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CLEAVAGE OF 2-AMINOBENZOTHIAZOLE IN ITS INTERACTION WITH PROPYLENE OXIDE

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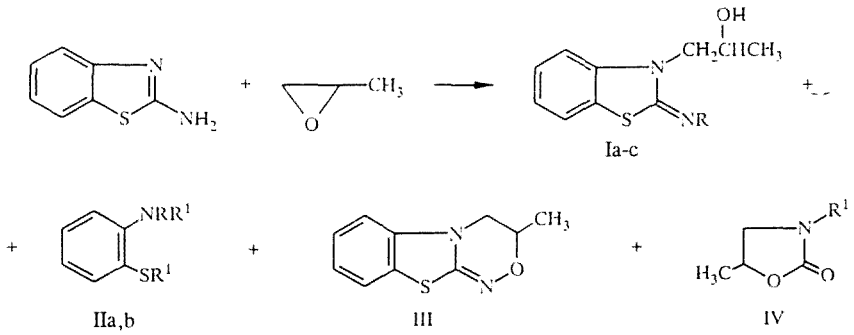
In the interaction of 2-aminobenzothiazole with propylene oxide in protic solvents, formation of the products of alkylation is accompanied by opening of the heteroring. It has been found that the nature of the solvent influences the course of the reaction. Mass spectrometry has been applied in studying the composition of the reaction mixtures and the dynamics of reaction product formation. The structures of the compounds that were isolated were confirmed by physicochemical methods of investigation.

The literature contains many reports on studies of reactions of many heterocyclic amines with oxiranes. These reactions usually proceed as hydroxyalkylation of the amino group, forming heterocyclic amino alcohols [1, 2]; however, secondary processes of alkylation may also take place [4], as well as intramolecular cyclization [4].

Continuing our systematic investigation of reactions of 2-aminobenzothiazoles with oxiranes [5-7], we have carried out the interaction of unsubstituted 2-aminobenzothiazole with propylene oxide in proton-donor solvents (methanol, glycerol) at a temperature of 20-25°C. We have found that along with the expected products from monoalkylation (Ia), dialkylation (Ib), and trialkylation (Ic) of the aminobenzothiazole, derivatives of o-aminothiophenol are formed (IIa,b), which are found in the reaction mixture in increasing amounts as the reaction time is extended. After 25-30 days of reaction, the total yield of compounds IIa,b amounts to about 90% [8].



Ia-c

IIa,b III IV

I a) R = H, b) R = $CH_2CH(OH)CH_3$, c) R = $CH_2CH(CH_3)OCH_2CH(OH)CH_3$;
II a) R = H, R^1 = $CH_2CH(OH)CH_3$, b) R = R^1 = $CH_2CH(OH)CH_3$;
IV R^1 = $CH_2CH(OH)CH_3$

We then investigated the reaction by means of mass spectrometry with ionization by electron impact, secondary-ion mass spectrometry using a liquid matrix (LSIMS), chemical ionization with registration of positive ions, deuteration with analysis of the deuterated products, and high-resolution mass spectrometry.

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TABLE 1. Mass Numbers and Relative Intensities of Key Ions in Spectra of Compounds Isolated

Compound	Ionization method	m/z (I, %)
Ia	Electron impact	208 M^+(5), 193(5), 164(16), 163(21), 150(100), 136(50), 123(8), 122(9), 109(29), 96(8)
	LSIMS	209[M+H]$^+$(100), 193(5), 151(12), 150(9), 136(5)
Ib	Electron impact	266 M^+(3), 251(3), 221(83), 208(27), 175(13), 163(100), 150(27), 136(55), 109(25)
	LSIMS	267 [M+H]$^+$(100), 221(4), 208(7), 164(5), 168(6), 150(8), 136(6)
	Chemical ionization	267 [M+H]$^+$(73), 248(22), 221(100), 207(48), 162(54), 149(18), 136(15), 109(7)
IIa	Electron impact	241 M^+(93), 223(3), 196(100), 183(7), 178(35), 166(8), 150(9), 145(12), 138(56), 136(60), 124(23)
	LSIMS	242 [M+H]$^+$(100), 241(47), 196(33), 182(20), 164(16), 138(31), 136(33), 124(18), 106(18)
IIb	Electron impact	299 M^+(8), 254(100), 196(6), 195(23), 182(6), 178(10), 164(12), 150(54), 136(31), 109(15)
	LSIMS	300[M+H]$^+$(100), 282(11), 254(83), 196(22), 195(18), 195(18), 164(28), 150(25), 136(44)
	Chemical ionization	300 [M+H]$^+$(55), 282(16), 254(100), 221(7), 194(9)
III	Electron impact	206 M^+(100), 164(28), 162(23), 150(20), 148(23), 136(26), 109(25)
	LSIMS	207 [M+H]$^+$(100), 206 M^+(95), 164(23), 163(20), 136(26)
IV	Electron impact	159 M^+(1), 115(100), 74(53), 70(17), 56(5)
	LSIMS	160 [M+H]$^+$(100), 319 [2M+H]$^+$(18), 478 [3M+H]$^+$(1)
	Chemical ionization	160(100), 142(56), 115(63), 102(12), 98(59), 74(10), 72(4)

TABLE 2. Relative Intensities of $[M + H]^+$ Ion Peaks for Compounds Ia-c and IIa,b in Secondary-Ion Spectra of Reaction Mixtures

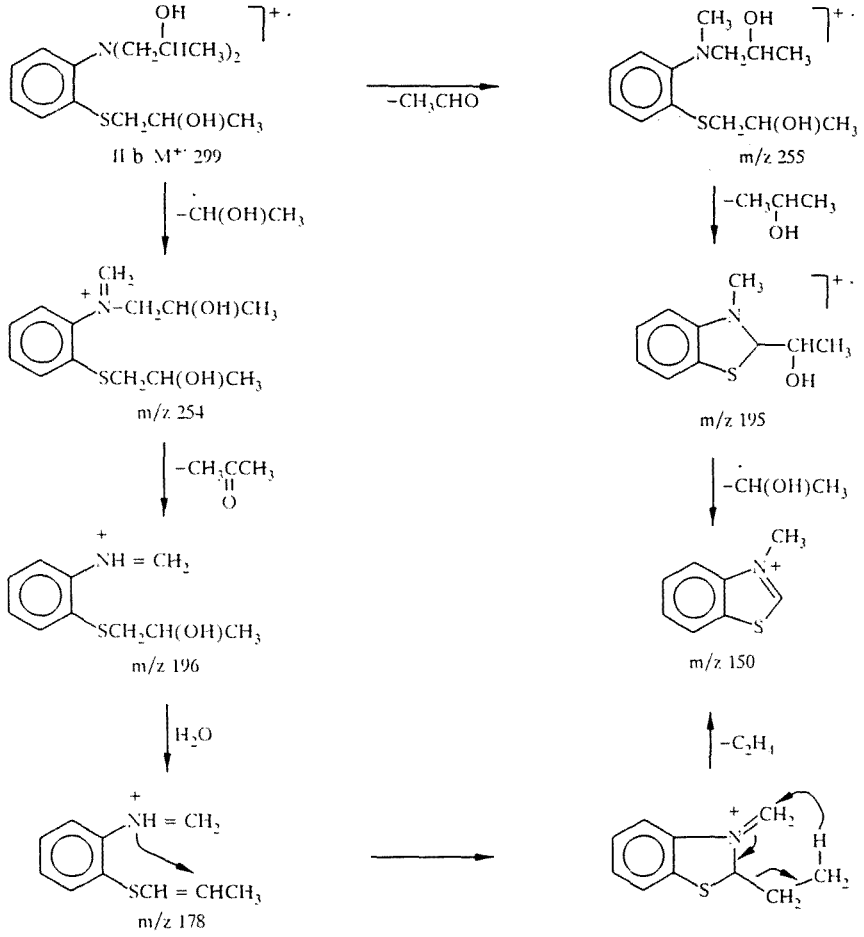
Solvent	Reaction time, days	I, %				
		Ia	Ib	Ic	IIa	IIb
Methanol	5	42	76	100	4	2
Glycerol	5	21	67	100	25	23
Methanol	12	9	29	100	10	4
Glycerol	12	9	22	100	41	56
Methanol	19	10	29	100	19	10
Methanol	19	4	24	82	55	100
Glycerol	48	6	17	100	35	18
Glycerol	48	1	5	75	60	100

In Table 1 we present mass spectrometric data, obtained with different methods of ionization, on the reaction products recovered in individual form by means of column or thin-layer chromatography.

In the electron-impact mass spectra of 2-imino- (Ia) and 2-(2-hydroxypropylimino)-3-(2-hydroxypropyl)benzothiazoline (Ib), the molecular ion peaks have low intensities (3-5%). The most stable are the fragments formed as a result of removal of an acetone molecule, or by successive removal of an acetone molecule and an ethoxy radical. In the case of derivatives of o-aminothiophenol, the main path of fragmentation is the detachment of the ethoxy radical.

In the LSIMS spectra of all of the compounds, the peak of the protonated molecular ion $(M + H)^+$ is the most intense.

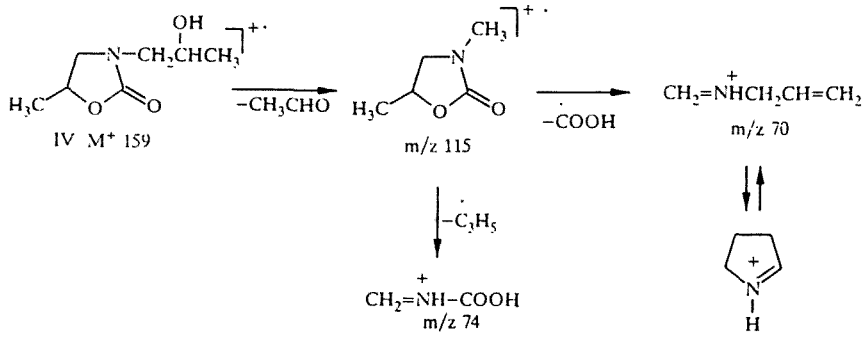
Since compound IIb could have not only the proposed structure but also a different structure that we will call IIc, with R = H and R^1 = $CH_2CH(CH_3OCH_2CH(OH)CH_3$, we carried out the deuteration of this compound, demonstrating that the molecule has three hydroxyl groups. Through analysis of data on the insertion of the deuterium label into the fragment ions and an analysis of metastable defocusing spectra, which enabled us to follow the formation of the fragments, we obtained unambiguous confirmation of the structure IIb.



Compound III with a molecular mass of 206, which was isolated from the reaction mixture in trace amounts, had the elemental composition $C_{10}H_{10}N_2OS$; i.e., the molecule has two protons less than in compound Ia. As shown by deuteration, it does not contain any active hydrogen atoms. It can be assumed that compound III represents the result of 1,3-dipolar cycloaddition of propylene oxide to the aminobenzothiazole, analogous to the formation of an oxazole ring from oxiranes and compounds with a C=N bond [9]; we can also assume that compound III very likely has the structure that we indicated in the reaction scheme. In addition to the products described above, we were able to register and isolate compound IV, which, judging from its PMR spectrum, does not contain an aromatic ring but does contain a carbonyl group. In its electron-impact mass spectrum, the maximum peak is that of an ion with m/z 115, having the composition $C_5H_9NO_2$. This is a fragment ion, since in the metastable defocusing spectrum this ion has a peak for the transition $115^+ \rightarrow 159^+$. We also noted the formation of ions with m/z 74 and 70, with respective compositions $C_2H_4NO_2$ and C_4H_8N.

In the LSIMS spectrum of compound IV, the peak of the protonated molecular ion with m/z 160 ($C_7H_{14}NO_3$) is the most intense. Also present are less-intense peaks of clusters with m/z 319 $[2M + H]^+$ and 478 $[3M + H]^+$.

In the chemical ionization mode, the substance IV gives a very characteristic spectrum. On the basis of all of the above data, we were able to assign to compound IV the structure 3-(hydroxypropyl)-5-methyloxazolidin-2-one [10].



Since the $[M + H]^+$ ions are very stable in the LSIMS mode, we were able to perform a qualitative analysis of reaction mixtures without separating them into their individual components. In the spectra of these mixtures we found an intense peak of an ion with m/z 325 ($[M + H]^+$, $C_{16}H_{24}N_2O_3S$), to which we ascribe the structure Ic. Also, at various times during the course of the reaction mixture, we were able to register and determine the elemental composition of the following trace components m/z 322 ($[M + H]^+$, $C_{15}H_{32}NO_6$); m/z 350 ($[M + H]^+$, $C_{16}H_{32}NO_7$); m/z 426 ($[M + H]^+$, $C_{20}H_{33}N_3O_5S$). These are probably products of the oligomerization of propylene oxide with the incorporation of other molecules.

The structures of compound Ia,b, IIa,b, III, and IV were further confirmed by IR, UV, and PMR spectroscopy.

Our work was also aimed at studying the dynamics of accumulation of the main reaction products. Secondary-ion mass spectrometry provides a means for not only qualitative but also semiquantitative analysis of reaction mixtures. In order to determine the relative sensitivity of the products under investigation, we first prepared 0.01 M solutions of samples Ia,b and IIa, b, and from these solutions we prepared equimolar solutions of mixtures of the compounds. On the basis of the relative intensity of the $[M + H]^+$ ions in the LSIMS spectra of the standard mixture, it was established that the relative sensitivity of compounds Ia,b and IIa,b is approximately identical; therefore, on the basis of the change in optical intensity of the peaks of the $[M + H]^+$ ions in the spectra of the reaction mixtures, we can judge the accumulation or decrease of content of these products (Table 2). It should be noted that product Ic was not isolated in individual form, and its relative sensitivity was not determined; hence we cannot draw any conclusion regarding its content in the reaction mixture on the basis of the intensity of the $[M + H]^+$ ion peak. It should also be noted that in the spectra of the reaction mixtures, the peaks of the $[M + H]^+$ ions of compounds III and IV are very low-intensity. One reason for this may be the small quantities of these compounds in the surface layer of the matrix.

As can be seen from Table 2, the cleavage process is most prominent in glycerol solution. In methanol, during the first two weeks, products of simple alkylation predominate: Ia-c. Products of heteroring opening — IIa,b — appear in trace quantities in only 5 days, and accumulate as times passes. Retardation of the accumulation of cleavage products is the result of a deficiency of propylene oxide in the reaction mixture. Analysis of spectra of the reaction mixture after adding propylene oxide shows a sharp increase in the content of the products IIa,b.

In order to elucidate the role of the solvent in this process, we investigated the reaction of 2-aminobenzothiazole with propylene oxide in aprotic solvents at a temperature of 20-25°C (Table 3). As can be seen from the data presented in Tables 2 and 3, the reaction medium has a substantial influence on not only the process rate, but also on the qualitative composition of the reaction mixtures. In aprotic solvents, no cleavage of the benzothiazole ring is observed. For the reaction in acetone solvent, we found, along with the original aminobenzothiazole and products of its alkylation Ia-c, products of dehydration of compounds Ia, b, with m/z 191 ($[M + H]^+$, $C_{10}H_{10}N_2S$) and m/z 249 ($[M + H]^+$, $C_{13}H_{16}N_2OS$).

In DMF, we found several groups of compounds of a different type, each of which consists of 2-6 members differing from each other in the number of propoxy units (i.e., by 58 amu). As can be seen from Table 3, the most numerous group represents products of alkylation of the aminobenzothiazole. In the LSIMS spectra there are peaks of $[M + H]^+$ ions of compounds Ib,c and also ions with mass numbers of 383, 441, 499, and 557, i.e., oligomeric products of alkylation. This means that the use of an aprotic bipolar solvent promotes processes of deeper alkylation of the 2-aminobenzothiazole. The ancestor of the other group is a product of dehydration of Ib, with m/z 249. Assigned to a third series are the peaks of two ions of unknown origin with m/z 278 and 346.

It must be noted that all of the products recovered in the alkylation of aminobenzothiazole by propylene oxide have the imine structure; i.e., the point of the initial attack is the endocyclic nitrogen atom of the ambifunctional system N−C=N−. Thus, we have detected for the first time the phenomenon of heteroring opening in reactions of heterocyclic amines with oxiranes.

TABLE 3. Secondary-Ion Mass Spectra of Reaction Mixtures in Aprotic Solvents

Solvent	Reaction time, months	m/z (I, %)
Acetone	4	151(67), 191(15), 209(100), 249(30), 267(27), 325(7)
DMF	6	267(23), 325(86), 383(100), 441(42), 499(9), 557(3), 249(17), 307(25), 365(12), 423(5), 278(23), 346(22)

EXPERIMENTAL

Mass spectrometric scans were recorded in an MKh-1310 instrument with double focusing. The electron-impact mass spectrometric scans were obtained under the following conditions: direct introduction of sample SVP 5, ionization chamber temperature 150-170°C, ampul—heater temperature 80-120°C, ionizing voltage 70 V, collector current 60 μA. The conditions under which the metastable defocusing spectra were obtained were as described in [11].

For registration of the secondary-ion spectra, we used an LSIMS ion source with a 7-keV energy of the beam of accelerated Cs^+ ions and an accelerating voltage of 5 kV. The samples were dispersed in glycerol and applied to the steel target of direct sample introduction. Chemical ionization spectra were obtained in an MS-25 RF chromatograph/mass spectrometer (England), combined source CI/EI, accelerating voltage 4 kV, ionizing voltage 75 V, temperature of source 300°C, temperature of direct sample introduction system 100-120°C, gas-reagent methane. The empirical compositions of the molecular and fragment ions were established on the basis of high-resolution mass spectra. IR spectra were taken in KBr tablets in a UR-20 spectrophotometer; UV spectra were taken in a Hitachi EPS-3T spectrometer in ethanol. PMR spectra were taken in a Jeol C-60-HL instrument in deuterochloroform, internal standard HMDS.

Interaction of 2-Aminobenzothiazole with Propylene Oxide. To a solution of 1.5 g (0.01 mole) of aminobenzothiazole in 10 ml of methanol, 2.9 g (0.05 mole) of propylene oxide was added, and the mixture was held at room temperature while shaking periodically. Then the methanol and the excess propylene oxide were evaporated. The residue was analyzed by mass spectrometry and was chromatographed in a column with L 100/160 silica gel (successive elution with hexane, benzene—hexane mixture, and benzene), or was chromatographed on Silufol UV-254 plates (elution with 2:1:1 acetone—benzene—chloroform, detection by UV light).

Compounds Ia,b, IIa,b, III, and IV are oily substances.

The interaction of 2-aminobenzothiazole with propylene oxide in other solvents was performed by the procedure described above. After evaporating the solvent (acetone or DMF), the residue was analyzed by mass spectrometry. The reaction mixture in glycerol was analyzed without removing the solvent.

2-Imino-3-(2-hydroxypropyl)benzothiazoline (Ia, $C_{10}H_{12}N_2OS$). R_f 0.28. IR spectrum, cm^{-1}: 1610 (C=N), 3300 (O—H, N—H). UV spectrum, λ_{max}, nm: 223, 263, 300. PMR spectrum, ppm: 1.15 (3H, d, CH_3), 3.85 (2H, d, CH_2), 4.15 (1H, m, CH), 5.8 (2H, br.s, NH, OH), 6.85-7.35 (4H, m, H_{arom}).

2-(2-Hydroxypropyl)imino-3-(2-hydroxypropyl)benzothiazoline (Ib, $C_{13}H_{18}N_2O_2S$). R_f 0.43. IR spectrum, cm^{-1}: 1630 (C=N), 3380 (O—H). UV spectrum, λ_{max}, nm: 225, 266, 305. PMR spectrum, ppm: 1.2 (6H, d, $2CH_3$), 3.3 (2H, m, CH_2), 4.0 (2H, m, CH_2), 4.1 (2H, m, 2CH), 6.8-7.4 (4H, m, H_{arom}). Hydrochloride, mp 199-200°C.

o-[N,S-Bis(2-hydroxypropyl)]aminothiophenol (IIa, $C_{12}H_{19}NO_2S$). R_f 0.69. IR spectrum, cm^{-1}: 3370 (N—H, O—H). UV spectrum, λ_{max}, nm: 210, 244, 257 sh, 312.5. PMR spectrum, ppm: 1.15 (6H, m, $2CH_3$), 2.4-3.25 (7H, m, $2CH_2$, 2CH, NH), 3.63 (1H, s, OH), 3.95 (1H, s, OH), 6.45-7.35 (4H, m, H_{arom}).

o-[N,N,S-Tri(2-hydroxypropyl)]aminothiophenol (IIb, $C_{15}H_{25}NO_3S$). R_f 0.56. IR spectrum, cm^{-1}: 3380 (O—H). UV spectrum, λ_{max}, nm: 207, 247, 312, sh. PMR spectrum, ppm: 1.05 (6H, d, $2CH_3$), 1.25 (3H, d, CH_3), 2.95 (5H, m, CH_2, 3OH), 3.7 (7H, m, $2CH_2$, 3CH), 7.2 (4H, m, H_{arom}).

3-Methyl-1,2,4-oxadiazino[3,4-b]benzothiazole (III, $C_{10}H_{10}N_2OS$). R_f 0.85. IR spectrum, cm^{-1}: 1660 (C=N). UV spectrum, λ_{max}, nm: 222, 247.5, 269 sh, 296.

3-(2-Hydroxypropyl)-5-methyloxazolidin-2-one (IV, $C_7H_{13}NO_3$). R_f 0.58. IR spectrum, cm^{-1}: 1735 (C=O), 3430 (O—H). PMR spectrum, ppm: 1.1 (3H, d, CH_3), 1.35 (3H, d, CH_3), 3.1-3.85 (6H, m, $2CH_2$, CH, OH), 4.6 (1H, m, CH).

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