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ON INTERACTION OF 2-AMINO-BENZOTHIAZOLES WITH HALOHYDRINS

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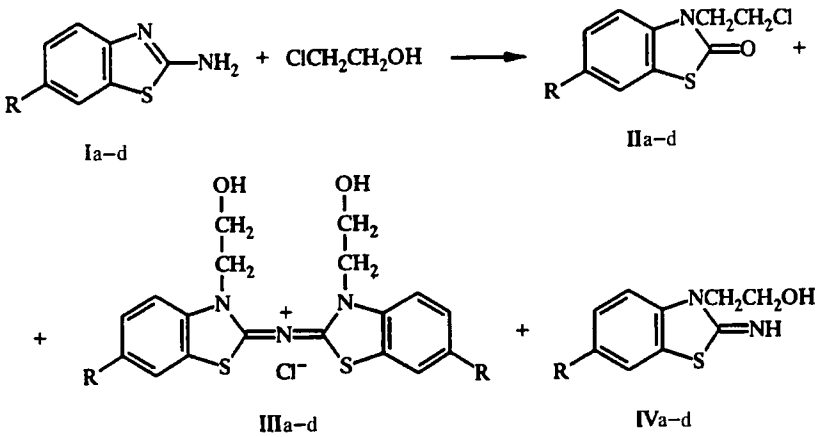
Interaction of 2-aminobenzothiazoles with ethylene chlorohydrin on boiling leads mainly to formation of the corresponding 3-(β-chloroethyl)benzothiazolin-2-ones. Reducing the reaction temperature increases the fraction of 2-imino-(3-β-hydroxyethyl)benzothiazolines. In both instances formation of bis[3-(β-hydroxyethyl)benzothiazol-2-ylidene]ammonium chlorides is observed. The reaction of 2-aminobenzothiazole with propylene bromohydrin gives only the corresponding amino alcohols. The anomalous products from the reaction of β-chloroethyl derivatives of benzothiazolinones result from a dominating side reaction of the starting 2-aminobenzothiazoles with the ethylene chlorohydrin thermolysis products that are formed on boiling.

We have reported previously [1, 2] that interaction of 2-aminobenzothiazole (Ia) and its 2-substituted derivatives with ethylene chlorohydrin upon boiling gives mainly 3-(β-chloroethyl)benzothiazolin-2-one (IIa), which is an uncharacteristic product of such reactions. We investigated this process further by reacting 6-substituted derivatives of 2-aminobenzothiazole (Ib-d) with ethylene chlorohydrin. Alkylation in neutral medium under conditions, where the reaction is strictly kinetically controlled, occurs mainly at the endocyclic nitrogen atom of the benzothiazole ring because the effect of the substituents on the aromatic ring of such heterocyclic amines is transferred mainly *via* this nitrogen atom [3, 4].

Boiling of amines Ib-d, which contain electron-donating substituents or halogen atoms on the aromatic ring, in solution of ethylene chlorohydrin gives mainly 6-substituted 3-(β-chloroethyl)benzothiazolin-2-ones (IIb-d). In addition, bis[3-(β-hydroxyethyl)-6-R-benzothiazol-2-ylidene]ammonium chlorides (IIIb-d) and small amounts of 2-imino-3-(β-hydroxyethyl)-6-R-benzothiazolines (IVb-d) are produced (Table 1). Therefore, the behavior is completely analogous to that of amine Ia [2].



a R = H, b R = CH_3, c R = CH_3O, d R = Cl

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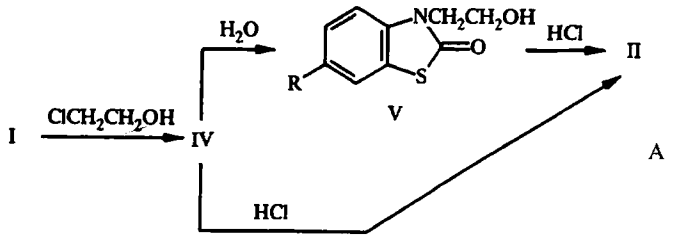
TABLE 1. Yields and Preparation Conditions of Compounds II-IV

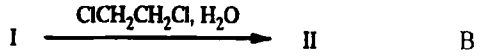
Starting amine	Reaction temperature, °C	Reaction time, h	Yield, %		
			II	III	IV
Ia	90-95	10	6	10	39
	130-135	2	55	15	10
Ib	90- 95	10	11	13	45
	130-135	2	62	27	3
Ic	90-95	10	7	6	48
	130-135	2	75	10	5
Id	90- 95	30	9	16	23
	130-135	4	56	17	9

The properties of II and III, which are described for the first time, are given in Table 2.

We proposed that the anomalous paths of the reaction of amines Ia-d with ethylene chlorohydrin depend on the conditions of interaction. Therefore, we performed these reactions at a lower temperature (90-95°C). In fact, amino alcohols IVa-d were the principal products of reaction under these conditions whereas benzothiazolinones IIa-d were isolated in small quantities (Table 1). Nevertheless, none of the reactions was selective. The reaction rate noticeably decreases if the temperature is lowered. The reaction time had to be increased to 30 h in order to get an acceptable yield of the desired products for the least reactive amine Id. In our opinion, the reason for such a specific temperature influence is as follows. A study of main regularities of the thermal decomposition of anhydrous ethylene chlorohydrin in liquid phase at 110-150°C has shown that the primary thermolysis products are 2-chloroethyl ether of ethylene glycol and hydrogen chloride. Secondary transformations of these compounds produce 1,2-dichloroethane, water, and several other compounds [5, 6]. Although ethylene chlorohydrin reacts to a small extent, the reactions are irreversible. Therefore, it is completely probable that benzothiazolinones IIa-d form by path A - amino alcohols IV obtained are hydrolyzed into the corresponding 3-(β-hydroxyethyl)benzothiazolin-2-ones (V). The hydroxyl group in these compounds is replaced by halogen under the action of hydrogen chloride simultaneously or sequentially:



Path B is also possible, where the starting amines I react preferentially with the decomposition products of ethylene chlorohydrin.

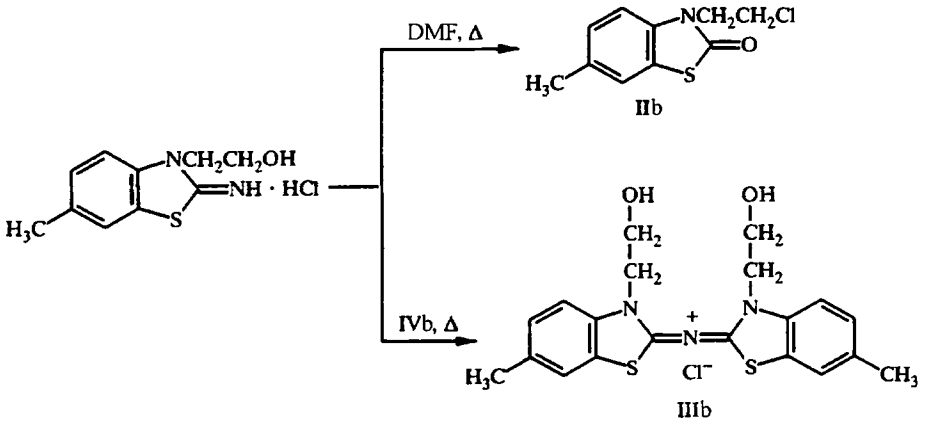


Obviously Path A is more realistic because amines Ia-d are in fact hydroxyethylated to give amino alcohols IVa-d if the temperature is lowered. Amino alcohols IV apparently transform into the β-chloroethyl derivatives II, bypassing the step of formation of V, because we did not observe benzothiazolinones V in the reaction mixtures. As for Path B, we boiled amine Ia for 5 h in both an equilibrium mixture of dichloroethane–water and in a dichloroethane–xylene mixture (xylene was chosen as an inert solvent with boiling point close to that of ethylene chlorohydrin) with an equimolar amount of water added in order to check the possibility that it occurs. However, product IIa was not identified in either instance.

TABLE 2. Characteristics of Synthesized Compounds

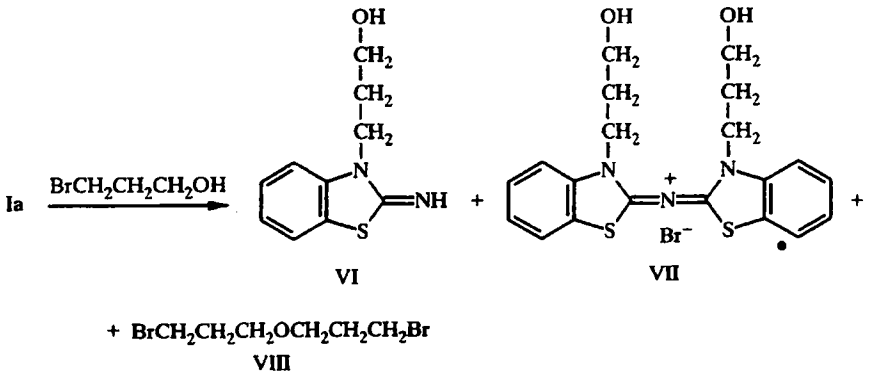
Compound	Empirical formula	Found, % / Calculated, %			mp, °C	IR spectrum, ν, cm^{-1}	UV spectrum, λ_{max}, nm	Mass spectrum, *m/z* (I_{rel}, %)	
		C	H	N				M^+	Fragment ions
IIb	$C_{10}H_{10}ClNOS$	52.67 / 52.75	4.17 / 4.43	6.03 / 6.15	98-99	1700, 1590,1495	216, 249, 287, 296.5	227(53)	178(42), 165(47), 150(100), 137(12), 123(13), 121(12), 109(11), 77(11)
IIc	$C_{10}H_{10}ClNO_2S$	49.02 / 49.28	4.18 / 4.14	5.59 / 5.75	74-75	1680, 1592, 1500	217, 255, 300	243(100)	194(52), 181(41), 166(91), 151(39), 136(23), 80(10)
IId	$C_9H_7Cl_2NOS$	43.60 / 43.56	2.85 / 2.84	5.41 / 5.64	149-150	1683, 1596,1480	220, 256, 294, 300.5	247(90)	198(59), 185(65), 170(100), 157(12), 134(14), 108(13)
IIIb	$C_{20}H_{22}ClN_3O_2S_2$	55.12 / 55.10	4.85 / 5.09	9.54 / 9.64	236-238	3280, 1608,1555	219, 228 (sh), 268, 376, 386	—	399(10), 235(100), 191(20), 165(12), 164(11)
IIIc	$C_{20}H_{22}ClN_3O_4S_2$	51.37 / 51.33	4.70 / 4.74	8.91 / 8.98	236-237	3271, 1602, 1514, 1488	214 (sh), 231 (sh), 274, 390	—	431(9), 251(100), 207(17), 181(14), 180(13), 166(11)
IIId	$C_{18}H_{16}Cl_3N_3O_2S_2$	45.12 / 45.34	3.27 / 3.38	9.04 / 8.81	240-242	3300, 3235, 1595, 1510	214 (sh), 269, 373, 386	—	439(5), 255(100), 211(20), 184(19), 170(12)
VI	$C_{10}H_{12}N_2OS$	57.90 / 57.67	5.67 / 5.81	13.49 / 13.45	Oil	3273, 1600, 1577	222, 263, 288	208(13)	164(30), 150(100), 136(12), 123(28), 96(22)
VII	$C_{20}H_{22}BrN_3O_2S_2$	49.85 / 50.00	4.60 / 4.62	8.57 / 8.75	237-239	3345, 3210, 1595, 1545	222(sh), 266, 303, 368, 379	—	399(17), 256(10), 235(100), 202(23), 200(19), 177(24), 164(31), 150(33), 149(34)

Compounds IIIa-d can be synthesized *via* acid-catalyzed condensation of two molecules of starting amines Ia-d with subsequent alkylation of the intermediate dibenzothiazolylammonium compounds by two molecules of ethylene chlorohydrin and *via* condensation of amino alcohols IVa-d occuring in the reaction mixture in the presence of hydrogen chloride. We attempted to prepare the compound IIIb by heating of IVb hydrochloride in DMF according to the literature method [7]. However, the main reaction product was the compound IIb, so confirming that Path A is the most probable.



At the same time condensation of amino alcohol IVb with equimolar amount of its hydrochloride in the absence of solvent upon heating gave the salt IIIb.

The nature of interaction of other halohydrins with 2-aminobenzothiazoles was also of interest. Thus, we carried out reaction of amine Ia with 3-bromopropan-1-ol. As it turned out, this reaction either with heating or at room temperature gave a mixture of amino alcohols VI and the corresponding ammonium salt VII. The properties of VI-VII are given in Table 2.



Di(γ-bromopropyl) ether (VIII) isolated from the reaction mixture is a transformation product of 3-bromopropan-1-ol. Consequently, transformation of halohydrins similar to their thermolysis may occur at room temperature or upon heating. Thermal decomposition of the isomeric 2-chloropropan-1-ol and 1-chloropropan-2-ol [6, 8] does not produce halo ethers of similar type although the corresponding halo ether was identified among the ethylene chlorohydrin thermolysis products [5], i.e., such ethers are apparently formed only from unbranched halohydrins.

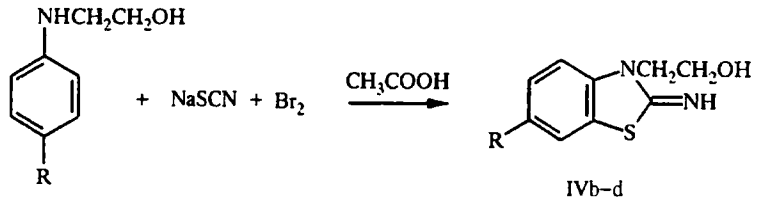
Thus, introduction of electron-donating substituents or halogen in the 6-position of the benzothiazole ring does not change the path of the reaction of 2-aminobenzothiazole with ethylene chlorohydrin. Composition of the products of these reactions depends mainly on the reaction conditions. If the reagents are boiled, the side reaction predominates in which the heterocyclic amino alcohols react mainly with the ethylene chlorohydrin decomposition products.

The structures of the synthesized compounds were established by performing an independent synthesis of compounds IIb and IIIb and using physicochemical methods of characterization (Tables 2 and 3).

TABLE 3. PMR Spectral Characteristics of Compounds II and VI

Compound	Chemical shifts, δ, ppm		
	CH_2	H_{arom} (m)	other protons
IIb	3.75 (t); 4.21 (t)	7.10-7.40 (3H)	2.30 (3H, s, Me)
IIc	3.78 (t); 4.20 (t)	6.76-7.31 (3H)	3.72 (3H, s, MeO)
IId	3.5 (t); 4.19 (t)	6.95-7.37 (3H)	—
VI	1.65-2.05 (m); 3.48 (t); 4.03 (t)	6.70-7.40 (4H)	5.30 (2H, br. s, NH, OH)

We previously synthesized amino alcohols IVb-d by thiocyanation of *p*-substituted N-β-hydroxyethylarylamines [9].



IVb–d

The IR spectra of chloroethyl derivatives IIb-d exhibit an intense absorption at 1680-1700 cm^{-1}, which is characteristic of the carbonyl group in benzothiazolin-2-ones. The lack of absorption bands at 3000-3500 cm^{-1} indicates that there are no NH or OH groups in these compounds. The UV spectra of compounds IIb,d, IIIb,d, and VII reveal fine vibrational structure of the long-wavelength maximum. This structure is not apparent for methoxy derivatives IIc and IIIc. A small shift of the B-band and a very large hypsochromic shift of the long-wavelength maximum are typical for salts IIIb-d and VII.

The mass spectra of IIb-d and VI have strong peaks for the molecular ions. In contrast with them, the electron-impact and liquid-desorption secondary-ion mass spectra of the compounds IIIb-d and VII lack peaks for the molecular ions. However, fragments formed by elimination of HCl (salts IIIb-d) or HBr (salt VII) from the molecular ions are seen (Table 2). Such behavior is characteristic of quaternary salts of heterocyclic amines [10]. These ions are protonated in the LSIMS spectra. PMR spectra of these compounds could not be recorded owing to low solubility of samples.

EXPERIMENTAL

The purity of the compounds was monitored by TLC on Silufol UV-254 plates. Silica gel of grade L100/160 was used for column chromatography. The eluent was hexane, benzene, or acetone.

IR spectra were recorded on a UR-20 spectrometer in KBr pellets; UV spectra were obtained on a Hitachi EPS-3T instrument in ethanol. PMR spectra of $CDCl_3$ solutions of IIc, VI, and the remaining compounds in deuteromethanol were measured on a Tesla BS-567 (100 MHz) spectrometer with HMDS as internal standard. Preliminary mass spectra and LSIMS were recorded on a MX 1310 instrument with direct-probe sample introduction, an ion source at 120-300°C, and 60-70 eV ionizing potential. The reference substance was perfluorokerosene. Secondary-ion mass spectra were obtained using an LSIMS ion source with a beam of Cs^+ ions accelerated to 7 keV. The accelerating potential was 5 kV. Samples were dispersed in glycerol and coated on a direct-probe steel target.

Starting amine Ia was obtained commercially. Amines Ib-d were synthesized by the literature methods [11-13].

3-(β-Chloroethyl)-6-R-benzothiazolin-2-ones (IIb-d) and Bis[3-(β-hydroxyethyl)-6-R-benzothiazol-2-ylidene]ammonium Chlorides (IIIb-d). Solution of one of the amines Ib-d (10 mmol) in ethylene chlorohydrin (3-4 ml) was boiled or heated on a boiling water bath under stirring (Table 1). The solvent was removed under vacuum. The oily crystalline mass was washed with water (3 × 5 ml) and extracted with boiling chloroform (2 × 10 ml). The residue was recrystallized from water or alcohol to give IIIb-d. The chloroform extract was evaporated. The

solid was recrystallized from hexane to give IIb-d. The washings were neutralized with base to give amino alcohols IVb-d [9]. The properties of IIb-d and IIIb-d, which were prepared for the first time, are listed in Table 2.

Amine Ia was reacted analogously with ethylene chlorohydrin at 90-95°C (Table 1).

Independent Synthesis of Benzothiazolinone IIb. Compound IVb (2.08 g, 10 mmol) was dissolved in conc. HCl (1 ml). The solution was evaporated to dryness. The resulting crystals of hydrochloride were suspended in DMF (5 ml) and boiled with stirring for 4 h. The reaction mixture was cooled and treated with methanol (10 ml) and ice water (10 ml). The oil that separated was crystallized upon standing. The solid was filtered, washed with water, dried, and recrystallized from hexane with activated carbon. Yield of compound IIb, 1.4 g (62%); mp 98-99°C.

Independent Synthesis of Compound IIIb. Mixture of amino alcohol IVb (0.13 g, 6.2 mmol) and its hydrochloride (0.15 g, 6.2 mmol) was heated on oil bath with stirring, increasing the temperature over 0.5 h to 150°C. The mixture was cooled and extracted with boiling benzene (5 ml) and water (3 × 5 ml). The solid was recrystallized from water. Yield 0.19 g (70%) of the compound IIIb; mp 235-238°C. The aqueous washings were neutralized with base to recover 0.05 g (19%) of the starting amino alcohol IVb.

2-Imino-3-(γ-hydroxypropyl)benzothiazoline (VI) and Bis[3-(γ-hydroxypropyl)benzothiazol-2-ylidene]ammonium Bromide (VII). A. Amine Ia (1.5 g, 10 mmol) was mixed with 3-bromopropan-1-ol (4.4 g, 32 mmol) and left at room temperature with periodic shaking for 2 months. The excess of propylene bromohydrin was evaporated under vacuum. The residue was dissolved in water and neutralized with NH_4OH. The oil that separated was removed from the aqueous solution, dried, and extracted with boiling benzene (3 × 5 ml). The solid was extracted with boiling ethanol (2 × 10 ml). The benzene extract was evaporated to dryness. The remaining oil was extracted with hexane (2 × 15 ml); hexane was evaporated. The residue was purified by column chromatography. Yield 0.16 g (4% based on 3-bromopropan-1-ol) of compound VIII [14]. Oil, R_f 0.95 in benzene–chloroform–acetone (1:1:1). $[M]^+$ 260 (mass spectrometry). Yield of compound VI 1.3 g (62%). Oil, R_f 0.45 in benzene–acetone (1:5). The alcohol extract was evaporated to give compound VII (0.37 g, 18%); mp 237-239°C (alcohol). The spectral properties of VI and VII are given in Tables 2 and 3.

B. Compound Ia (0.75 g, 5 mmol) and 3-bromopropan-1-ol (0.7 g, 5 mmol) were heated with stirring on an oil bath to 120°C and then held at that temperature for 1 h. The mixture was cooled and treated with water (5 ml). The solid was filtered to give 0.2 g of VII (19%). The aqueous solution was neutralized with base. The oil that separated was extracted with chloroform (2 × 10 ml). The chloroform extract was dried with $CaCl_2$, evaporated, and purified by column chromatography. Yield of VI 0.7 g (67%).

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