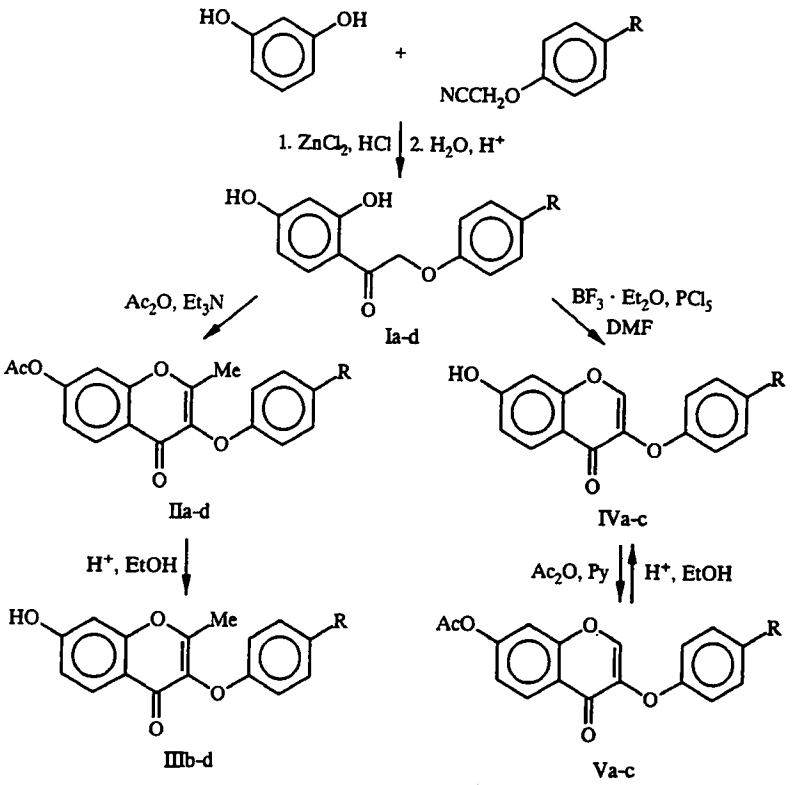
2,4-Dihydroxyphenoxyacetophenones were obtained by the reaction of resorcinol with phenoxyacetonitrile under the conditions of the Houben–Hoesch reaction. Their cyclization under the conditions of acid and alkaline catalysis gave new derivatives of 3-phenoxychromone.

The search for new highly effective drugs among the modified isoflavonoids is extremely promising. The broad spectrum of chemical and therapeutic activity with low toxicity in a series of natural isoflavones, coupled with an adequate degree of study of the products of their metabolism, creates real prospects for the comprehensive application of the substances in medical practice. Synthetic products are becoming more and more interesting in addition to the products isolated from natural raw material [2]. Of undoubted interest among the synthetic products are the 3-phenoxyl derivatives of chromone, which exhibit cholagogue [3], antioxidant [3], hepatoprotective [3], hypolipemic [3, 4], analeptic [3, 4], and anabolic [5] activity. It becomes clear from analysis of these data that it is necessary to prepare new modified analogs of 3-phenoxychromone and study their properties.



*For Communication 18, see [1].

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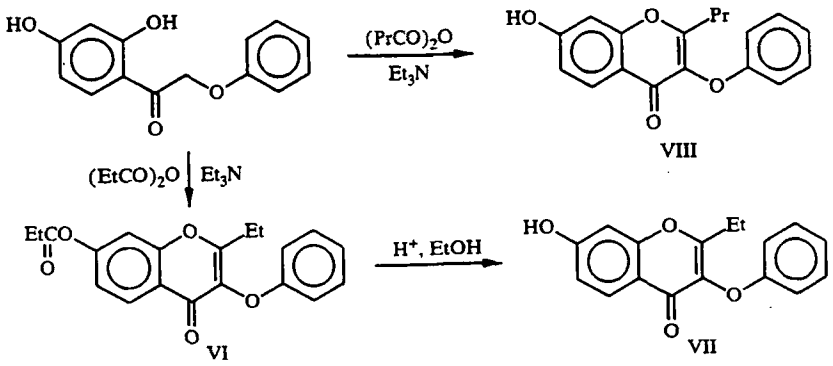

I-V a R = CH_3, b R = C_2H_5, c R = C_3H_7, d R = $CH(CH_3)_2$

The key compounds for the synthesis of 3-aryloxy derivatives of chromone were α-phenoxy-2,4-dihydroxyacetophenones (Ia-d). They were obtained by the condensation of the corresponding aryloxyacetonitriles with resorcinol under the conditions of the Houben–Hoesch reaction in ether–benzene in the presence of zinc chloride. The ketones (Ia-d) are high-melting colorless crystalline substances, readily soluble in most organic solvents. They all give an intense brown or brown-black color with an alcohol solution of ferric chloride, due to the formation of an intramolecular complex. The structure of the ketones was established on the basis of elemental analysis and PMR spectroscopy. Thus, the PMR spectra of the ketones (Ia-d) in deuteroacetone contain signals for the protons of the hydroxyl groups 2-OH and 4-OH. The proton of the 2-OH hydroxyl group, which takes part in the formation of an intramolecular hydrogen bond with the carbonyl group, appears in the form of a singlet at 12.19-12.23 ppm, while the 4-OH proton resonates in the region of 9.5-9.6 ppm. The aromatic phenolic protons 3-H, 5-H, and 6-H resonate at 6.31-6.35, 6.42-6.43, and 7.81-7.85 ppm respectively, forming an ABX spin system with spin–spin coupling constants $J_{(H5,H3)}$ = 2.4 Hz, $J_{(H6,H5)}$ = 8.8 Hz, and $J_{(H3,H6)} < 1$ Hz (Table 1).

The reaction of the ketones (Ia-d) with acetic anhydride and of α-phenoxy-2,4-dihydroxyacetophenone [6] with propionic and butyric anhydrides in triethylamine with heating at 125-150°C for 4-5 h led to the formation of a carbanion at the methylene group followed by closure of the pyrone ring of 2-methyl-, 2-ethyl-, and 2-propylchromones (IIa-d, VI, VIII) respectively. Removal of the acetyl group, leading to the 7-hydroxy derivatives, was realized by boiling alcohol solutions of the chromones (IIb-d), (VI) with hydrochloric acid. In the case of the chromone (VIII) the carboxylic acid residue was removed immediately when the reaction mixture was poured into acidified water.

The 3-aryloxychromones (IVa-d) were synthesized by adding boron trifluoride etherate to a solution of the α-aryloxy-2,4-dihydroxyacetophenones (Ia-c) in dimethylformamide followed by the addition of phosphorus pentachloride, keeping the reaction mixture at 60-75°C for 30-40 min, and treatment with hot water.

The reaction products were purified by preparation of the corresponding 7-acetoxy derivatives (Va-c) and their subsequent deacylation by heating with hydrochloric acid in ethanol.

The structure of the obtained 3-aryloxychromones (IV, V) was established by elemental analysis and PMR spectroscopy (Tables 2 and 3).

In the PMR spectra of compounds (IVa-c) (in DMSO-d_6) the singlet of the 2-OH hydroxyl proton of the ketone and the two-proton singlet of the α-methylene unit disappear. A well-defined singlet appears for the 2-H proton at 8.8 ppm, indicating the formation of the chromone ring. In the region of 8.0 ppm there is a doublet belonging to the aromatic proton 5-H, subject to the descreening effect of the adjacent carbonyl group. The downfield shift of the signals of the protons at positions 6 and 8 is due to the redistribution of electron density between the oxygen atoms after ring closure. The signal of the 5-H proton is observed in the same region of the spectrum as the signal of the 6-H proton in the initial ketone. The aromatic protons 5-, 6-, and 8-H form a spin system with coupling constants of 8.9-9.0 Hz for the *ortho* protons, 2.0-2.5 Hz for *meta*, and less than 1 Hz for *para*. The proton of the hydroxyl group at position 7 appears at 10.9 ppm. The signal of the acetoxy protons appears at 2.46 ppm (deuterochloroform).

During the formation of the 2-alkyl derivatives of chromone, the spectrum contains the three-proton singlets of the 2-methyl (2.36) and 7-acetoxy (2.46 ppm) groups in deuterochloroform. In DMSO-d_6 the protons of the 2-ethyl and 2-propyl groups [compounds (VII, VIII)] absorb at 2.66 and 1.17 ppm and at 2.69, 1.67, and 0.89 ppm respectively.

In the PMR spectra of compounds (Ib, IIa) the signals of the aromatic protons of the 4-alkylphenoxy groups (doublets, J = 8 Hz) are observed in the regions of 6.81-6.84 and 7.06-7.12 ppm. It was noticed that the signals in the region of 7.06-

TABLE 1. PMR Spectra of the Ketones (Ia-d)

Compound	Chemical shifts (acetone-d_6), δ, ppm						
	protons of the phenol part						protons of the phenoxyl fragment
	2-OH	3-H	4-OH	5-H	6-H	α-CH_2	
Ia	12,23	6,35	9,54	6,43	7,85	2,37	7,15 (3'-H, 5'-H), 6,81 (2'-H, 6'-H), 2,20 (4'-CH_3)
Ib	12,22	6,34	9,50	6,42	7,83	2,36	7,20 (3'-H, 5'-H), 6,80 (2'-H, 6'-H), 2,43, 1,10 (4'-C_2H_5)
Ic	12,19	6,31	9,58	6,42	7,82	2,36	7,05 (3'-H, 5'-H), 6,81 (2'-H, 6'-H), 2,44, 1,52, 0,82 (4'-C_3H_7)
Id	12,19	6,32	9,56	6,42	7,81	2,36	7,10 (3'-H, 5'-H), 6,82 (2'-H, 6'-H), 2,78, 1,11 (4'-$CH(CH_3)_2$)

TABLE 2. PMR Spectra of the Chromones (IIIb-d, IVa-c, VII, VIII)

Compound	Chemical shifts (DMSO-d_6), δ, ppm								
	protons of the heterocycle								protons of the phenoxyl fragment
	2-H	2-Me	2-Et	2-Pr	5-H	6-H	7-OH	8-H	
IIIb	—	2,32	—	—	7,87	6,93	10,83	6,89	7,11 (3'-H, 5'-H), 6,83 (2'-H, 6'-H), 2,50, 1,40 (4'-C_2H_5)
IIIc	—	2,33	—	—	7,86	6,92	10,84	6,89	7,10 (3'-H, 5'-H), 6,85 (2'-H, 6'-H), 2,48, 1,55, 0,88 (4'-C_3H_7)
IIId	—	2,34	—	—	7,85	6,95	10,84	6,89	7,12 (3'-H, 5'-H), 6,85 (2'-H, 6'-H), 2,85, 1,16 (4'-$CH(CH_3)_2$)
IVa	8,55	—	—	—	7,91	6,95	10,91	6,91	7,09 (3'-H, 5'-H), 6,85 (2'-H, 6'-H), 2,23 (4'-CH_3)
IVb	8,55	—	—	—	7,92	6,95	10,90	6,91	7,11 (3'-H, 5'-H), 6,87 (2'-H, 6'-H), 2,55, 1,14 (4'-C_2H_5)
IVc	8,55	—	—	—	7,91	6,95	10,89	6,90	7,10 (3'-H, 5'-H), 6,87 (2'-H, 6'-H), 2,50, 1,55, 0,87 (4'-C_3H_7)
VII	—	—	2,66, 1,17	—	7,86	6,91	10,83	6,90	7,40...6,80 (2'-H—6'-H)
VIII	—	—	—	2,69, 1,67, 0,89	7,88	6,92	10,80	6,89	7,38...6,80 (2'-H—6'-H)

7.12 ppm were broadened, and it was suggested that this took place as a result of the spin–spin coupling of the 3'-H and 5'-H protons with the protons of the alkyl groups ($J < 1$ Hz). On this basis it is possible to assign the signals in the region of 7.06-7.12 ppm to the 3'-H and 5'-H protons and the signals in the region of 6.84-6.91 ppm to the 2'-H and 6'-H protons. In order to confirm this assignment, the spectra of compounds (Ib) and (IIa) were measured under double resonance conditions. The suggestion was confirmed, since saturation at the frequency of the signal of the 4'-methyl group in compound (IIa) (2.28 ppm) and of the signal of the CH_2 protons of the ethyl group in compound (Ic) (2.43 ppm) led to a decrease in the line width of the signals at 7.06 and 7.12 ppm respectively.

Thus, new 3-aryloxychromone derivatives containing electron-donating substituents at position 2 of the chromone ring and in the phenoxyl fragment were obtained as a result of the cyclization of α-aryloxy-2,4-dihydroxyacetophenones under the conditions of base and acid catalysis. The structure and purity of the obtained final compounds and intermediates were determined by means of the PMR spectra, TLC, and elemental analysis. The biological activity of the new compounds is being studied.

TABLE 3. PMR Spectra of the Chromones (IIa-d, Va-c, VI)

Compound	Chemical shifts (deuterochloroform), δ, ppm								
	protons of the heterocycle								protons of the phenoxyl fragment
	2-H	2-Me	2-Et	5-H	6-H	7-AcO	7-EtCO	8-H	
IIa	—	2,48	—	8,25	7,16	2,37	—	7,31	7,08 (3'-H, 5'-H), 6,84 (2'-H, 6'-H), 2,28 (4'-CH_3)
IIb	—	2,42	—	8,25	7,15	2,36	—	7,31	7,11 (3'-H, 5'-H), 6,85 (2'-H, 6'-H), 2,58, 1,19 (4'-C_2H_5)
IIc	—	2,43	—	8,24	7,15	2,36	—	7,31	7,09 (3'-H, 5'-H), 6,81 (2'-H, 6'-H), 2,52, 1,60, 0,92 (4'-C_3H_7)
IId	—	2,43	—	8,25	7,15	2,36	—	7,31	7,12 (3'-H, 5'-H), 6,81 (2'-H, 6'-H), 2,85, 1,22 (4'-$CH(CH_3)_2$)
Va	7,9	—	—	8,30	7,19	2,36	—	7,33	7,15 (3'-H, 5'-H), 6,92 (2'-H, 6'-H), 2,30 (4'-CH_3)
Vb	7,9	—	—	8,29	7,17	2,32	—	7,32	7,15 (3'-H, 5'-H), 6,92 (2'-H, 6'-H), 2,59, 1,20 (4'-C_2H_5)
Vc	7,9	—	—	8,30	7,17	2,32	—	7,32	7,15 (3'-H, 5'-H), 6,92 (2'-H, 6'-H), 2,59, 1,20 (4'-C_2H_5)
VI	—	—	2,79, 1,30	8,23	7,12	—	2,65, 1,28	7,35	7,20...6,89 (2'-H—6'-H)

*The chemical shifts of the aromatic protons of the phenolic and phenoxyl parts are similar to the corresponding data for compounds (Ia-d).

TABLE 4. Characteristics of the Ketones (Ia-d) and Chromones (IIa-d, IIIb-d, IVa-c, Va-c, VI, VII, VIII)

Compound	Found, %		Molecular formula	Calculated, %		mp, °C	Yield, %
	C	H		C	H		
Ia	69,46	5,30	$C_{15}H_{14}O_4$	69,76	5,46	171...172	95
Ib	70,31	5,60	$C_{16}H_{16}O_4$	70,57	5,92	147...148	84,5
Ic	69,93	6,00	$C_{17}H_{18}O_4$	71,31	6,34	167	90
Id	70,91	6,02	$C_{17}H_{18}O_4$	71,31	6,34	149...150	88
IIa	70,24	4,72	$C_{19}H_{16}O_5$	70,36	4,97	128...129	88
IIb	71,25	5,57	$C_{20}H_{18}O_5$	71,00	5,36	109...110	90
IIc	71,21	5,36	$C_{21}H_{20}O_5$	71,58	5,72	99,5...100	96
IId	71,30	5,44	$C_{21}H_{20}O_5$	71,58	5,72	121	96
IIIb	73,25	5,78	$C_{18}H_{16}O_4$	72,96	5,44	228	95
IIIc	73,13	5,68	$C_{19}H_{18}O_4$	73,53	5,85	232	90
IIId	73,27	5,47	$C_{19}H_{18}O_4$	73,53	5,85	261	90
IVa	72,00	4,73	$C_{16}H_{12}O_4$	71,64	4,51	220...221	94
IVb	73,60	5,23	$C_{17}H_{14}O_4$	71,33	5,00	190...191	96
IVc	73,30	5,81	$C_{18}H_{16}O_4$	72,96	5,44	217	92,5
Va	70,16	4,75	$C_{18}H_{14}O_5$	69,67	4,55	128	96
Vb	70,70	5,11	$C_{19}H_{16}O_5$	70,36	4,96	135	97
Vc	71,34	5,51	$C_{20}H_{18}O_5$	71,00	5,36	123...134	94
VI	71,38	5,72	$C_{20}H_{18}O_5$	71,00	5,36	105...106	85
VII	72,70	5,30	$C_{17}H_{14}O_4$	72,33	5,00	224	95
VIII	72,69	5,13	$C_{18}H_{16}O_4$	72,96	5,44	182...183	92,5

EXPERIMENTAL

The purity of the obtained compounds and the reactions were monitored by TLC on Silufol UV-254 plates. A 9:1 mixture of chloroform and methanol was used as eluant. The PMR spectra were recorded on a Bruker WP-100SY spectrometer. The chemical shifts were determined with reference to TMS as internal standard.

The elemental analyses of the new compounds for C and H agreed with the calculated data. The physicochemical constants and the yields of the obtained compounds are given in Table 4.

2,4-Dihydroxy-α-phenoxyacetophenones (Ia-d). Dry hydrogen chloride was passed into a solution of 0.1 mole of the respective phenoxyacetonitrile in 75 ml of absolute benzene at 0°C for 1 h. A solution of 13.2 g (0.12 mole) of resorcinol and 6.8 g (0.05 mole) of freshly calcined zinc chloride in 50 ml of dry ether was then added. The passage of hydrogen chloride was continued, and the reaction mixture was left overnight. The next day the liquid over the precipitate was decanted, 400 ml of hot water was added to the residue, and the mixture was boiled for 1 h. After cooling, the precipitate was filtered off and washed on the filter with water to pH 7. The product was crystallized from isopropyl alcohol, and compounds (Ia-d) were obtained.

2-Methyl-3-phenoxy-7-acetoxychromones (IIa-d). A mixture of 10 mmole of the ketone (Ia-d) in 4.7 ml (50 mmole) of acetic anhydride and 5.6 ml (56 mmole) of triethylamine was kept at 125-130°C for 4 h. After cooling, the reaction mixture was poured into 200 ml of cold water. The precipitate was filtered off, washed thoroughly on the filter with water, and crystallized from ethanol. Compounds (IIa-d) were obtained.

2-Methyl-3-phenoxy-7-hydroxychromones (IIIb-d). To a solution of 10 mmole of the chromone (IIb-d) in the smallest amount of ethanol we added 1 ml of concentrated hydrochloric acid. The mixture was boiled until the initial compound had disappeared in TLC. The solvent was evaporated under the vacuum of a water-jet pump. The crystals were separated and recrystallized from ethanol. Compounds (IIIb-d) were obtained.

3-Phenoxy-7-hydroxychromones (IVa-c). To a solution of 50 mmole of the ketone (Ia-c) in 75 ml (100 mmole) of DMFA we added 12 ml (100 mmole) of boron trifluoride etherate. Without pausing, we added in portions 60 mmole of phosphorus pentachloride. When all the reagents had been mixed, the mixture was kept at 50-60°C while the released ether was collected. The reaction mixture was poured into 400 ml of water and boiled for 30 min. After cooling, the precipitate was filtered off, dried in air, and acylated by the corresponding amount of acetic anhydride with the addition of 1 ml of pyridine. The constants and yields of the 7-acetoxy derivatives were obtained similarly to the hydrolysis of 7-acetoxy-2-methylchromones.

2-Ethyl-7-propionyloxy-3-phenoxychromone (VI). To a solution of 2.44 g (10 mmole) of α-phenoxy-2,4-dihydroxyacetophenone [7] in 5.6 ml (56 mmole) of triethylamine we added dropwise 6.5 g (50 mmole) of propionic anhydride. The mixture was heated at 150°C until the initial compound had disappeared in TLC. The mixture was then poured into 200 ml of cold water. The precipitate was filtered off and crystallized from isopropyl alcohol. Compound (VI) was obtained.

2-Ethyl-7-hydroxy-3-phenoxychromone (VII). This compound was obtained by a procedure similar to that used for the production of 2-methyl-7-hydroxychromones (IIIb-d).

2-Propyl-7-hydroxy-3-phenoxychromone (VIII). To a solution of 2.44 g (10 mmole) of α-phenoxy-2,4-dihydroacetophenone [7] in 5.6 ml (56 mmole) of triethylamine we added dropwise 7.91 g (50 mmole) of butyric anhydride. The mixture was heated at 150°C until the initial compound had disappeared in TLC. The cooled mixture was then poured into 200 ml of cold water. The precipitate was filtered off and crystallized from toluene, and compound (VIII) was obtained.

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