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REACTION OF EPICHLOROHYDRIN WITH 2-AMINOBENZOTHIAZOLE AND ITS DERIVATIVES

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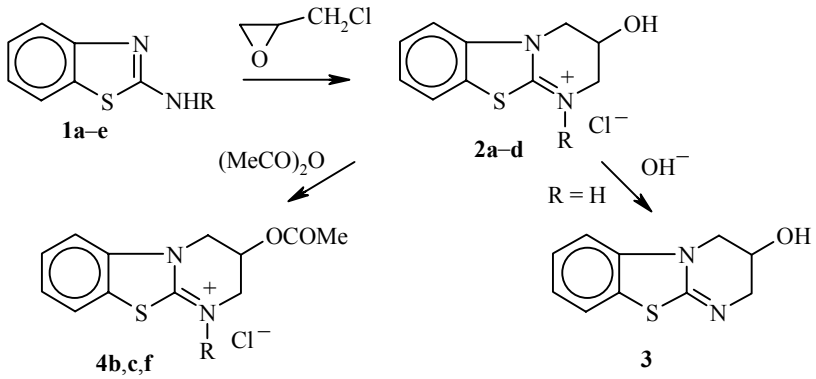
We have shown that 2-aminobenzothiazoles when reacted with epichlorohydrin form 3-hydroxytetrahydropyrimido[2,1-b]benzothiazolium chlorides, while 2-iminobenzothiazolines form 2-(γ-chloro-β-hydroxypropyl)iminobenzothiazolines.

Keywords: 2-aminobenzothiazole, tetrahydropyrimidobenzothiazolium chlorides, epichlorohydrin, alkylation, spectral characteristics.

The reaction of epichlorohydrin with aliphatic and aromatic amines leads to formation of products of different structures [1, 2]. Heterocyclic amines behave similarly. Thus ambifunctional nucleophiles of the 2-aminoimidazole type, depending on the reaction conditions, form heterocyclylhalohydrins, epoxyalkyl derivatives, or products with a bis-heterocyclic structure [3, 4].

The goal of our work was to study the reaction of aminobenzothiazoles and iminobenzothiazolines with epichlorohydrin. In neutral medium (benzene, methanol, acetone), 2-aminobenzothiazole (**1a**) and its 2-alkyl derivatives **1b-d** at 20°C form the products of reaction at both reaction centers of the ambifunctional system of atoms H_2N–C=N: tetrahydropyrimidobenzothiazolium chlorides **2a-d**, but their yield is at most 2%.



a R = H, **b** R = Me, **c** R = Et, **d** R = CH_2Ph, **e** R = Ph, **f** R = COMe

Raising the reaction temperature up to 60-65°C leads to polymerization of the reaction mixture. In the literature, cases are noted of spontaneous polymerization even at room temperature upon reaction of epichlorohydrin with such nitrogen-containing heterocycles as benzimidazole [5] and 4-amino-1,2,4-triazole [6].

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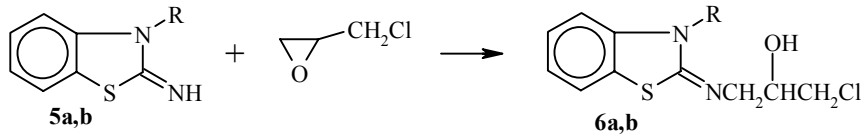
In acid medium at 60-65°C, no polymerization is observed. The reaction products even under these conditions are the quaternary salts **2a-d**, but their yield is significantly higher (Table 1). In the case of amine **1e**, no reaction product could be obtained. Thermostatting the reaction made it possible to establish that introducing an alkyl substituent into the 2-aminobenzothiazole molecule (compounds **1b,c**) insignificantly reduces the yield of products, while the presence of an aralkyl substituent (compound **1d**) has a clearly negative effect.

By neutralization of the quaternary salt **2a**, we can isolate the corresponding base **3**. We studied the chemical properties of the products **2a-c** for the example of the acetylation reaction, which leads to O-acyl- (compounds **4b,c**) or N,O-diacyl- (compound **4f**) derivatives.

Reaction of 3-substituted 2-iminobenzothiazolines **5a,b** with epichlorohydrin in ethanol upon heating occurs regioselectively at the imino group, and cyclization of the 2-(γ-chloro-β-hydroxypropyl)iminobenzothiazolines **6a,b** does not occur.



a R = Me, **b** R = Ph

This fact allows us to hypothesize that the intermediates in reaction of compounds **1a-d** with epichlorohydrin are the products of alkylation at the endocyclic nitrogen atom. Otherwise, intramolecular cyclization would not occur under the reaction conditions. Polymerization of the products in these cases is also not observed, although the reactions are carried out in neutral medium.

Conclusions concerning the structure of the synthesized compounds were drawn on the basis of combined analysis of the mass (Table 2), IR, and ^{1}H NMR (Table 3) spectra, which agree well with their structure and are confirmed by elemental analysis (Table 1). In the mass spectra of salts **2c**, **2d**, and **4f**, no molecular ions are detected but we observe $[M\text{-}HCl]^+$ (except for compound **4f**) and $[M\text{-}RCl]^+$ ion peaks. The mass spectrum of the quaternary salt **2a** is identical to the mass spectrum of the base **3**.

TABLE 1. Characteristics of Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	R_f	Yield, %
		C	H	N			
2a	$C_{10}H_{11}ClN_2OS$	49.36 / 49.48	4.48 / 4.54	11.55 / 11.55	276 dec.	0.10	61
2b	$C_{11}H_{13}ClN_2OS$	51.62 / 51.46	5.09 / 5.07	11.04 / 10.92	233-235	0.16	60
2c	$C_{12}H_{15}ClN_2OS$	53.55 / 53.23	5.74 / 5.58	10.62 / 10.35	150-152	0.24	55
2d	$C_{17}H_{17}ClN_2OS$	61.59 / 61.34	5.10 / 5.15	8.51 / 8.40	124-125	0.42	28
3	$C_{10}H_{10}N_2OS$	58.36 / 58.25	4.91 / 4.85	13.73 / 13.59	244 dec.	0.21	90
4b	$C_{13}H_{15}ClN_2O_2S$	52.05 / 52.26	4.97 / 5.03	9.23 / 9.38	253-254	0.32	92
4c	$C_{14}H_{17}ClN_2O_2S$	53.92 / 53.76	5.54 / 5.44	9.15 / 8.96	194-196	0.36	94
4f	$C_{14}H_{15}ClN_2O_3S$	51.15 / 51.45	4.71 / 4.63	8.64 / 8.57	143-145	0.34	75
6a	$C_{11}H_{13}ClN_2OS$	51.29 / 51.46	4.96 / 5.07	10.90 / 10.92	90-91	0.74	50
6b	$C_{16}H_{15}ClN_2OS$	60.47 / 60.28	4.84 / 4.71	8.91 / 8.79	79.5-81	0.73	32

TABLE 2. Mass Spectra of Synthesized Compounds

Compound	*m/z* (intensity, %)
2b	258 (3), 256 (8), 220 (61), 206 (90), 189 (50), 187 (100), 178 (59), 163 (62), 162 (55), 149 (49), 136 (75), 135 (81)
2c	234 (25), 206 (40), 191 (35), 187 (31), 178 (39), 163 (97), 150 (100), 149 (35), 136 (52), 135 (70)
2d	297 (2), 207 (16), 206 (100), 189 (8), 164 (40), 163 (44), 147 (7), 137 (14), 136 (53), 127 (57)
3	206 (100), 189 (28), 175 (14), 163 (78), 162 (67), 161 (14), 149 (22), 137 (11), 136 (28), 135 (89), 134 (11)
4c	314 (26), 312 (61), 248 (15), 216 (15), 203 (17), 188 (55), 187 (100), 178 (24), 163 (53), 150 (33), 136 (31), 135 (40)
4f	249 (5), 206 (11), 189 (66), 188 (100), 177 (38), 164 (13), 163 (15), 150 (24), 137 (30), 136 (53)
6a	258 (2), 256 (5), 206 (3), 178 (4), 177 (16), 176 (100), 164 (5), 150 (4), 149 (8), 137 (4), 136 (34), 135 (5), 109 (16)
6b	320 (4), 318 (12), 269 (6), 241 (7), 240 (20), 239 (100), 225 (3), 212 (5), 211 (6), 198 (3), 180 (7), 149 (3)

In the ^{1}H NMR spectra of compounds **2-4**, signals from methylene groups bonded to cyclic nitrogen atoms appear as rather narrow multiplets with unresolved structure due to hindrance of rotation about the C=N bond. Signals from methine groups appear similarly.

Thus the structure of the reaction products for the derivatives of 2-aminobenzothiazole reacted with epichlorohydrin depends on the amino or imino structure of the substrate.

TABLE 3. IR and ^{1}H NMR Spectra of Synthesized Compounds

Com-pound	IR spectrum, ν, cm^{-1}		^{1}H NMR spectrum, δ, ppm			
	OH, (CO)	C=N	CH_3	CH_2–N	CH, (OH)	H_{arom}, m
2a	3250	1630	—	3.5 m; 4.0 m	4.6 m (8.2 s)	6.75-7.54
2b	3165	1635	3.07 s	3.65 m; 4.07 m	4.7 m	7.02-7.50
2c	3220	1620	1.05 t	3.32 q; 3.55 m; 4.05 m	4.68 m	7.15-7.50
2d	3400	1615	—	3.53 m; 4.08 m; 4.45 s	4.53 m	6.80-7.51
3	3150	1630	—	3.45 m; 4.0 m	4.6 m	6.77-7.48
4b	(1740)	1635	1.70 s; 3.05 s	3.6 m; 4.09 m	5.55 m	7.20-7.40
4c	(1740)	1625	1.08 m; 1.78 s	3.40 m; 3.62 m; 4.12 m	5.55 m	7.02-7.45
4f	(1720), (1750)	1630	1.75 s; 2.25 s	3.85-4.73 m (4H)	5.7 m	7.10-7.72
6a	3260	1615	3.30 s	3.20 d; 3.55 d*	(3.0 br. s) 3.8-4.05 q	6.70-7.30
6b	3320	1610	—	3.25 d; 3.45 d*	(2.8 br. s) 3.7-4.05 q	6.52-7.50

* Signals from CH_2Cl.

EXPERIMENTAL

The IR spectra were taken on a UR-20 spectrophotometer in KBr pellets. The ^{1}H NMR spectra of compounds **2a, 6a,** and **6b** in CDCl3 and the rest of the compounds in trifluoroacetic acid were recorded on a Tesla BS-567 (100 MHz) at 20-25°C, internal standard HMDS. The mass spectra were obtained on an MKh-1310 with ionization energy 50 eV, with direct injection of the sample into the ion source. For the TLC, we used Silufol UV-254 plates and visualization by iodine vapor. Compounds **6a,b** were chromatographed in the system 1:1:2 benzene–chloroform–acetone; the rest of the compounds were eluted with ethanol.

2-Aminobenzothiazole **1a** was a commercial product. The compounds listed below were synthesized by familiar procedures: **1b,c** [7], **1d** [8], **1e** [9], **5a** [10], **5b** [11].

1-R-3-hydroxy-2,3,4,5-tetrahydropyrimido[2,1-*b*]benzothiazolium Chlorides (2a-d). Epichlorohydrin (20 mmol) was added to a solution of amine **1a-d** (10 mmol) in glacial acetic acid (15 ml), and then stirred at 65°C for 7 h. The acetic acid was driven off at reduced pressure; distilled water (50 ml) was added to the oily residue. The unreacted amine **1a-d** precipitated and was filtered off. The filtrate was evaporated off, the residue was treated with dry acetone (50 ml), the insoluble residue was filtered off and recrystallized from absolute ethanol.

3-Hydroxy-2,3,4,5-tetrahydropyrido[2,1-*b*]benzothiazole (3). Salt **2a** (2.43 g, 10 mmol) was dissolved in water (20 ml) and then neutralized with NH_4OH solution until it tested alkaline. The precipitate was filtered off, washed with water, and recrystallized from ethanol. Compound **3** 1.85 g (90%) was obtained; mp 244°C (decomp.).

1-R-3-acetoxy-2,3,4,5-tetrahydropyrimido[2,1-*b*]benzothiazolium Chlorides (4b,c,f). A mixture of the quaternary salt **2a-c** (5 mmol) and acetic anhydride (20 mmol) were boiled for 2.5 h. The excess anhydride was driven off under vacuum. The residue was recrystallized from absolute ethanol.

2-(γ-Chloro-β-hydroxypropyl)imino-3-methylbenzothiazoline (6a). Epichlorohydrin (1.85 g, 20 mmol) was added to a solution of 2-imino-3-methylbenzothiazoline (1.64 g, 10 mmol) in ethanol (15 ml). This was stirred for 5 h at 65°C. The ethanol was driven off, the residue was extracted several times with hexane. The solvent was removed from the extract. Yield of compound **6a** 1.28 g (50%); mp 90-91°C (benzene–hexane, 1:1).

2-(γ-Chloro-β-hydroxypropyl)imino-3-phenylbenzothiazoline (6b). Obtained similarly from 2-imino-3-phenylbenzothiazoline (1.13 g, 5 mmol) and epichlorohydrin (0.92 g, 10 mmol) in ethanol (15 ml). The product was purified by chromatographing on a column with silica gel L 100/160, eluting with a 1:1 mixture of benzene–chloroform. Yield 0.51 g (32%); mp 79.5-81°C (hexane).

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