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SYNTHETIC ANALOGS OF NATURALLY OCCURRING FLAVOLIGNANS. XI. REACTION OF SYNTHETIC FLAVONE ANALOGS WITH HYDRAZINE HYDRATE AND ITS DERIVATIVES

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Reactions of 1,3-benzodioxane and 1,4-benzodioxane analogs of flavones with hydrazine derivatives are studied. The hydrazines recyclize the new flavones into 3,5-diarylpyrazoles. Their PMR spectra confirm their structures.

Key words: 1,3-benzodioxane and 1,4-benzodioxane analogs of flavones, reaction, hydrazines.

Chromones can react with hydrazines to give several compounds depending on whether the carbonyl group reacts or the pyrone ring opens to yield pyrazoles, which can exist as isomers. For this reason, results, especially the early ones, were incorrectly interpreted for hydrazines and hydroxylamine [1].

Baker et al. [2, 3] studied the reaction of 4-thioflavones with hydrazine and its derivatives. They found that the reaction can proceed in two directions, depending on the nature of the starting materials. Hydrazones and phenylhydrazones or pyrazole derivatives can form. They also found that the first reaction is characteristic of nearly all 4-thioflavones. Flavonehydrazone [4], 7-methoxyflavonehydrazone [2] with traces of the isomeric pyrazole, and flavonephenylhydrazone [4] were prepared.

Hydrazones of flavones can be converted into the isomeric pyrazoles by boiling in an alcoholic solution of hydrazine [2].

The reaction of flavones with hydrazines was studied by a Hungarian group in 1965-1973. They demonstrated that the normal reaction of flavones in acidic medium produces the carbonyl derivatives. Flavone *p*-tosylhydrazone [5, 6] and flavone thiosemicarbazone [7] were produced from flavone and the hydrazines. The most basic hydrazine under ordinary conditions cannot produce flavone hydrazone because the medium is alkaline, which leads to 3-(2-hydroxyphenyl)-5-phenylpyrazole [7]. Kallay et al. [7, 8] described the isomerization of flavone hydrazones into pyrazoles via heating the hydrazones above their melting point.

We found that the nature of the products formed in the reactions of chromones with hydrazine hydrate depends on the structure of the starting chromones. Thus, hydrazine hydrate rearranges flavones **1d** and **2a**, **-c**, **-e**, and **-f** into the 2-hydroxyphenyl-5-hetarylpyrazole derivatives **3d** and **4a**, **-c**, **-e**, and **-f**. The products are readily soluble in 2 N NaOH. This is consistent with the presence of a free phenol hydroxyl. Compounds **3** and **4** form bluish-green chelate complexes with an alcoholic solution of iron chloride owing to the presence of a hydroxyl in the position *ortho* to the N atom of the pyrazole ring. The physical constants and PMR data of **3** and **4** are given in Tables 1 and 2.

The separately observed singlets for the NH and 2-OH groups are consistent with the pyrazole structure for **3** and **4**. The first singlet is located at weak field (12.5-13.8 ppm) whereas the second appears at 9.9-11.0 ppm. The diamagnetic shift of the phenol H-3 by 0.7 ppm compared with the corresponding proton in the starting flavone also indicates that the flavone changed to pyrazole.

Thus, the study of the reaction of benzodioxane flavone analogs with hydrazine derivatives shows that these compounds are convenient intermediates for the synthesis of 3,5-diarylpyrazoles. Pyrazoles are readily formed in high yield, which makes this recyclization useful for preparative purposes.

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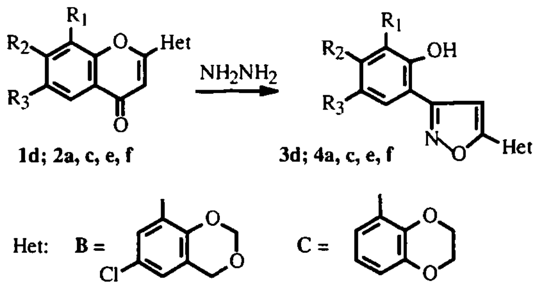
TABLE 1. Properties of **3** and **4**

Compound	Yield, %	mp, °C	Emp. formula	Recryst. solvent
3d	94	236-237	$C_{17}H_{12}C_{12}H_2O_3$	EtOH
4a	99.9	163-164	$C_{17}H_{14}N_2O_3$	EtOH/H_2O
4c	89	201-202	$C_{19}H_{18}N_2O_3$	C_6H_6
4e	87	190-191	$C_{17}H_3FN_2O_3$	EtOH
4f	83	248-249	$C_{17}H_{12}Cl_2N_2O_3$	EtOH

TABLE 2. PMR Chemical Shifts (δ, ppm, J, Hz) of Pyrazoles **3** and **4** (in DMSO-d_6)

Compound	Phenol protons					Pyrazole protons		Heterosubstituent protons			
	OH-2, s	R_1-3	R_2-4	R_3-5	H-6	N-H, s	H-4, s	H-5 d (2.0)	H-7dd (8.0; 2.0)	H-8 d (8.0)	O-$(CH_2)_n$-O
3d	10.96; 10.65	7.02d (8.79)	7.28dd (8.8; 2.44)	-	7.83 2.44	13.50	7.57	7.28 (2.44)	7.90d (2.44)	-	5.48:5.02
4a	10.35 11.00	6.90	7.20	7.20	7.34	12.80 (1.50)	7.74	7.39	6.97	6.97	4.30
4c	9.87 10.67	6.72	2.18	2.18	7.35	12.59 13.36	7.50	7.17	7.30	6.96	4.28
4e	10.77	7.27	7.27	-	7.60	13.54	7.37	7.00m	7.00m	7.00m	4.29
4f	11.91		7.84		7.49	13.77	7.45	7.36	7.32	6.99	4.30



a: R = R_1 = R_2 = R_3 = H; c: R_1 = H, R_2 = R_3=Me; d: R_1 = R_2 = H, R_3 = Cl;
c: R_1 = R_2 = H, R_3 = F; f: R_2 = H, R_1 = R_3 = Cl; **1**, **3**: Het = B; 2, 4: Het = C

EXPERIMENTAL

The course of the reactions and the purity of the products were monitored by TLC on Silufol UV-254 plates. The eluent was benzene-ethanol (9:1). PMR spectra were measured in DMSO-d_6 with TMS internal standard on a Bruker WP-100 SU instrument. Elemental analyses of all compounds agreed with the calculated values.

3-(2-Hydroxyphenyl)-5-hetarylpyrazoles (3, 4). A hot solution of the appropriate chromone (5 mmole) in alcohol (or a mixture of alcohol and dioxane, 45-50 ml) was treated with hydrazine hydrate (80%, 0-5 ml), boiled for 6-20 h, and diluted with water. The precipitate was filtered off and crystallized from a suitable solvent.

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