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SYNTHETIC AND MODIFIED ISOFLAVONOIDS XVI. THE INTERACTION OF SYNTHETIC ISOFLAVONE ANALOGS WITH HYDROXYLAMINE

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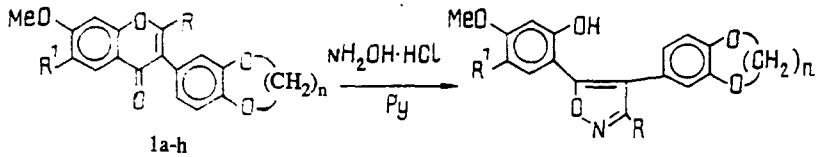
Under the action of hydroxylamine, 1,3-benzodioxolane, 1,4-benzodioxane, and 1,5-benzodioxepane analogs of isoflavones recyclize into 5-(2-hydroxyphenyl)isoxazole derivatives. Their structures have been shown by their PMR spectra.

The action of hydroxylamine on chromones has been studied by many authors [2-4]. According to the reports of earlier work, the interaction of chromones with hydroxylamine forms chromone oximes. In recent years it has been shown that the products of the reaction of hydroxylamine with chromone derivatives are not oximes but derivatives of isomeric isoxazoles [5].

In the light of the above-mentioned facts, the reaction of hydroxylamine with isoflavones might be expected to form both an oxime and two isomeric isoxazoles in each case.



1a-h 2 a-h

a: R=Me, R¹=H, n=2; b: R=Me, R¹=Pr, n=2; c: R=H, R¹=Pr, n=1; d: R=H, R¹=H, n=2; e: R=H, R¹=Et, n=2; g. R=H, R¹=Pr, n=2; h: R=H, R¹=Pr, n=3

TABLE 1. Characteristics of Compounds (2)

Compound	Yield, %	mp, °C	Empirical formula	Reaction time, h
2a	60	153	$C_{19}H_{17}NO_5$	3.5
2b	74	176	$C_{22}H_{23}NO_5$	4
2c	71	142—143	$C_{20}H_{19}NO_5$	5
2d	57	157—158	$C_{18}H_{15}NO_5$	3
2e	52	145—147	$C_{20}H_{19}NO_5$	10
2g	46	173—175	$C_{21}H_{21}NO_5$	10
2h	42	185	$C_{22}H_{23}NO_5$	14

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TABLE 2. Chemical Shifts in the PMR Spectra (δ, ppm, J, Hz) of the 4-Hetaryl-5-(2-hydroxyphenyl)isoxazoles (2a-h)

Compound	Protons of the phenol moiety					Isoxazole protons	Protons of the hetero residue	
	OH-2, s	H-3, s	MeO-4, s	R^1-5	H-6, s	R-3, s	H-4(H-5) or (H-6) H-6(H-7) or (H-8) H-7(H-8) or (H-9)	$-O(CH_2)_nO-$ n=1, 2, 3,
2a	9.9	6.46 d, (2.0)	3.74	6.40 d.d, (8.0; 2.0)	7.05 d, (8.0)	2.28	6.73 m	4.23 s
	7.07*	6.52 d, (2.0)	3.78	6.37 d.d, (8.0; 2.0)	7.11 d, (8.0)	2.28	6.78 m	4.29 s
2b	9.68	6.51	3.79	2.42 t; 1.48 m; 0.79 t	6.86	2.30	6.91 m	4.24 s
	6.92*	6.51	3.84	2.40 t; 1.42 m; 0.81 t	6.92	2.31	6.81 m	4.31 s
2c	9.86	6.62	3.80	2.49 t; 1.55 m; 0.86 t	7.03	8.94	6.90 m	5.99 s
	6.48*	6.48	3.77	2.43 t; 1.48 m; 0.83 t	7.02	8.32	6.76 m	5.91 s
2d	10.08	6.60 d, (2.0)	3.80	6.54 d.d, (8.0; 2.0)	7.23 d, (8.0)	8.93	6.86 m	4.22 s
	6.51*	6.51 d, (2.0)	3.78	6.46 d.d, (8.0; 2.0)	7.25 d, (8.0)	8.31	6.81 m	4.24 s
2e	9.82	6.59	3.81	2.51 q; 1.07 t	7.02	8.89	6.87 m	4.25 s
	6.38*	6.48	3.82	2.49 q; 1.04 t	7.1	8.33	6.84 m	4.26 s
2g	9.89	6.64	3.83	2.53 t; 1.54 m; 0.87 t	7.03	8.92	6.88 m	4.23 s
	6.43*	6.50	3.81	2.43 t; 1.49 m; 0.84 t	7.06	8.33	6.83 m	4.24 s
2h	6.50*	6.50	3.87	2.34 t; 1.51 m; 0.88 t	7.04	8.29	6.94 m	4.28 t; 2.34 q

*The PMR spectra of the compounds were measured in $CDCl_3$; in the unmarked cases the PMR spectra of the same compounds were measured in DMSO-d_6

We have established that the interaction of 3-(1,4-benzodioxan-6-yl)-7-methoxy-2-methylchromones and their dioxolane and dioxepane analogs (1a-h*) [6] with hydroxylamine hydrochloride in pyridine at 90-100°C for 3.5-4 h leads to the 5-(2-hydroxyphenyl)isoxazole derivatives (2a-h).

It must be mentioned that, on reaction with hydroxylamine, the 2-methylisoflavones (1a, b) gave only one product (2a, b) in each case, while isoflavones with 1,3-benzodioxolane, 1,4-benzodioxane, and 1,5-benzodioxepane nuclei unsubstituted in position 2 [6-8] form complex mixtures of products, although by repeated crystallization it has been possible to isolate only one of them (2c-h), in each case.

In contrast to the reaction of hydroxylamine with 3-hetarylchromones possessing nitrogen-containing residues [9, 10], its reaction with benzodioxolane, benzodioxane, and benzodioxepane analogs of isoflavone takes place relatively slowly (3-14 h) and is accompanied by the formation of mixtures of products difficult to separate and identify.

As compared with the initial isoflavones, the isoxazoles (2a-h) are distinguished by higher chromatographic mobilities in benzene—ethanol (9:1), which permits a qualitative analysis of the reaction mixtures.

The analytical and spectral characteristics of the isoxazoles are given in Tables 1 and 2.

A characteristic feature of the PMR spectra of isoxazoles (2c-h) is a paramagnetic shift of the H-3 protons of the isoxazole rings by an average of 0.5 ppm in comparison with the chemical shifts of the H-3 protons of the initial isoflavones (1c-h). The nature of the solvent affects the position of the signals of the H-3 protons of the isoxazole nuclei of the compounds under investigation. Thus, for example, in dimethyl sulfoxide solution the H-3 protons of compounds (2c-h) have a chemical shift of 8.9 ppm, and in deuterochloroform one of 8.3 ppm. Such a difference in the chemical shifts of the H-3 protons is probably due to the greater descreening of these protons by the electron-accepting nitrogen atoms in DMSO. Also in favor of the isoxazole structure of the compounds obtained are the upfield shifts in the PMR spectra of the signals of the H-6 protons of the phenol moieties of the molecules by 0.8-1.0 ppm in comparison with the initial isoflavones. This is connected with the fact that the H-6 protons fall into the regions of screening by the ring currents of rhe isoxazole rings, while in the initial compounds the opposite action is exerted by the carbonyl oxygen atoms. The signals of the phenolic OH groups of isoxazoles (2a-h) are observed in the 9.7-10.0 ppm region (in DMSO). This suggests that under these conditions the above-mentioned hydroxyls participate in the formation of intermolecular hydrogen bonds with the solvent.

Thus, isoflavones are convenient intermediates for the synthesis of 4-aryl-5-(2-hydroxyphenyl)isoxazole derivatives. The time required for the recyclization of the isoflavones into the corresponding isoxazoles increases successively on passing from the benzodioxolane to the benzodioxane and benzodioxepane derivatives.

EXPERIMENTAL

The course of the reactions and the purity of the compounds obtained were monitored by TLC on Silufol UV-254 plates in benzene-ethanol (9:1). PMR spectra were measured on a Bruker WP-100 SU instrument in DMSO-d_6 and $CDCl_3$ with TMS as internal standard. The analyses of the compounds synthesized corresponded to the calculated figures.

4-Hetaryl-5-(2-hydroxy-4-methoxyphenyl)isoxazoles (2a-h). A mixture of 2 mmole of one of the 7-methoxyisoflavones (1a-h), 0.42 g (6 mmole) of hydroxylamine hydrochloride, and 2 ml of dry pyridine was heated at 90-100°C for 3-14 h, after which it was poured into water acidified with hydrochloric acid. The precipitate that deposited was filtered off and crystallized from alcohol.

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*No compounds (1f) and (2f) are mentioned in this paper.

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