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INTERACTION OF 2-(R-AMINO)-BENZOTHIAZOLES WITH 3-FURFURYLOXY-1,2-EPOXYPROPANE

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3-Furfuryloxy-1,2-epoxypropane reacts with 2-aminobenzothiazole at the endo- and exocyclic nitrogen atoms but its R-amino derivatives – only at the nitrogen atom of the thiazole ring. Compounds isomeric with the obtained products were prepared by interaction of the same oxirane with 2-imino-3-methylbenzothiazolines and also with methylamine with subsequent treatment with 2-chlorobenzothiazole.

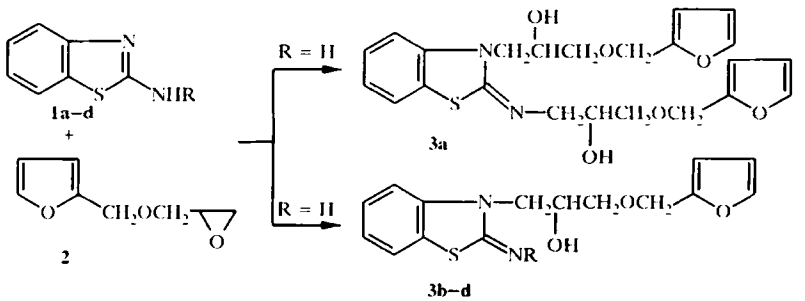
Keywords: furfuryl glycidyl ether, 2-aminobenzothiazole, alkylation, reactivity, spectroscopic parameters.

Amino alcohols, molecules of which contain heterocycles, are undoubtedly of interest due to the diversity of their chemical reactions and also the high biological activity of many compounds of this series [1, 2].

In continuation of a systematic study of 2-aminobenzothiazoles in reactions with oxiranes [3-5], we have investigated now the reaction of 2-(R-amino)benzothiazoles Ia-d with 3-furfuryloxy-1,2-epoxypropane (**2**).

Reactions of oxirane **2** with heterocyclic amines have not been studied previously. Only a few examples of the hydroxyalkylation of aliphatic amines by this compound have been reported [6-8]. Introduction of the furan ring into the molecule of epoxide **2** might be expected to lead to an increased reactivity of the oxirane ring due to the appreciable electron acceptor nature of this substituent. However, as a result of the rapid attenuation of the inductive effect and the easy oxidizability of furfuryl derivatives it is impossible to predict, *a priori*, the activity of oxirane **2** in nucleophilic substitution reactions.

Treatment of unsubstituted 2-aminobenzothiazole **1a** with an excess of epoxide **2** at 100°C in the presence of a catalytic amount of water gives the bis-addition product **3a** (i.e. hydroxylation of both the endo- and exocyclic nitrogen atoms takes place). Opening of the epoxide ring, in agreement with the Krasuskii rule [9], occurs at the less substituted cyclic carbon atom.



a R = H, b R = Me, c R = C_2H_5, d R = COMe

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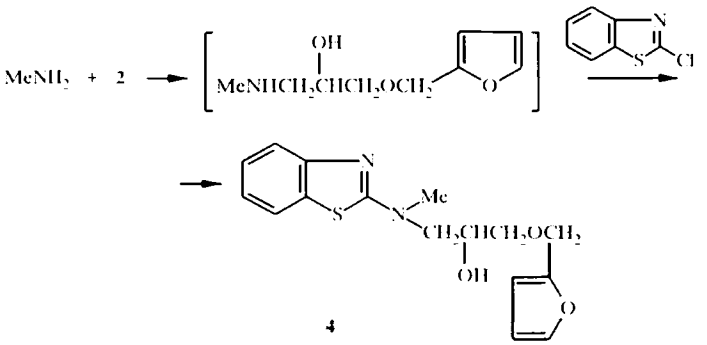
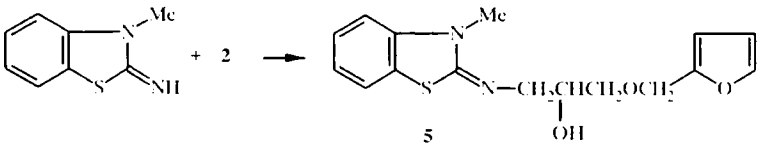
For the substituted amines **1b-d**, under the same conditions, hydroxyalkylation occurs only at the cyclic nitrogen atom to give the corresponding products **3b-d**. Exchange of an alkyl residue for acyl has a negative effect on the yield of product **3d** (see Table 1). The yields of compounds **3a-d** are not significantly different to the yields of the products of reaction of amines **1a-d** with glycidyl phenyl ether [10]. Hence exchange of the phenyl group for furfuryl does not change the reactivity of oxirane.

Using epoxide **2** we have synthesized aminobenzothiazoles **4** and **5** which contain the α-furfuryloxy-β-hydroxypropyl substituent only at the exocyclic nitrogen atom. Hence the amino alcohol **4** was obtained by condensation of methylamine with oxirane **2** and subsequent treatment of the obtained adduct with 2-chlorobenzothiazole.



The amino alcohol **5** is isomeric with compounds **3b** and **4** and is formed as a result of the reaction of oxirane **2** with 2-imino-3-methylbenzothiazoline.



Judging by the yield of compound **5**, hydroxyalkylation of iminobenzothiazoline occurs much less readily than with the amino isomer **1b**.

TABLE 1. Characteristics of Compounds **3** and **4**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	R_f	Yield, %
		C	H	N			
3a	$C_{13}H_{16}N_2O_4S$	60.06 / 60.26	5.51 / 5.68	6.30 / 6.11	Oil*	0.66	22
3b	$C_{10}H_{18}N_2O_4S$	60.51 / 60.38	5.82 / 5.66	8.92 / 8.81	86-87.5	0.32	48
3c	$C_{17}H_{20}ON_2O_4S$	61.27 / 61.45	6.20 / 6.02	8.65 / 8.43	83.5-85	0.36	62
3d	$C_{17}H_{18}N_2O_4S$	59.19 / 58.96	5.41 / 5.20	8.32 / 8.09	108-109	0.77	19
4	$C_{16}H_{18}N_2O_4S$	60.55 / 60.38	5.80 / 5.66	9.01 / 8.81	76-78	0.67	74
5	$C_{16}H_{18}N_2O_4S$	60.13 / 60.38	5.85 / 5.66	8.68 / 8.81	Oil*[2]	0.71	23

* mp of hydrochloride 148-150°C

*[2] mp of hydrochloride 146-147°C

TABLE 2. Spectral Characteristics of the Compounds Synthesized

Compound	IR spectrum, ν, cm^{-1}		UV spectrum, λ_{max}, nm	PMR spectrum, δ, ppm*	Mass spectrum, m/z, (I, % of I_{max})			
	OH	C=N			M^+	X	Y	other ions
3a	3430	1630	222, 266, 303	3.50-3.85 (6H, m, CH_2N, $2CH_2O$); 4.30-4.61 (8H, m, 2CH, $2CH_2O$, CH_2N); 6.19-6.50 (4H, m, H_{fur}); 7.05-7.65 (6H, m, H_{arom})	458(10)	304(45)	317(100)	378(11), 377(42), 347(28), 318(23), 305(11), 221(13), 208(25), 193(10), 164(18), 163(39), 150(17), 136(16), 81(40)
3b	3240	1620	222, 262, 303	3.05 (3H, s, CH_3); 3.50 (2H, d, CH_2O); 3.95-4.23 (3H, m, CH, CH_2N); 4.45 (2H, s, CH_2O); 6.00 (1H, br. s, OH); 6.35 (2H, d, H_{fur}); 7.12-7.50 (5H, m, H_{arom})	318(15)	164(100)	177(17)	238(16), 237(10), 208(10), 207(54), 178(20), 166(15), 165(24), 163(14), 136(28), 135(12)
3c	3210	1620	230, 265, 303	1.23 (3H, t, CH_3); 2.95-3.50 (4H, m, CH_2O, CH_2CH_3); 3.95-4.24 (3H, m, CH_2N, CH); 4.31 (2H, s, CH_2O); 6.30-6.45 (3H, m, OH, H_{fur}); 6.95-7.45 (5H, m, H_{arom})	332(15)	178(100)	191(16)	252(12), 251(58), 222(11), 221(55), 192(11), 179(25), 177(25), 164(12), 163(27), 150(36), 136(23), 134(20), 109(14), 81 (24)
3d	3415	1600*[2]	208, 233 (sh.), 313	2.25 (3H, s, CH_3); 3.50 (2H, d, CH_2O); 4.10-4.35 (1H, m, CH); 4.40 (2H, s, CH_2O); 4.50 (2H, d, CH_2N); 5.41 (1H, br. s, OH); 6.36 (2H, d, H_{fur}); 7.33-7.75 (5H, m, H_{arom})	346(12)	192(58)	205(7)	265(51), 250(37), 245(44), 223(40), 206(22), 194(12), 193(71), 191(20), 177(11), 175(13), 164(20), 163(23), 151(29), 150(100), 136(20), 81(61)
4	3260	1570	223, 273	3.13 (3H, s, CH_3); 3.50 (2H, d, CH_2O); 3.71 (2H, dd, CH_2N); 3.95-4.25 (1H, m, CH); 4.50 (2H, s, CH_2O); 4.92 (1H, br. s, OH); 6.35 (2H, d, H_{fur}); 6.95-7.75 (5H, m, H_{arom})	318(35)	164(62)	177(100)	237(26), 207(36), 179(12), 178(34), 165(13), 163(10), 149(25), 136(41), 135(12), 120(10), 109(11), 81(15)
5	3470	1645	222, 264, 301	3.70 (3H, s, CH_3); 3.55-3.85 (4H, m, CH_2N, CH_2O); 4.43-4.73 (3H, m, CH, CH_2O); 6.27-6.45 (2H, m, H_{fur}); 7.08-7.73 (5H, m, H_{arom})	318(35)	164(10)	177(84)	237(10), 223(18), 222(100), 207 (20), 205(12), 179(24), 178(62), 163(10), 149(16), 136(51), 135(11), 109(21), 81(19)

* H_{arom} , protons of the C_6H_4 fragment and H_{fur}.

*[2] Vibrations of the C=N–C=O conjugated system.

The structure of the synthesized compounds agrees with the results of elemental analysis and is confirmed by PMR, IR, and UV spectroscopic data (Table 2), and in the case of alcohols **3b**, **4**, and **5**, also by comparison of these spectroscopic parameters. Hence, in their IR spectra, the stretching absorption bands of the exocyclic (in compounds **3a-d**, **5**) and the endocyclic (compound **4**) C=N bonds are significantly different.

In their UV spectra, on the transition from aminobenzothiazole **4** to iminobenzothiazolines **3a-d**, there appears a long-wavelength maximum which undergoes a significant hypsochromic shift in the presence of conjugated chain of atoms C=N–C=O (see **3d**).

In the PMR spectra, the signals for the methylene protons next to the endocyclic nitrogen atom are found at a lower field than the signals for the same protons on the exocyclic nitrogen atom. In their mass spectra the ratio of the intensity of the ion peaks for $[M\text{-}CH_2CH(OH)CH_2OCH_2Fur]^+$ (ions X in Table 2) and $[M\text{-}CH(OH)CH_2OCH_2Fur]^+$ (ions Y in Table 2) clearly characterize both the amino- or imino structure of heterocyclic amino alcohol and the spatial location of the hydroxyalkyl substituent [11].

EXPERIMENTAL

Mass spectra were recorded on an MX-1303 spectrometer (direct sample introduction) and PMR spectra for solutions of compounds **3a**, **5** in deuteropyridine and compounds **3b-d** and **4** in deuterochloroform were measured on a Jeol C-60 HL spectrometer using TMS as internal standard. IR spectra were taken on a UR-20 instrument for KBr tablets and UV spectra – on a Hitachi EPS-3T spectrometer for solutions in ethanol. Separation and purification of the materials were carried out on L 100/125 silica gel columns with consecutive elution using hexane, benzene, and acetone. The purity of the compounds prepared was monitored using TLC on Silufol UV-254 plates in the system benzene–chloroform–acetone (1:1:2) for compounds **3a,d**, **4**, and **5** and in benzene–acetone (5:1) for compounds **3b,c**.

2-Aminobenzothiazole (1a) was a commercial product. The following compounds were synthesized by known methods : **1b** [12], **1c** [13], **1d** and 2-imino-3-methylbenzothiazoline [14], 2 [6], and 2-chlorobenzothiazole [15].

2-(γ-Furfuryloxy-β-hydroxypropyl)imino-3-(γ-furfuryloxy-β-hydroxypropyl)-2,3-dihydrobenzothiazole (3a), 2-R-Imino-3-(γ-furfuryloxy-β-hydroxypropyl)-2,3-dihydrobenzothiazoles (3b-d), 2-(γ-Furfuryloxy-β-hydroxypropyl)-3-methyl-2,3-dihydrobenzothiazole (5). Water (1 drop) was added to mixture of aminobenzothiazole **1a-d** (10 mmol) and oxirane **2** (15 mmol) and the product obtained was stirred for 20 h at 100°C. After cooling, the corresponding products **3a-d** were isolated from the reaction mixture using column chromatography. They were recrystallized from benzene (compound **3b**), a mixture of hexane and benzene (5:1) (compound **3c**) or from ethanol (compound **3d**, hydrochlorides of compounds **3a** and **5**).

2-[N-Methyl-N-(γ-furfuryloxy-β-hydroxypropyl)amino]benzothiazole (4). Oxirane **2** (2 g, 13 mmol) was poured into a solution of methylamine (3.72 g, 120 mmol) in absolute methanol (15 ml) and the mixture obtained was held in a sealed ampoule for 10 h at 100°C. After cooling, the solvent and excess methylamine were evaporated and 2-chlorobenzothiazole (1.34 g, 8 mmol) was poured into the product which was then stirred for 2 h at 130°C, cooled, and washed with water. The product **4** was separated from the washed, dry reaction mass by column chromatography and it was recrystallized from ethanol.

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