SYNTHETIC ANALOGS OF NATURAL FLAVOLIGNANS. XII.* SYNTHESIS OF 3,5-DIARYLSUBSTITUTED PYRAZOLINES BASED ON 1,3-BENZODIOXANE AND 1,4-BENZODIOXANE CHALCONE ANALOGS

A. Aitmambetov,[1] Z. Yu. Ibragimova,[2] and A. Tokhtybaeva[2]

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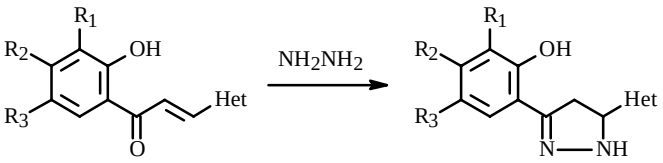
3,5-Diarylsubstituted pyrazolines were synthesized by reaction of 1,3-benzodioxane and 1,4-benzodioxane chalcone analogs with hydrazine hydrate. The structures of the products were confirmed by PMR spectroscopy.

Key words: chalcones, properties, hydrazine, pyrazoline.

2′-Hydroxychalcones, which have structures similar to many natural pigments containing polyhydroxy- and polymethoxychalcones and related flavones and flavonols, are some of the most interesting derivatives of β-phenylacrylophenones. Chalcones are known to be convenient synthons for various heterocyclic compounds.

Pyrazoline derivatives possess various biological activity. Compounds characterized by antispasmodic, bactericidal, fungicidal, antiestrogen, and therapeutic activity and monoamineoxidase inhibitors have been found among them [1].

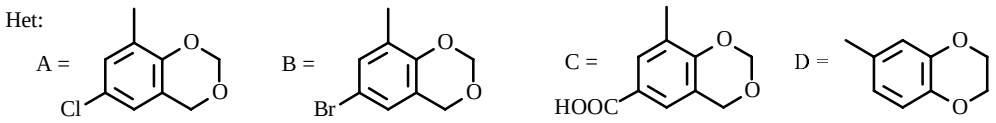
In order to prepare new bioactive compounds, we studied the reaction of 1,3-benzodioxane and 1,4-benzodioxane analogs of chalcone with hydrazine hydrate. Reaction of hydrazine hydrate with **1-4** [2-4] in alcohol at the boiling point of the reaction mixture produced a pyrazoline ring to form 3-(2-hydroxyphenyl)-5-hetarylpyrazolines **5-8** [5].



1 - 4 **5 - 8**

5c, d, f, g, Het = A; **6d, g,** Het = B; **7g,** Het = C; **8a, e, f, g, h,** Het = D

a: $R_1 = R_2 = R_3 = H$; **c:** $R_1 = R_3 = H$, $R_2 = CH_3$
d: $R_1 = R_3 = H$, $R_2 = OMe$; **e:** $R_1 = R_3 = H$, $R_2 = Cl$
f: $R_1 = R_2 = H$, $R_3 = Cl$; **g:** $R_1 = R_2 = H$, $R_3 = F$
h: $R_1 = R_2 = Cl$, $R_3 = H$



*For part XI, see [6].

1) Nukus Filial, Tashkent SAU, Nukus, 742009, ul. Kh. Abdambetova; 2) Complex Institute of Natural Sciences, Karakalpak Division, Academy of Sciences of the Republic of Uzbekistan, Nukus, 742006, pr. Berdakha, 41. Translated from Khimiya Prirodnykh Soedinenii, No. 6, pp. 446-447, November-December, 2004. Original article submitted May 26, 2003.

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TABLE 1. Physicochemical Constants of 3-(2-Hydroxyphenyl)-5-hetarylpyrazolines **5-8**

Compound	Empirical formula	Yield, %	mp, °C
5c	$C_{18}H_{17}ClN_2O_3$	97	114-115
5d	$C_{18}H_{17}ClN_2O_4$	79	124-125
5f	$C_{17}H_{14}Cl_2N_2O_3$	88	164-165
5g	$C_{17}H_{14}ClFN_2O_3$	73	168-169
6d	$C_{18}H_{17}BrN_2O_4$	92	141-142
6g	$C_{17}H_{14}BrFN_2O_3$	89	167-168
7g	$C_{18}H_{15}FN_2O_5$	58	208-209
8a	$C_{17}H_{16}N_2O_3$	64	104-105
8e	$C_{17}H_{15}ClN_2O_3$	67	131-132
8f	$C_{17}H_{15}ClN_2O_3$	88	138-139
8g	$C_{17}H_{15}FN_2O_3$	75	124-125
8h	$C_{17}H_{14}Cl_2N_2O_3$	96	134-136

TABLE 2. PMR Spectra of 3-(2-Hydroxyphenyl)-5-hetarylpyrazolines (δ, ppm, DMSO-d_6, J/Hz)

Compound	Protons									
	OH-2, br.s	H-3	R_2-4	R_3-5	H-6	Ha-4′, dd	Hb-4′, dd	Hc-5′, dd	N-H	2H-2″, 2H-4″,*
5c	11.03	6.73	2.26	6.69	7.15	3.59 (J = 10.3; 17.1)	2.90 (J = 10.3; 17.1)	4.85 (J = 10.3)	7.67	5.3; 4.9
5d	11.29	6.50	3.75	6.45	7.21	3.57 (J = 10.3; 17.1)	2.89 (J = 10.3; 17.1)	4.89 (J = 10.3; 3.4)	7.55	5.3; 4.9
5f	11.14	6.92	7.22	-	7.34	3.62 (J = 10.7; 17.6)	2.98 (J = 10.7; 17.6)	4.98 (J = 10.7; 2.9)	7.89	5.4; 4.9
5g	10.89	7.06 m	7.06 m	-	7.06 m	3.60 (J = 11.2; 17.1)	2.96 (J = 11.2; 17.1)	4.98 (J = 11.2)	7.89	5.4; 4.9
6d	11.28	6.50	3.75	6.45	7.20	3.58 (J = 10.5; 17.3)	2.87 (J = 10.5; 17.3)	4.90 (J = 10.5; 3.7)	7.56	5.3; 4.9
6g	10.88	7.04 m	7.04 m	-	7.04	3.61 (J = 10.3; 17.1)	2.94 (J = 10.3; 17.1)	4.94 (J = 10.3)	7.04	5.4; 4.9
7g	10.94	6.8-7.22 m		-	6.8-7.2 m	3.62 (J = 11.2; 17.1)	2.95 (J = 10.3; 17.1)	4.20 (J = 10.3; 3.4)	7.93	5.4; 4.97
8a	11.19	6.92	7.20	6.94	7.28	3.54 (J = 10.8; 17.2)	2.96 (J = 10.8; 17.2)	4.75 (J = 4.8; 10.8)	7.77 7.80	4.21; 4.22
8c	11.44	6.91	-	6.91	7.29	3.53 (J = 10.8; 17.2)	2.95 (J = 10.8; 17.2)	4.76 (J = 10.8)	7.80	4.22
8f	11.24	6.93	7.23	-	7.32	3.54 (J = 10.3; 17.2)	2.99 (J = 10.3; 17.2)	4.78 (J = 10.3)	7.90	4.22
8g	10.98	6.93	7.03	-	7.13	3.53 (J = 10.8; 17.2)	2.97 (J = 10.8; 17.2)	4.78 (J = 10.8)	7.89	4.22
8h	11.97	-	8.10	-	7.32	3.50 (J = 10.2; 16.6)	2.95 (J = 10.2; 17.3)	4.79 (J = 10.7)	7.49	4.21

Protons of 1,3-benzodioxane and 1,4-benzodioxane:

1,3-benzodioxane: 6.9-7.3 (1H, d, 2.5 Hz, H-5), 7.1 (1H, J = 2.5 Hz, H-7), **3g**: 7.78 (H-5), 7.63 (H-7), 12.73 (1H, br.s, COOH-6); 1,4-benzodioxane: **8a**: 6.86 m (3H, m, H-5, H-7, H-8); **8e**: 6.92 m (3H, m, H-5, H-7, H-8); **8f**: 6.84 (1H, d, H-5), 6.86 m (2H, m, H-7, H-8); **8g**: 6.84 (1H, d, H-5), 6.86 m (2H, m, H-7, H-8).

*–$O(CH_2)_2O$–.

The structures of **5-8** were confirmed by elemental analysis and PMR spectroscopy in DMSO (Tables 1 and 2). These compounds dissolve readily in NaOH solution (5%) and form bluish-green complexes with alcoholic iron chloride (**3**). The PMR spectra of **5-8** contain signals for the OH-2 protons at weak field at 10.3-11.4 ppm because they participate in intramolecular H-bonds with the N atom of the pyrazoline ring. The N–H proton appears near 7.0-7.9 ppm and disappears first if heavy water is added. The H-6 proton of the phenol group is shifted to strong field by 0.8-1.0 ppm compared with the analogous protons in the starting chalcones. The CH_2-4 protons of the pyrazoline ring appear as two doublets with spin—spin coupling constants (SSCC) 10.2-11.2 Hz and 17.0-17.7 Hz. Proton H-5 resonates as doublets at 4.8-5.0 ppm with SSCC 10.2-11.2 Hz.

Thus, reaction of substituted 1,3-benzodioxane and 1,4-benzodioxane analogs of chalcones with hydrazine hydrate produce in good yields 3,5-diarylsubstituted pyrazolines.

The study of the biological activity of the substituted pyrazolines prepared by us showed that several of them possess neuroleptic activity.

EXPERIMENTAL

The course of reactions and purity of products were monitored by TLC on Silufol UV-254 plates using benzene as eluent. PMR spectra were recorded on a Bruker WP-100 SY spectrometer at working frequency 100 MHz in DMSO-d_6 with TMC as an internal standard. Elemental analyses of **5-8** agreed with those calculated.

3-(2-Hydroxyphenyl)-5-hetarylpyrazolines (5-8). A hot solution of the appropriate 2-hydroxychalcone (**1-4**, 10 mmol) in ethanol (100 mL) was treated with hydrazine hydrate (1 mL, 80%) and boiled for 20 min. The reaction mixture was poured into water (100-150 mL). The resulting precipitate was filtered off and crystallized from ethanol.

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