α-OXIDES IN REACTIONS WITH N – H ACIDS OF THE HETEROCYCLIC SERIES

I. ALKYLATION OF 3-NITRO-5-BROMO-1,2,4-TRIAZOLE WITH EPOXIDES

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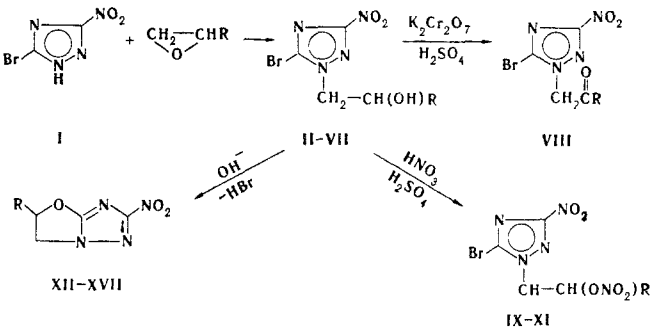
The reaction of epoxides with 3-nitro-5-bromo-1,2,4-triazole gave a series of 1-(β-hydroxyalkyl)-3-nitro-5-bromo-1,2,4-triazoles, which, under the influence of bases, undergo intramolecular cyclization with HBr elimination to give an ew heterocyclic system – 2-nitro-5,6-dihydrooxazolo[2,3-e]-1,2,4-triazole.

The alkylation of N–H acids of the nitroazole series by epoxides has not been systematically studied. The published communications with regard to this problem touch upon only the synthesis of N-β-hydroxyalkyl derivatives of 5-nitroimidazole [1] and 5-nitropyrrole [2]. The reactions of 3(5)-nitro-1,2,4-triazoles with epoxides have not been investigated.

The reaction of 3-nitro-5-bromo-1,2,4-triazole (I) with epoxides gives β-hydroxyalkyl derivatives (II-VII), during which the oxide ring in the unsymmetrically substituted epoxides opens in conformity with the Krasuskii rule. Compounds II-VII were obtained as undistillable oils and were identified by synthesis of derivatives VIII-XI (Table 1). The formation of secondary alcohols was confirmed by oxidation of 1-(β-hydroxypropyl)-3-nitro-5-bromo-1,2,4-triazole (III) to the corresponding ketone (VIII).



II, XII R=H; III, VIII, IX, XIII R=CH_3; IV, X, XIV R=CH_2Cl; V, XV R=CH_2OH; VI, XVI R=CH_2ONO_2; VII, XVII R=CH_2OCH_3

The alkylation of triazole I with epoxides in aqueous alcohol media proceeds both in the presence and in the absence of bases and is accompanied by a regular increase in the pH of the medium, which is associated with consumption of the acidic component. The buildup of alkylation products II-VII, the bulk of which (up to 60%) is formed at the instant the pH of the medium reaches a value that excludes the presence of the free NH acid in solution (pH > 5, pK_a 3.05), is simultaneously noted.*

*Determined by potentiometry.

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TABLE 1. 1-(β-Nitrohydroxyalkyl)-3-nitro-5-bromo-1,2,4-triazoles

Compound	R	mp, °C	Empirical formula	Found					Calculated					Yield, %
				C, %	H, %	Br, %	N, %	M	C, %	H, %	Br, %	N, %	M	
IX	CH_3	114	$C_5H_6BrN_5O_5$	20,5	2,3	27,5	23,6	307	20,3	2,0	27,0	23,6	296	53
X	CH_2Cl	100	$C_5H_5BrClN_5O_5$	18,0	1,4	—	21,2	326	18,1	1,5	—	21,2	330	63
XI	CH_2OCH_3	69	$C_6H_8BrN_5O_6$	21,8	1,9	24,9	21,6	322	22,1	2,4	24,5	21,5	326	52

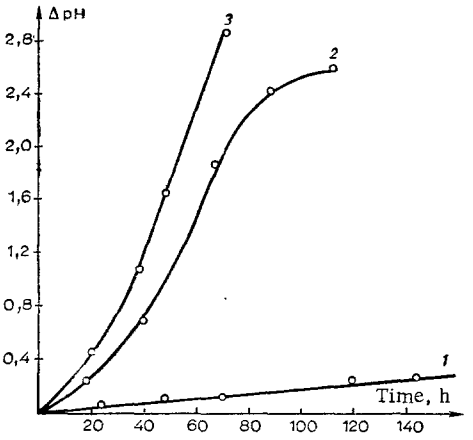
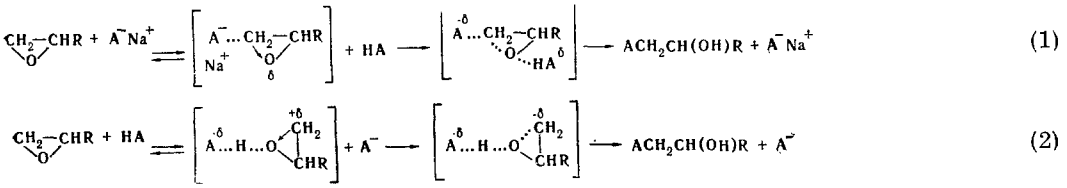


Fig. 1. Change in the pH of the medium during the alkylation of triazole I with epichlorohydrin as the base (NaOH) concentration (mole/liter) is varied: 1) 0; 2) 0.0526; 3) 0.115. The reagent concentrations (mole/liter) were as follows: I 0.0526, epichlorohydrin 1.115 (the medium was 80% ethanol).

The experimental data on the alkylation of I under various conditions indicate a substantial dependence of the rate of the process on the base concentration (Fig. 1), the reactivity of the epoxide (Fig. 2), and the properties of the medium (Table 2).

The successful alkylation of 3-nitro-5-bromo-1,2,4-triazole in aprotic and proton-donor solvents in the absence of an external catalyst attests to possible realization of the process during acid catalysis (H^+ or H^+A^-) via the scheme adopted in the modern chemistry of epoxides [3, 4]. In this case, the acceleration of the process in ether as compared with ethanol is evidently explained by the absence of solvation of the oxygen of the oxide ring at which primary attack of the starting acid occurs. On the other hand, the acceleration of the alkylation in ethanol when base is introduced (Fig. 1) indicated the participation of the anion of I in the reaction. In this case, an increase in its concentration should affect the processes catalyzed by both acids (2) and bases (1).



Kinetically speaking, these variants are indistinguishable, while the probability of one or the other process is determined by the acidity of the substrate [5]. However, the fact that propylene oxide proved to be more reactive than epoxides with electron-acceptor substituents in the reaction with triazole I apparently is evidence in favor of the scheme presented above, which is more realistic for reagent I – a substrate of sufficiently high acidity.

Judging from the identical character of the nitrates obtained in the nitration of the crude alkylation products, the reaction of triazole I with epichlorohydrin under various conditions leads to the predominant

TABLE 2. Alkylation of 3-Nitro-5-bromo-1,2,4-triazole with Epoxides [RCH—CH_2 (I) 0.526 mole/liter, epoxide 1.15 mole/liter]
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Compound	R	Temperature, °C	Solvent	NaOH, M	pH of medium		Time, h	Yield, %
					start	end		
II	H	20	80% Ethanol	0,0526	2,54	5,84	110	62
	H	20	Ether	0	1,25	4,01	120	60
III	CH_3	20	80% Ethanol	0,0526	2,95	6,08	90	62
	CH_3	20	Ether	0	2,00	5,57	96	72
IV	CH_2Cl	20	80% Ethanol	0,115	2,88	5,73	69	68
	CH_2Cl	20	80% Ethanol	0,0526	2,78	5,91	160	67
	CH_2Cl	20	80% Ethanol	0	1,93	2,91	864	28
	CH_2Cl	50	80% Ethanol	0	1,91	4,10	55	46
	CH_2Cl	20	Ether	0	1,24	3,35	90	42
V	CH_2OH	20	80% Ethanol	0.0526	2,44	5,62	215	52
VI	CH_2ONO_2	20	80% Ethanol	0,0526	2,63	5,64	145	62
VII	CH_2OCH_3	20	80% Ethanol	0,0526	2,41	5,41	208	65

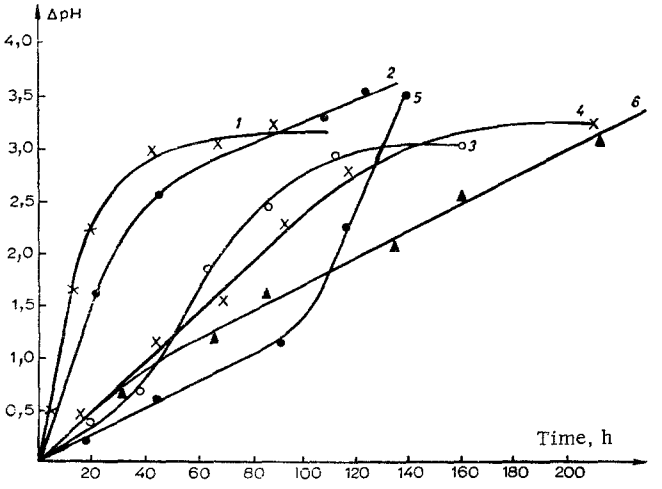
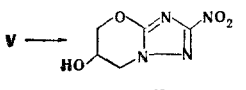


Fig. 2. Change in the pH during the alkylation of triazole I with epoxides: 1) propylene oxide; 2) ethylene oxide; 3) epichlorohydrin; 4) glycidol; 5) nitroglycidol; 6) methoxyglycidol [the reagent concentrations (mole/liter) were as follows: I 0.526, NaOH 0.0526, and epoxide 1.16].

formation of vicinal halohydrin IV, the structure of which might have been proven by dehydrochlorination to the corresponding epoxide. However, the substance that we obtained upon alkaline treatment of IV did not correspond to the target epoxide with respect to its chemical properties and spectral and analytical data. Similar compounds that do not contain a hydroxyl group and bromine were obtained by reaction of other 1-(β-hydroxyalkyl)-3-nitro-5-bromo-1,2,4-triazoles with bases.

On the basis of the data obtained in this study and considering the known tendency of bromine in 3-nitro-5-bromo-1,2,4-triazole derivatives to undergo nucleophilic substitution [6], we concluded that alcohols II-VII undergo intramolecular cyclization with HBr elimination to give a new heterocyclic system – 2-nitro-5,6-dihydrooxazolo-[2,3-e]-1,2,4-triazole (Table 3). An example of analogous cyclization to give a two-ring structure is known for 1-(β-hydroxyethyl)-2-acyl-5-nitropyrrole derivatives [2].

The formation of different two-ring derivatives – 2-nitro-6-hydroxymethyl-5,6-dihydrooxazolo[2,3-e]-1,2,4-triazoles (XV) when the secondary hydroxyl group participates in the reaction and 2-nitro-6-hydroxy-5,6,7-trihydro-1,3-oxazino[2,3-e]-1,2,4-triazole (XVIII) for reaction with the primary hydroxyl group – is fundamentally possible in the cyclization of diol V.



XVIII

TABLE 3. 2-Nitro-5-R-5,6-dihydroxazolo [2,3-e]-1,2,4-triazoles

Compound	R	mp, °C	Crystallization solvent	Empirical formula	Found, %			Calculated, %			Yield, %
					C	H	N	C	H	N	
XII	H	141	Ethanol	$C_4H_4N_4O_3$	31,2	2,2	35,2	30,8	2,6	35,9	85
XIII	CH_3	85	CCl_4—Hexane (1 : 2)	$C_5H_6N_4O_3$	34,7	3,6	32,8	35,3	3,5	32,9	86
XIV	CH_2Cl*	153	CCl_4 — $CHCl_3$, (1 : 1)	$C_5H_5ClN_4O_3$	29,3	2,6	26,9	29,3	2,4	27,4	89
XV	CH_2OH	129	CH_2Cl_2	$C_5H_6N_4O_4$	31,9	3,1	30,0	32,3	3,2	30,1	78
XVI	CH_2ONO_2	124	Ethanol	$C_5H_5N_5O_6$	26,2	1,7	30,4	26,0	2,2	30,3	81
XVII	CH_2OCH_3	113	CCl_4	$C_6H_8N_4O_4$	35,8	3,7	27,6	36,0	4,0	28,0	85

*Found: Cl 17.39%. Calculated: Cl 17.36%.

TABLE 4. Parameters of the PMR Spectra of 1-(β-Hydroxyalkyl)-3-nitro-5-bromo-1,2,4-triazoles and Their Nitrates

Compound*	R	δ_{CH_2}	δ_{CH}	δ_{CH_2O}	δ_{OCH_3}	δ_{CH_3}	δ_{CH_2Cl}
II	H	4,35 (t)† J=6 Hz	—	4,50 (t) J=6 Hz	—	—	—
III	CH_3	4,45 (d) J=6 Hz	3,85(m)†	—	—	1,20(d) J=7 Hz	—
V	CH_2OH	5,20 (d) J=5 Hz	4,50 (m)	4,05 (d) J=6 Hz	—	—	—
VII	CH_2OCH_3	5,20 (d) J=6 Hz	4,50 (m)	3,65 (d) J=5 Hz	3,40 (s)†	—	—
IX	CH_3	4,75 (d) J=5 Hz	5,72 (m)	—	—	1,52(d) J=7 Hz	—
X	CH_2Cl	4,98 (d) J=6 Hz	6,02 (m)	—	—	—	4,22(d) J=5 Hz
XI	CH_2OCH_3	4,92 (d) J=6 Hz	5,90 (m)	3,90 (d) J=5 Hz	3,40 (s)	—	—

*The spectra of II, V, and VII were obtained from nitrobenzene solutions, while the spectra of the remaining compounds were obtained from acetone solutions.
†Symbols: s is singlet, d is doublet, t is triplet, and m is multiplet.

The formation of structure XV was proved by conversion to the corresponding nitrate, which was identical to product XVI obtained by cyclization of VI.

It should be noted that intramolecular cyclization of N-substituted β-hydroxyalkyl-3-nitro-5-bromo-1,2,4-triazoles with HBr elimination to give XII-XVII is possible only if alkylation of triazole I with epoxides proceeds at the $N_{(1)}$ heteroatom. Substitution at the other ring nitrogen atoms [$N_{(2)}$ and $N_{(4)}$] during cyclization would lead to elimination of the more labile (as compared with halogen) nitro group [7].

The structures of the compounds obtained were confirmed by means of their PMR spectra. The spectral parameters of alcohols II, III, V, and VII and nitrates IX-XI are presented in Table 4.

A rigid system of rings is formed during closing of the dihydrooxazole ring (XII-XVII), and this leads to a complex PMR spectrum of the ABX or AA'BB' type due to the nonequivalence of the protons of the methylene group. In the alcohols and nitrates in which free rotation of the methylene group is possible, its protons are equivalent and give simple first-order PMR spectra.

A detailed stereochemical analysis of the PMR spectra of the dihydrooxazolotriazoles will be presented in our next communication.

EXPERIMENTAL

The PMR spectra were recorded with a Perkin-Elmer spectrometer with an operating frequency of 60 MHz. The internal standard was hexamethyldisiloxane (HMDS). The IR spectra were recorded with a UR-20 spectrometer.

1-(β-Hydroxyalkyl)-3-nitro-5-bromo-1,2,4-triazoles (II-VII). A mixture of 5 g (26.3 mmole) of triazole I [8], 0.106 g (26 mmole) of sodium hydroxide, and 52.6 mmole of the epoxide was placed in a 50-ml

volumetric flask and diluted to the mark with 80% ethanol. The reaction mixture was maintained in a sealed volume with periodic monitoring of the pH of the medium. When the pH was greater than 5.5, the mixture was diluted to twice its volume with water, the ethanol was evaporated, and the residue was extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate, the solvent was removed, and the residue was subjected to further treatment without purification.

1-(β-Nitrohydroxyalkyl)-3-nitro-5-bromo-1,2,4-triazoles (IX-XI). A total of 5 g of III, IV, or VII was added with cooling and stirring to 20 ml of an acidic mixture prepared from equal volumes of concentrated H_2SO_4 and HNO_3 (sp. gr. 1.51), after which the mixture was held at 5-10° for 4 h. It was then poured over ice, and the resulting precipitate was removed by filtration, washed with water, and purified by crystallization (Table 1).

1-(β-Oxopropyl)-3-nitro-5-bromo-1,2,4-triazole (VIII). A solution of 1 g of alcohol III in 3 ml of concentrated H_2SO_4 was added to a mixture of 10 ml of water, 4 ml of concentrated sulfuric acid, and 1 g (6.5 mmole) of potassium dichromate heated to 60°, and the mixture was held at 60° for 30 min. It was then cooled, and the precipitate was removed by filtration and washed with water to give a product with mp 123-124° (from chloroform) in 60% yield. Found: C 24.4; H 2.1; Br 32.6; N 23.0%. $C_5H_5BrN_4O_3$. Calculated: C 24.1; H 2.0; Br 32.1; N 22.5%. IR spectrum: 1560, 1315 (nitro group), 1100, 1745 cm^{-1} (C=O).

2-Nitro-5-R-5,6-dihydrooxazolo[2,3-e]-1,2,4-triazoles (XII-XVII). A 10% solution of sodium hydroxide [1.2 mole per mole of starting 1-(β-hydroxyalkyl)-3-nitro-5-bromo-1,2,4-triazole] was added in portions with cooling to 5 g of alcohols II-VII in 50 ml of dioxane. After 2 h, the reaction mixture was diluted to twice its volume with water and extracted with ethyl acetate. The solvent was removed, and the product was purified by crystallization (Table 3).

2-Nitro-5-nitroxy-5,6-dihydrooxazolo[2,3-e]-1,2,4-triazole (XVI). This compound was also obtained by nitration of XV under conditions similar to those used in the synthesis of IX-XI.

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