CHEMISTRY OF MODIFIED FLAVONOIDS. 24*. SYNTHESIS OF 4- ARYLOXY-3-(2-HYDROXY-4-HYDROXY/ALKOXYPHENYL)PYRAZOLES

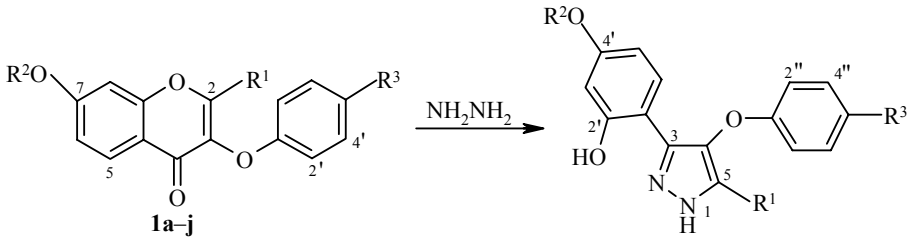
V. V. Arkhipov, M. M. Garazd, M. N. Smirnov, and V. P. Khilya

3-Aryloxychromones are recyclized under the action of hydrazine into derivatives of 4-aryloxy-3-(2,4-dihydroxyphenyl)pyrazole.

Keywords: 3-aryloxychromones, 4-aryloxy-3-(2-hydroxy-4-hydroxy/alkoxyphenyl)pyrazoles, recyclization.

The interaction of hydrazine and its derivatives with compounds containing the chromone system may be effected in two main directions, with the formation of hydrazones or by recyclization of the chromone fragment. It is known that isoflavones and 3-hetarylchromones are readily recyclized under the action of hydrazine exclusively into 4-aryl- and 4-hetarylpyrazole derivatives [2-5].

In the present work we have studied the interaction of 7-hydroxy- and 7-alkoxy-3-aryloxychromones **1a-j** with hydrazine. The synthesis of 3-phenoxychromones **1a-d** by the heterocyclization of the corresponding α-aryloxy-2,4-dihydroxyacetophenones under conditions of acid and base catalysis has been described previously [6-7]. Like the preparation of chromone **1b** [7], the use of the modified Kostanecki–Robinson method and subsequent acid hydrolysis of the resulting acetate led to compound **1e**. The 7-alkoxy derivatives **1f-j** were obtained by the alkylation of the corresponding 7-hydroxy derivatives with alkyl halides in acetone in the presence of potassium carbonate by the known procedure of [7]. The physicochemical properties of the new chromone derivatives **1e-j** are given in Tables 1 and 2.



1, **2 a** $R^1 = R^2 = R^3 = H$, **b** $R^1 = Me$, $R^2 = R^3 = H$, **c** $R^1 = CF_3$, $R^2 = R^3 = H$, **d** $R^1 = COOH$, $R^2 = R^3 = H$, **e** $R^1 = Me$, $R^2 = H$, $R^3 = OEt$, **f** $R^1 = R^2 = Me$, $R^3 = H$, **g** $R^1 = Me$, $R^2 = Et$, $R^3 = H$, **h** $R^1 = Me$, $R^2 = Bu$, $R^3 = H$, **i** $R^1 = Me$, $R^2 = CH_2Ph$, $R^3 = H$, **j** $R^1 = R^2 = Me$, $R^3 = OEt$

* For Part 23 see [1].

Kiev Taras Shevchenko University, Kiev 02033, Ukraine; e-mail: ishchenko@mail.univ.kiev.ua.
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TABLE 1. Physicochemical Properties of Compounds **1e-j** and **2a-j**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
1e	$C_{18}H_{16}O_5$	69.18 / 69.22	5.0 / 5.16	—	184	87
1f	$C_{17}H_{14}O_4$	72.28 / 72.33	4.92 / 5.00	—	168	91
1g	$C_{18}H_{16}O_4$	72.94 / 72.96	5.38 / 5.44	—	160	88
1h	$C_{20}H_{20}O_4$	74.0 / 74.06	6.18 / 6.21	—	131	81
1i	$C_{23}H_{18}O_4$	76.99 / 77.08	5.0 / 5.06	—	135	76
1j	$C_{19}H_{18}O_5$	69.90 / 69.93	5.52 / 5.56	—	126	87
2a	$C_{15}H_{12}N_2O_3$	67.14 / 67.16	4.47 / 4.51	10.21 / 10.44	179	89
2b	$C_{16}H_{14}N_2O_3$	67.00 / 67.18	4.85 / 5.00	9.98 / 9.92	171	90
2c	$C_{16}H_{11}F_3N_2O_3$	57.08 / 57.15	3.27 / 3.30	8.19 / 8.33	169	48
2d	$C_{16}H_{12}N_2O_5$	61.50 / 61.54	3.90 / 3.87	8.82 / 8.97	185	60
2e	$C_{18}H_{18}N_2O_4$	66.15 / 66.25	5.52 / 5.56	8.51 / 8.58	163	94
2f	$C_{17}H_{16}N_2O_3$	68.94 / 68.91	5.48 / 5.44	9.35 / 9.45	155	93
2g	$C_{18}H_{18}N_2O_3$	69.68 / 69.66	5.90 / 5.85	9.17 / 9.03	142	94
2h	$C_{20}H_{22}N_2O_3$	71.02 / 70.99	6.57 / 6.55	8.28 / 8.48	105	96
2i	$C_{23}H_{20}N_2O_3$	74.00 / 74.18	5.35 / 5.41	7.69 / 7.52	135	95
2j	$C_{19}H_{20}N_2O_4$	67.15 / 67.05	5.98 / 5.92	7.99 / 8.23	116	96

As a result of brief heating of alcoholic solutions of compounds **1a-j** with an excess of hydrazine, opening of the pyrone ring occurs with subsequent cyclization into 4-aryloxy-3-(2-hydroxy-4-hydroxy/alkoxyphenyl)pyrazoles **2a-j**. Their structure was confirmed by the results of elemental analysis (Table 1), data of ^{1}H NMR spectra (Table 2) etc. The pyrazoles obtained were dissolved in dilute alkali and with an alcoholic solution of ferric chloride they form blue-green chelate complexes by means of the phenolic hydroxyl and a nitrogen atom of the pyrazole ring. In their ^{1}H NMR spectra, measured in DMSO-d_6, signals characteristic of such structures were observed in the 9.4-13.2 ppm region. The protons of the pyrazole ring NH group were displayed as strongly broadened peaks at lowest field (12.9-13.2 ppm). A singlet was observed for the 2'-OH group proton at 10.8-11.3, and for the 4'-OH group proton at 9.1-9.6 ppm. In the case of compounds **2f-j** in place of the singlet for the 4'-hydroxy group signals were present in the spectrum for the corresponding alkoxy substituent. Displacement of the 6'-H proton signal in the spectra of pyrazoles **2** by 1.0-1.2 ppm towards high field, compared with the position of the peak of the same proton in the spectra of the initial chromones **1** (found in position 5 in them), is explained by the formation of the chelate structure [8].

3-Phenoxychromones, like other isoflavones, are therefore readily cyclized in high yield into the corresponding pyrazoles, which enables this reaction to be used for preparative purposes for the synthesis of derivatives of 4-aryloxy-3-(2,4-dihydroxyphenyl)pyrazole unavailable by other methods.

TABLE 2. ^{1}H NMR Spectra of 3-Aryloxychromones **1e-j**

Com-pound	Signals of protons, δ, ppm, coupling constants (*J*, Hz)*							
	2-Me (3H, s)	5-H (1H, d, *J* = 8.0)	6-H (1H, dd, *J* = 2.0; 8.0)	7-OR[2]	8-H (1H, d, *J* = 2.0)	2'-H, 6'-H (2H, m)	3'-H, 5'-H (2H, m)	4'-R[3]
1e*[2]	2.36	7.97	7.10	10.65 (1H, s, H)	7.30	6.83 (s)	6.83 (s)	1.28 (3H, t, CH_3); 3.93 (2H, q, CH_2)
1f	2.39	8.00	7.10	3.97 (3H, s, CH_3)	7.20	7.05	7.00	7.00 (1H, m, H)
1g	2.39	8.00	7.10	4.23 (2H, q CH_2); 1.44 (3H, t, *J* = 7.0, CH_3)	7.20	7.00	6.95	6.95 (1H, m, H)
1h	2.39	8.00	7.10	3.88 (2H, t, OCH_2); 1.59 (2H, m, $OCH_2\underline{CH_2}$); 1.36 (2H, m, $\underline{CH_2}CH_3$); 0.89 (3H, t, *J* = 7.0, CH_3)	7.20	7.05	7.00	7.00 (1H, m, H)
1i	2.38	8.00	7.15	7.50 (5H, m, Ph); 5.33 (2H, s, CH_2)	7.20	7.05	7.00	7.00 (1H, m, H)
1j	2.38	8.00	7.00	3.95 (3H, s, CH_3)	7.20	6.90 (s)	6.90 (s)	3.95 (2H, q CH_2); 1.33 (3H, t, CH_3)

* In $(CD_3)_2CO$.
*[2] In DMSO-d_6.

TABLE 3. ^{1}H NMR Spectra of Substituted Pyrazoles **2a-j**

Compound	Solvent	Signals of protons, δ, ppm, coupling constants (*J*, Hz)									
		1-H (1H, s)	5-R[1] (s)	2'-OH (1H, s)	3'-H (1H, d, *J* = 2.0)	4'-OR[2]	5'-H (1H, dd, *J* = 2.0; 8.0)	6'-H (1H, d, *J* = 8.0)	2"-H, 6"-H, (2H, m)	3"-H, 5"-H, (2H, m)	4"-R[3]
2a	DMSO-d_6	12.90	7.78	10.76	6.36	9.15 (1H, s)	6.22	7.45	7.28	7.00	7.00 (1H, m)
2b	$(CD_3)_2CO$	12.09	2.17 (3H, CH_3)	11.11	6.38	8.40 (1H, s)	6.25	7.58	7.28	7.00	7.00 (1H, m)
2c	DMSO-d_6	13.40	—	10.25	6.41	9.63 (1H, s)	6.17	7.28	7.20	6.90	6.90 (1H, m)
2d	$(CD_3)_2CO$	13.00	13.00 (1H, COOH)	10.19	6.36	9.49 (1H, s)	6.18	7.28	7.28	6.84	6.84 (1H, m)
2e	DMSO-d_6	12.75	2.07 (3H, CH_3)	10.95	6.21	9.45 (1H, s)	6.18	7.38	6.84 (s)	6.84 (s)	1.29 (3H, t, CH_3), 3.95 (2H, q, CH_2)
2f	$(CD_3)_2CO$	12.13	2.19 (3H, CH_3)	11.18	6.48	3.74 (3H, s, CH_3)	6.32	7.65	7.28	7.00	7.00 (1H, m)
2g	$(CD_3)_2CO$	12.13	2.18 (3H, CH_3)	11.15	6.43	1.31 (3H, t, *J* = 7.0); 3.98 (2H, q, *J* = 7.0, CH_2)	6.32	7.65	7.28	7.00	7.00 (1H, m)
2h	$(CD_3)_2CO$	12.17	2.17 (3H, CH_3)	11.14	6.45	3.88 (2H, t, *J* = 7.0, OCH_2); 1.59 (2H, m, $OCH_2\underline{CH_2}$); 1.36 (2H, m, $\underline{CH_2}CH_3$); 0.89 (3H, t, *J* = 7.0, CH_3)	6.31	7.65	7.28	7.00	7.00 (1H, m)
2i	DMSO-d_6	12.70	2.08 (3H, CH_3)	11.15	6.55	7.40 (5H, m, Ph); 5.05 (2H, s, CH_2)	6.43	7.48	7.28	7.00	7.00 (1H, m)
2j	DMSO-d_6	12.86	2.07 (3H, CH_3)	11.08	6.41	3.69 (3H, s, CH_3)	6.36	7.51	6.83 (s)	6.83 (s)	1.29 (3H, t, CH_3), 3.95 (2H, q, CH_2)

EXPERIMENTAL

The progress of reactions and the purity of compounds obtained were checked by TLC on Silufol UV 254 plates in the systems chloroform—methanol, 9 : 1 and
19 : 1. The ^{1}H NMR spectra were measured on Bruker WP 100SY and Varian VXR 300 instruments (100 and 300 MHz respectively) in DMSO-D_6 and $(CD_3)_2CO$ relative to TMS (internal standard).

3-(4-Ethoxyphenoxy)-7-hydroxy-2-methylchromone (1e). A mixture of α-(4-ethoxyphenoxy)-2,4-dihydroxyacetophenone (2.58 g, 10 mmol), acetic anhydride (4.7 ml: 50 mmole), and triethylamine (5.6 ml, 40 mmol) was maintained at 125-130°C for 4 h. After cooling, the reaction mixture was poured into cold water (200 ml), the precipitated solid 7-acetoxy derivative was filtered off, washed thoroughly on the filter with water, and crystallized from ethanol. The crystals obtained were dissolved in the minimum amount of ethanol, concentrated hydrochloric acid (1 ml) was added to the solution, and the mixture boiled until disappearance of the starting material (TLC). The crystals of product **1e,** precipitated on cooling, were separated and crystallized from ethanol.

7-Alkoxy-3-aryloxy-2-methylchromones (1f-j) (General Method). The appropriate alkyl halide (5.5 mmol) was added to a solution of chromone **1b,e** (5 mmol) in absolute acetone (50 ml) containing powdered freshly calcined potassium carbonate (2.07 g, 15 mmol) with vigorous stirring and heating. The reaction mixture was maintained at 50-60°C for 1-3 h (the end of the reaction was determined by TLC). After cooling, the mixture was transferred to 1 N sulfuric acid solution (100 ml), the solid product was filtered off, and crystallized from 2-propanol.

4-Aryloxy-3-(2-hydroxy-4-hydroxy/alkoxyphenyl)pyrazoles (2a-j) (General Procedure). A solution of 85% hydrazine hydrate (0.5 ml) in ethanol (5 ml) was added to a hot solution or suspension of the appropriate 3-aryloxychromone **1a-j** (4 mmol) in ethanol (20 ml). The reaction mixture was boiled for 5-30 min (the end of the reaction was determined by TLC) and transferred to ice water (200 ml) (in the case of acid **2d** the resulting mixture was acidified with dilute hydrochloric acid to pH 6). The precipitate of product **2** was filtered off, and crystallized from 50% ethanol.

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