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STABILITY OF 2-AMINOBENZOXAZOLE AND 2-AMINOBENZIMIDAZOLE HETEROCYCLES IN REACTIONS WITH PROPYLENE OXIDE

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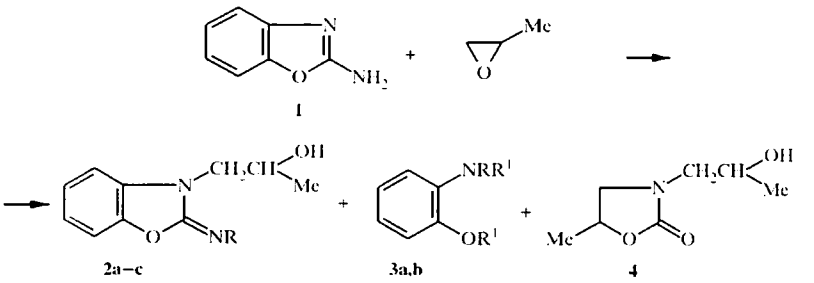
In reaction of 2-aminobenzoxazole with propylene oxide in protic solvents, opening of the heterocycle ring occurs along with alkylation. In the case of 2-aminobenzimidazole, only alkylation occurs under similar conditions. We have studied the compositions of the reaction mixtures and the dynamics of formation of the reaction products by mass spectrometry.

Keywords: 2-aminobenzimidazole, 2-aminobenzoxazole, propylene oxide, alkylation, mass spectra, heterocycle ring opening.

Earlier we observed a novel reaction in the heterocyclic amine series: cleavage of a heterocycle when treated with oxiranes [1-3]. With the objective of extending the limits of this reaction and also studying routes for transformation of 2-aminobenzoxazole (**1**) and its derivatives in reactions with oxiranes, we have investigated the reaction of compound **1** with propylene oxide in proton-donor solvents. We should note that the reactions of 2-aminobenzoxazoles with oxiranes have not been studied until now. As a result of holding amine **1** with a five-fold molar excess of oxirane in methanol at 20-25°C, after 5-24 days a complex mixture is formed containing both products of alkylation of the heterocycle **2a-c** as well as products of cleavage of the oxazole ring: hydroxypropyl derivatives of *o*-aminophenol **3a,b** and 3-(β-hydroxypropyl)-5-methyloxazolidin-2-one (**4**).



2a R = H, **b** R = $CH_2CH(OH)Me$, **c** R = $CH_2CH(Me)OCH_2CH(OH)Me$;
3a R = H, R^1 = $CH_2CH(OH)Me$; **b** R = R^1 = $CH_2CH(OH)Me$

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The qualitative composition of the reaction mixtures was established based on results of secondary-ion mass spectrometry using liquid matrices (LSIMS) without separation into individual components. Compound **4** was isolated previously in reaction of 2-aminobenzothiazole with propylene oxide [2]. In the spectra of the mixtures obtained, we observe intense ion peaks $[M + H]^+$ which were assigned to compounds **2-4** in analogy with the products of reaction between unsubstituted 2-aminobenzothiazole and propylene oxide. This assignment was confirmed by mass spectrometric determination of the elemental composition of the ions. In addition to the indicated products, in the spectra of the reaction mixtures we record unidentified ion peaks with *m/z* 217 (elemental composition $C_{10}H_{21}N_2O_3$) and 321 (elemental composition $C_{15}H_{31}NO_6$) of moderate intensity.

Based on the fact that in the case of analogous products of reaction of 2-aminobenzothiazole and propylene oxide we can use the change in the relative intensity of the ion peaks $[M + H]^+$ in the spectra of the reaction mixtures to decide if there is a buildup or a decrease in the content of the corresponding products (except for oxazolidone **4**), we studied the formation of compounds **2-3** over time. As we see from Table 1, mainly products of simple alkylation **2a-c** are present initially in the reaction mixture, and the fraction of product **2c** (containing three oxirane residues) increases over time; but even after 24 days, the products of heterocycle ring opening **3a,b** predominate in the reaction mixture. For a lengthy holding time (180 days), in the reaction mixture in fact we detect only trihydroxypropyl-substituted *o*-aminophenol **3b**.

Analogous results with respect to the qualitative composition of the products were obtained in the case of reaction of 2-aminobenzoxazole with propylene oxide in glycerin. But the dynamics for buildup of the products were different: in glycerin, the process of cleavage occurs much faster, and the alkylated *o*-aminophenol **3b** is detected earlier than the alkylated aminobenzoxazoles **2a-c** (Table 1).

Comparison of the behavior of 2-aminobenzoxazole and 2-aminobenzothiazole [2] in reaction with propylene oxide shows that in both methanol and glycerin opening of the oxazole ring occurs much more efficiently than for the thiazole ring. Furthermore, in the case of 2-aminobenzothiazole, it was difficult to say whether it underwent cleavage itself or if only its alkylation products were involved, since first of all the products of simple alkylation of 2-aminobenzothiazole predominated initially while hydroxypropyl derivatives of *o*-aminothiophenol were detected in fairly small amounts; and secondly, 2-(dimethylamino)benzothiazole, in contrast to isomeric 2-methylimino-3-methylbenzothiazoline, does not undergo cleavage in a methanol solution of propylene oxide [3], i.e., more likely the iminobenzothiazoline compounds are cleaved. Regarding 2-aminobenzoxazole, observation of a peak from compound **3b** with 100% intensity and the virtual absence of peaks from the alkylation products **2a-c** in the mass spectrum of the glycerin solution after 5 days suggests that the heterocycle of 2-aminobenzoxazole itself undergoes cleavage.

TABLE 1. Relative Intensities of $[M + H]^+$ Ion Peaks for Compounds **2-3** in Secondary Ion Spectra of the Reaction Mixtures

Solvent	Reaction time, days	Intensity (I), %				
		2a ($C_{10}H_{12}N_2O_2$, m/z 193)	**2b** ($C_{13}H_{18}N_2O_3$, m/z 251)	**2c** ($C_{16}H_{24}N_2O_4$, m/z 309)	**3a** ($C_{12}H_{19}NO_3$, m/z 226)	**3b** ($C_{15}H_{25}NO_4$, m/z 284)
Methanol	5	25	100	95	3	9
Glycerin	5		1			100
Methanol	12	9	52	100	23	55
Glycerin	12	1	70	13	10	100
Methanol	19	4	25	67	23	100
Glycerin	19		3	7	4	100
Methanol	24	1	25	66	24	100
Glycerin	24			6	2	100
Methanol	180				1	100

We conducted the reaction of 2-aminobenzimidazole with propylene oxide under analogous conditions. Analysis of the reaction mixture by LSIMS after 24, 60, and 180 days showed absence of ion peaks $[M + H]^+$ for the hypothetical products of cleavage of the benzimidazole ring, i.e., hydroxypropyl derivatives of *o*-phenylenediamine with *m/z* 225, 283, 341, and 399, and also oxazolidone **4** with *m/z* 160. In the mass spectrum of the reaction mixture, we detected only ion peaks $[M + H]^+$ of the alkylation products of the heterocycle, the molecules of which contain one, two, three, or four C_3H_7O residues with *m/z* 192 (12%), 250 (45%), 308 (100%), and 366 (18%) respectively (these are the intensities of the ion peaks for reaction time 180 days). We also noted traces of a compound containing five of the indicated residues.

Thus in contrast to 2-aminobenzoxazole, the 2-aminobenzimidazole heterocycle does not undergo cleavage in reaction with propylene oxide.

EXPERIMENTAL

The mass spectra were recorded on an MX-1310 using an SVP-5 system for direct injection of the sample, ionization chamber temperature 150-170°C, temperature of the heater ampul 80-130°C, ionizing potential 70 eV, collector current 60 μA. To record the secondary ion spectra, we used an LSIMS ion source, energy of the accelerated Cs^+ beam 7 keV, accelerating potential 5 kV. The samples were dispersed in glycerin and applied to a steel target for direct injection of the sample. The empirical composition of the molecular ions was established based on the high-resolution mass spectra.

The starting 2-aminobenzoxazole was synthesized by the procedure in [4].

Reaction of 2-Aminobenzoxazole or 2-Aminobenzimidazole with Propylene Oxide. Propylene oxide (2.9 g, 50 mmol) was added to a solution of aminobenzoxazole (1.3 g, 10 mmol) or aminobenzimidazole (1.18 g, 10 mmol) in solvent (10 ml). The mixture obtained was held at room temperature and periodically shaken. Then methanol and the excess propylene oxide were evaporated, and the residue was analyzed by mass spectrometry. The reaction mixture in glycerin was analyzed without evaporating the solvent.

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