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SYNTHETIC ANALOGS OF NATURALLY OCCURRING FLAVOLIGNANS. X. REACTION OF FLAVONES AND THEIR THIODERIVATIVES WITH HYDROXYLAMINE

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1,3-Benzodioxoles, 1,4-benzodioxanes, and 1,5-benzodioxepanes are flavone analogs that hydroxylamine recyclizes into derivatives of 5-(2-hydroxyphenyl)isoxazoles. They react with thioderivatives with retention of the pyrone ring and formation of oximes. Their structures are proven using PMR spectra.

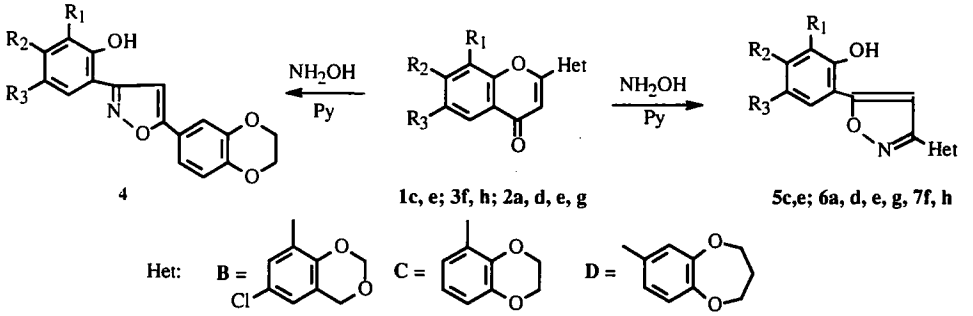
Key words: flavones, reaction with hydroxylamine, isoxazoles.

Flavonoids react readily with hydroxylamine. However, the reaction follows several paths and, despite the fact that the first studies in this area were reported in the early 1900s, the published results are still being reviewed and refined. In addition, ways to develop this reaction further are being explored. Many researchers have mistakenly made assumptions about the mechanism of formation of chromone oximes and, consequently, about the structure of intermediates and final products.

The reaction of chromones and their derivatives with hydroxylamine proceeds mainly along two paths, in which the pyrone ring is retained (formation of chromone oximes) or in which the pyrone ring is opened and the intermediates are cyclized to reaction products containing the isomeric isoxazoles.

Basinski and Jerzmanowska [1] and Krolikowska [2] studied the reaction of flavones with hydroxylamine in dry pyridine and found that flavone oximes can form simultaneously with isoxazoles. If only the isoxazoles were obtained, then the oximes isomeric to them were synthesized from the corresponding 4-thioflavones [1, 2].

Previous studies [3-5] suggest that the reaction of a chromone and its derivatives, regardless of the nature of the substituent on the C-2 atom, produce mainly the isoxazoles. Beugelmans and Morin [3-5] proposed a direct method for producing chromone oximes. They found that oximes are produced only in dry methanol with a chromone-to-hydroxylamine-hydrochloride ratio of 1:3.



a: $R_1=R_2=R_3=H$; **c:** $R_1=R_3=H$, $R_2=Me$; **d:** $R_1=H$, $R_2=R_3=Me$;
e: $R_1=R_2=H$, $R_3=Cl$; **f:** $R_1=R_3=H$, $R_2=OMe$; **g:** $R_1=R_3=Cl$, $R_2=H$;
h: $R_1=R_2=H$, $R_3=NO_2$; **1, 5:** Het=B, **2, 4, 6:** Het=C; **3,7:** Het=D

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TABLE 1. Properties of **5-7***

Compound	Yield, %	mp, °C	Emp. formula
5c	53	223-224	$C_{18}H_{14}ClNO_4$
5e	71	224-225	$C_{17}H_{11}Cl_2NO_4$
6a	31	232-233	$C_{17}H_{13}NO_4$
6d	63	>290	$C_{17}H_{13}NO_4$
6e	65	274-275	$C_{17}H_{13}ClNO_4$
6g	69	234-235	$C_{17}H_{11}Cl_2NO_4$
7f	67	187-188	$C_{19}H_{17}NO_5$
7h	73	>290	$C_{18}H_{14}N_2O_6$

*Crystallized from EtOAc.

TABLE 2. Chemical Shifts in PMR Spectra (δ, ppm, J, Hz) of Isoxazoles **5-7** (in DMSO-d_6)

Compound	Phenol protons					Isoxazole protons	Heterosubstituent protons			
	OH-2, s	H-3	R_2-4	R_3-5	H-6	H-4, s	H-5(6) d (2.0)	H-7(8) dd (8.0; 2.0)	H-8(9) d (8.0)	2-CH_2C, 4-CH_2C or O-$(CH_2)_n$-O
5c	10.84	7.23	2.35	7.07	7.77	7.28	7.29	7.71	-	5.41;4.95
5e	10.46	7.09	7.39	-	7.76	7.42	7.34	7.7	-	5.47;4.96
6a	10.64	6.95	7.36m	7.36m	7.36m	7.43	7.26	6.99	7.08	4.32
6d	10.15	6.86	2.2	2.2	7.54	7.13	7.36d (2.5)	7.36dd (8.5;2.5)	6.96d (8.5)	4.3
6e	10.92	7.06d (8.75)	7.31dd (8.75;2.4)	-	7.75d (2.44)	7.3	7.41d (2.44)	7.41dd (8.8;2.44)	6.975d (8.79)	4.31
6g	10.67	-	7.74d 2.5	-	7.66d (2.5)	7.34	7.39	7.39	6.98	4.31
7f	10.66	6.61	3.76	6.57	7.7	7.1	7.47	7.47	7.06	4.18t (2.16q)
7h	12.26	7.21 (9)	8.20dd (9.0;3.0)	-	8.55d (3)	7.39	7.5	7.5	7.07	4.21t (2.15q)

*Crystallized from EtOAc.

Benzofuran analogs of flavone [6] are recyclized by hydroxylamine primarily to isoxazole derivatives. Under special conditions [7], oximes can be prepared. On the other hand, thioderivatives of 2-benzofurylchromones react with hydroxylamine with retention of the pyrone ring to form oximes.

Isoxazoles are known [8] to act as antituberculosis and antileprosy agents. Therefore, the synthesis of 1,3-benzodioxane analogs of flavonoids with hydroxylamine is interesting.

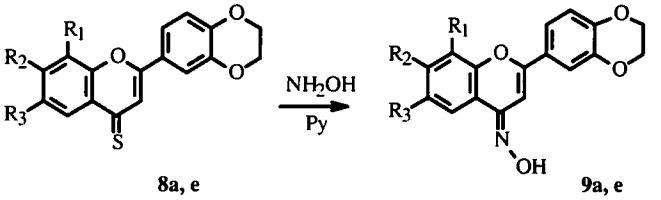
We found that heating flavones **1-3** [9-11] with hydroxylamine hydrochloride in pyridine at 100°C forms a mixture of isomeric isoxazoles **4** and **5-7**.

Fractional crystallization isolated the principal reaction products **5-7**. We isolated pure isomeric isoxazole **4a** using column chromatography. The isomeric isoxazole derivatives can be differentiated by the reactions in alcohol with iron chloride and by their chromatographic mobilities. Compound **4a**, in contrast with **6a**, has a high R_f value and forms a colored chelate owing to the phenol hydroxyl and the N atom of the isoxazole ring. The physical constants and spectral parameters are listed in Tables 1 and 2.

Several features characteristic of isoxazoles **4-7** that are prepared via recyclization of the flavones can be seen in their PMR spectra. Opening of the pyrone ring and closing of the isoxazole ring is always accompanied by a significant diamagnetic shift of the phenol protons. The diamagnetic shift of phenol proton H-3 averages 0.7 ppm compared with the corresponding

proton of the starting flavone. It is interesting that the signal of isoxazole proton H-4 moves to weaker field by 0.4 ppm compared to the position of this same proton in the starting flavone.

Thioflavones **8a** and **-e** [12, 13] react with hydroxylamine in pyridine over 15-20 min with retention of the pyrone ring and formation of oximes **9a** and **-e**.



8a, e **9a, e**

The lack of a reaction with alcoholic iron chloride and warm 2 N NaOH argues in favor of the oxime structure.

A comparison of the PMR spectra of oximes **9** and the corresponding flavones **8** suggests that the chemical shifts of the chromone protons do not change much on going from the flavone to the oxime. This similarity in the chemical shifts indicates that the starting material and the reaction product contain the chromone ring.

We used NMR and the nuclear Overhauser effect (NOE) to choose confidently between the alternative structures **6e** and **9e** for the product. Measuring the NOE for the hydroxyl proton showed an increase in the intensity for the doublet with the ortho-constant (8 Hz) by 30%; for the singlet, by 10%. Such an increase in the intensity of these signals is possible only for protons located in the vicinity of the hydroxyl proton. This corresponds to proton H-3 of the phenol ring and H-4 of the isoxazole ring.

EXPERIMENTAL

The course of the reactions and the purity of the products were monitored by TLC on Silufol UV-254 plates using benzene—ethanol (9:1). PMR spectra were measured on a Bruker WP-100 SY instrument in DMSO-d_6 with TMS internal standard. Analytical data of all compounds agreed with those calculated.

3-(2-Hydroxyphenyl)-5-(1,4-benzodioxan-6-yl)isoxazole (6a) and 3-Hetaryl-5-(2-hydroxyphenyl)isoxazoles (5-7). Solutions (6 mM) of the appropriate flavone and hydroxylamine hydrochloride (1.35 g, 18 mmole) in absolute pyridine (15 ml) were heated at 110-115°C for 10 h. The mixture was diluted with water. The precipitate was filtered off and crystallized from the appropriate solvent (see Table 1). The mother liquor of **6a** was evaporated, from which the second isomeric isoxazole **4a** was isolated by column chromatography on silica gel using benzene—ethanol (9:1) (0.15 g, 8.5% yield), mp 120-122°C (from alcohol), $C_{17}H_{13}NO_{14}$. PMR spectrum (ppm): phenol protons, 9.58 (s, 1H, OH-2), 7.08 (dd, 1H, H-3), 6.97 (td, 1H, H-4), 6.97 (td, 1H, H-5), 7.54 (dd, 1H, H-6); isoxazole protons, 6.76 (s, 1H, H-4); benzodioxane protons, 7.30 (m, H-5, -6, -7, -8), 4.30 (s, 4H, $-OCH_2CH_2O$).

2-(1,4-Benzodioxan-6-yl)chromone Oximes (9a and -e). A mixture of the appropriate 4-thioflavone (5 mmole, **8a** and **8e**) and hydroxylamine hydrochloride (1.04 g, 15 mmole) in dry pyridine (10 ml) was heated at 110-115°C for 30-40 min. The precipitate that formed after pouring the reaction mixture into water (100 ml) was filtered off and washed with water. Compound **9a**, yield 1.2 g (81.6%), mp 228 - 229°C (from isopropanol), $C_{17}H_{13}NO_4$. PMR spectrum (ppm): chromone protons, 6.97 (s, 1H, H-3), 10.91 (s, 1H, OH–N), 7.88 (dd, 1H, H-5), 7.26 (td, 1H, H-6), 7.49 (td, 1H, H-7), 6.99 (dd, 1H, H-8); benzodioxane protons, 6.99 (m, H-5, -7, -8), 4.31 (s, 4H, $-OCH_2CH_2O-$). Compound **9e**, Cl 10.3, N 4.3%, $C_{17}H_{13}ClNO_4$. PMR spectrum (ppm): chromone protons, 6.95 (s, 1H, H-3), 11.1 (s, 1H, HO–N), 7.77 (d, 1H, J = 2.4 Hz, H-5), 7.41 (m, 2H, H-7, -8); benzodioxane protons, 7.41 (m, 2H, H-5, -7), 6.97 (d, 1H, J = 9.0 Hz, H-8), 4.20 (s, 4H, $-OCH_2CH_2O$).

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