

18. O. Schickh, A. Binz, and A. Schulz, Ber., 69, 2593 (1936).
19. G. Del Corona, G. G. Massaroli, and G. Signorelli, Boll. Chim. Farm., 109, 665 (1970).
20. J. W. Clark-Lewis and R. P. Singh, J. Chem. Soc., 2379 (1962).

α -OXIDES IN REACTIONS WITH NH ACIDS OF THE HETEROCYCLIC SERIES.

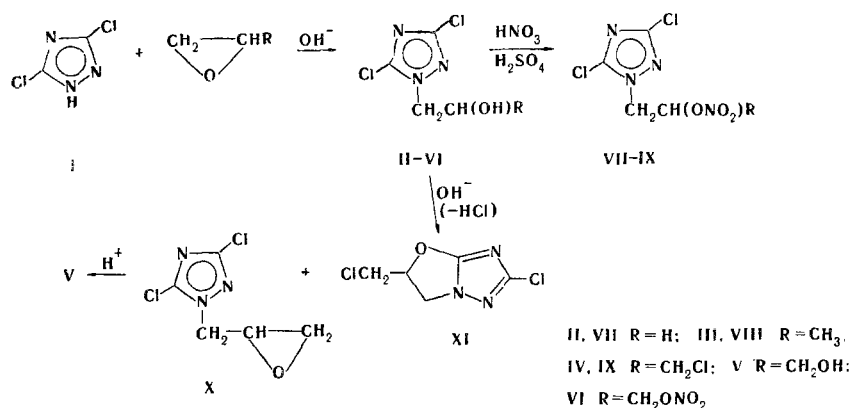
III.* ALKYLATION OF 3,5-DICHLORO-1,2,4-TRIAZOLE WITH α -EPOXIDES

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UDC 547.792'787.3:542.953

A number of 1-(2-hydroxyalkyl)-3,5-dichloro-1,2,4-triazoles and their derivatives were obtained by reaction of 3,5-dichloro-1,2,4-triazole with α -oxides in proton-donor media in the presence of bases.

The alkylation of 3,5-dichloro-1,2,4-triazole (I) with α -epoxides leads to 1-(2-hydroxyalkyl)-3,5-dichloro-1,2,4-triazoles (II-VI) (Table 1). Compounds V and VI were isolated in pure form; alcohols II and IV were identified by nitration to nitrate derivatives VII-IX (Table 2).



The formation of secondary alcohols in the reaction of unsymmetrical α -epoxides with triazole I was confirmed by the PMR spectra of II-IX. The stability of the signal of the methylene group bonded to the triazole ring in the case of primary alcohol II and alcohols III and VI, the nonequivalence of the methylene groups in the spectrum of diol V, and the shift to weak field of the signal of the methyldyne proton on passing from alcohols III and IV to nitrates VIII and IX are due to the 1-(2-hydroxyalkyl)-3,5-dichloro-1,2,4-triazole structure for III-VI.

In contrast to the more acidic 3,5-dinitro-1,2,4-triazoles (pK_a -0.66 [3]) and 3-nitro-5-bromo-1,2,4-triazole (pK_a 3.05 [2]), 3,5-dichloro-1,2,4-triazole (pK_a 5.22 [4]) does not react with α -epoxides at room temperature in the absence of bases in either aprotic (ether, acetone, and dioxane) or proton-donor media (water and alcohols). The acidity of this substrate is probably insufficient for realization of a process catalyzed by the NH acid itself.

*See [1] for communication II.

Lensovet Leningrad Technological Institute. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1281-1285, September, 1976. Original article submitted July 8, 1975.

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TABLE 1. 1-(2-Hydroxylalkyl)-3,5-dichloro-1,2,4-triazoles (II-VI)

Compound	n_D^{20} , mp, °C (crystallization solvent)	IR spectra, cm ⁻¹		PMR spectra,* δ , ppm (J , Hz)				Alkylation conditions†				
		ν_{OH}	ν_{ring}	CH ₂ N	CH ₂ OH	CHOH	R	pH of the medium		Δ pH	time, h	Yield, %
								start	finish			
II	1,5165	1080, 3200—3600	1110, 1300, 1390, 1450, 1490	4,24t (6)	3,93t (6)	—	—	5,02	7,55	2,53	77	76
III	1,5132	1070, 3200—3600	1120, 1300, 1390, 1455, 1490	4,08d (6)	—	~4,3m	1,19d (6)	5,15	7,65	2,50	89	82
V	1,5230	1080, 3200—3600	1120, 1300, 1390, 1450, 1490	4,28d (6)	—	~4,1m	3,7d (6)	5,06	7,62	2,56	36	78
IV	69—70 (chloroform)	1050, 1080, 3200—3600	1120, 1300, 1390, 1460, 1490	4,14d (6)	3,46d (6)	~3,86m	—	4,86	7,42	2,56	130	54
VI‡	.71—72 (carbon tetrachloride)	1100, 3200—3600	1135, 1300, 1390, 1450, 1490	4,43d (6)	—	~4,5m	4,75d (6)	4,93	7,45	2,52	61	61

*Abbreviations: d is doublet, t is triplet, and m is multiplet.

†Alkylation conditions: [I] = 0.263 mole/liter, [epoxide] = 0.526 mole/liter, [NaOH] = 0.0263 mole/liter, at 20°C in 80% ethanol.

‡ ν_{ONO_2} 1290, 1660 cm⁻¹.

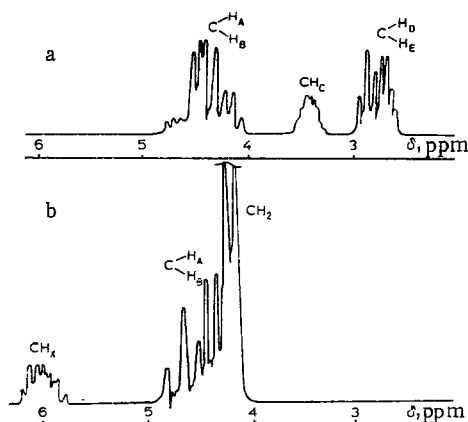


Fig. 1. PMR spectra in deuteroacetone: a) 1-(2,3-epoxypropyl)-3,5-dichloro-1,2,4-triazole (X); b) 2-chloro-5-chloromethyl-5,6-dihydroazolo[3,2-b]-1,2,4-triazole (XI).

Alkylation of triazole I with α -epoxides to give alcohols II-VI under the same conditions is observed only when bases are introduced. The process is accompanied by a regular increase in the pH of the medium associated with consumption of the NH acid (Table 3). The alcohol accumulates simultaneously, and the yield of the alcohol reaches a maximum at pH 7.5-8. Reaction at pH > 8 leads to dehydrochlorination of the desired alcohol.

TABLE 2. 1-(2-Nitratoalkyl)-3,5-dichloro-1,2,4-triazoles (VII-IX)

Compound	mp, °C (crystallization solvent)	Empirical formula	Found, %				Calc., %				M_{found}	M_{calc}	IR spectra, cm^{-1}		PMR spectra,* δ , ppm (J, Hz)				Yield, %
			C	H	Cl	N	C	H	Cl	N			ν_{ONO_2}	ν_{ring}	CH_3N	CHONO_2	CH_2ONO_2	R	
VII	37--38 (hexane)	$\text{C}_4\text{H}_4\text{Cl}_2\text{N}_4\text{O}_3$	21.0	2.0	30.8	24.7	21.1	1.8	31.2	24.6	218	227	1285, 1650	1120, 1370, 1450	4.69t (6)	—	5.08t (6)	—	68
VIII	45--46 (methanol)	$\text{C}_8\text{H}_6\text{Cl}_2\text{N}_4\text{O}_3$	25.0	2.2	29.3	23.3	24.9	2.5	29.5	23.2	239	241	1285, 1645	1125, 1390, 1445	4.47d (6)	5.70 m	—	1,46d (6)	76
IX	78--79 (CCl_4)	$\text{C}_8\text{H}_6\text{Cl}_3\text{N}_4\text{O}_3$	21.6	1.9	38.2	20.2	21.8	1.8	38.7	20.3	270	275.5	1290, 1660	1135, 1380, 1450	4.73d (6)	5.82m	—	4,12d (6)	75

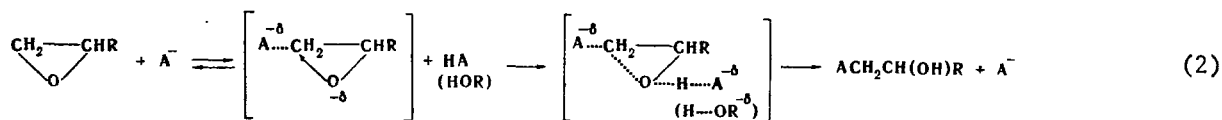
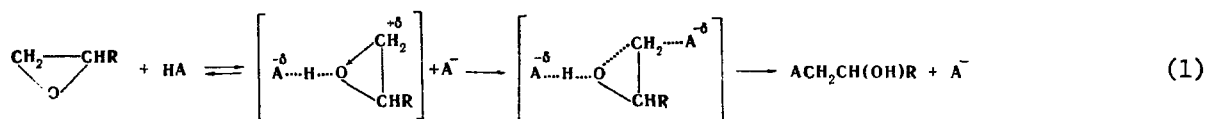
*Abbreviations: d is doublet, t is triplet, and m is multiplet.

TABLE 3. Alkylation of 3,5-Dichloro-1,2,4-triazole (I) with Epichlorohydrin (ECH) ([I] = 0.263 mole/liter, [ECH] = 0.526 mole/liter, in 80% ethanol at 20°C)

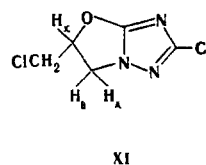
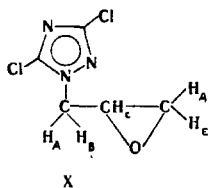
No.	NaOH, M	H of the medium		ΔpH	Time, h	Yield, %
		start	finish			
1	0,005	4,21	6,77	2,51	204	88
2	0,013	4,53	7,05	2,52	74	85
3	0,017	4,75	7,25	2,50	54	80,5
4	0,026	5,08	7,59	2,51	40	76
5*	0,013	4,66	7,25	2,61	8	62

*At 50°C.

The increase in the pH of the medium ($\Delta pH = pH_T - pH_0$), as a direct index of the reaction rate, was used to monitor the reaction and also to make a relative evaluation of the rate as the conditions and reagents were varied. The experimental data on the alkylation of triazole I with α -oxides indicate a substantial dependence of the reaction rate on the base concentration, reaction temperature, and reactivity of the epoxide (Tables 1 and 3). Moreover, one should note the change in the order of the reactivities of the epoxides for triazole I as compared with 3-nitro-5-bromo-1,2,4-triazole (epichlorohydrin and nitroglycidol ahead of propylene oxide). These experimental facts can be explained proceeding from the possibility of transition from primarily acid catalysis [reaction (1)] to primarily basic catalysis [reaction (2)] as the pK_a of the substrate increases; this has already been noted in the case of phenols [5].



When reaction (2) is realized, primary attack by the nucleophile should be facilitated for epoxides with electron-acceptor substituents, whereas the medium can act as the proton-donor agent in the absence of an undissociate NH acid ($pH > 7$). The latter circumstance determines the need to carry out the reaction in proton-donor or aqueous aprotic solvents (80% dioxane, acetone, and acetonitrile).



Alkaline dehydrochlorination of halohydrin IV leads to 1-(2,3-epoxypropyl)-3,5-dichloro-1,2,4-triazoles (X) mixed with isomeric 2-chloro-5-chloromethyl-5,6-dihydrooxazolo[3,2-b]-1,2,4-triazole (XI); the isomer ratio is 1:7.5, respectively [by gas-liquid chromatography (GLC)].

We have previously described the synthesis of two-ring structures analogous to oxazolo-triazole X [1, 2]; the formation of an α -oxide from 1-(2-hydroxy-3-chloropropyl)-5R-1,2,4-triazole was noted for the first time in this research.

In contrast to halohydrin IV, which has a first-order PMR spectrum, its dehydrochlorination products give complex PMR spectra of the ABCDE (epoxide, Fig. 1a) and ABX (oxazolo-triazole, Fig. 1b) types; this is due to the steric nonequivalence of their protons, which is manifested as a result of the formation of a new ring.

In contrast to two-ring system XI, which is resistant to the action of mineral acids, α -epoxide X is readily hydrolyzed to diol V, which is identical to the product of alkylation of 3,5-dichloro-1,2,4-triazole with glycidol.

EXPERIMENTAL

The PMR spectra of deuterioacetone solutions of the compounds were recorded with a Perkin-Elmer R-12 spectrometer (60 MHz) with hexamethyldisiloxane as the internal standard. The IR spectra of films of the compounds were recorded with a UR-20 spectrometer. Gas-liquid chromatography (GLC) was carried out with a Vyukhrom chromatograph with a 300 by 0.3 cm column filled with Chezasorb impregnated with 15 wt. % SE-30 silicone. The column temperature was 240°, the detector temperature was 270°, and the vaporizer temperature was 300°. The carrier-gas (helium) flow rate was 20 cm³/min.

1-(2-Hydroxyalkyl)-3,5-dichloro-1,2,4-triazoles (II-VI). A mixture of 3.6 g (26 mmole) of sodium hydroxide, and 52.6 mmole of α -oxide 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 measurement of the pH of the medium. At pH 7.5-8 the mixture was diluted to twice its volume with water, and the ethanol was evaporated. The residual mixture was extracted with four 30-ml portions of ether, and the extract was dried over anhydrous magnesium sulfate. The solvent was evaporated, and alcohols II-IV were nitrated without preliminary purification; V and VI were purified by crystallization.

1-(2,3-Dihydroxypropyl)-3,5-dichloro-1,2,4-triazole (V). Found: C 28.4; H 3.2; Cl 33.3; N 19.6%. M 210. C₅H₇Cl₂N₃O₂. Calculated: C 28.3; H 3.3; Cl 33.5; N 19.8%. M 212.

1-(2-Hydroxy-3-nitratopropyl)-3,5-dichloro-1,2,4-triazole (VI). Found: C 23.4; H 2.5; Cl 27.6; N 22.0%; M 252. C₅H₆Cl₂N₄O₄. Calculated: C 23.3; H 2.3; Cl 27.6; N 21.8%; M 257.

1-(2-Nitratoalkyl)-3,5-dichloro-1,2,4-triazoles (VII-IX). A 5-g sample of alcohol II, III, or IV was added with cooling and stirring to 20 ml of an acidic mixture prepared from equal volumes of concentrated H₂SO₄ and HNO₃ (sp. gr. 1.51), and the mixture was cooled at 10-15° for 4 h. It was then poured over ice, and the precipitated product was removed by filtration, washed with water, and purified by crystallization (Table 2).

Dehydrochlorination of 1-(2-Hydroxy-3-chloropropyl)-3,5-dichloro-1,2,4-triazole (IV). A solution of 6.25 g (156 mmole) of sodium hydroxide in 60 ml of water was added in portions with cooling to a solution of 30 g (130 mmole) of alcohol IV in 200 ml of dioxane. After 3 h, the mixture was diluted to twice its volume with water, the dioxane was evaporated, and the residual mixture was extracted with four 100-ml portions of ether. The extract was dried over magnesium sulfate, the solvent was removed, and the residue was vacuum fractionated.

1-(2,3-Epoxypropyl)-3,5-dichloro-1,2,4-triazole (X). This compound had bp 110-112° (0.5 mm) and n_D^{20} 1.5185. IR spectrum, cm⁻¹: 860, 910, 1240 (oxide ring); 1130, 1290, 1440, 1490, and 1560 (triazole ring). Found: C 30.5; H 2.7; Cl 36.6; N 21.6%; M 196. C₅H₅Cl₂N₃O. Calculated: C 30.9; H 2.6; Cl 36.6; N 21.6%; M 194. The yield was 1.9 g (7.5%).

2-Chloro-6-chloromethyl-5,6-dihydroxazolo[3,2-b]-1,2,4-triazole (XI). This compound had bp 159-161° (0.5 mm) and n_D^{20} 1.5357. IR spectrum, cm⁻¹: 1280, 1330, 1430, and 1550 (triazole ring); 1230, 1570 (oxazole ring). Found: C 30.6; H 2.3; Cl 36.8; N 21.5%. C₅H₅Cl₂N₃O. Calculated: C 30.9; H 2.6; Cl 36.6; N 21.6%. The yield was 17.6 g (70%).

Hydrolysis of Epoxide X. A 1.9-g (9.8 mmole) sample of epoxide X was added to 20 ml of 5% H₂SO₄, and the mixture was stirred at room temperature for 5 h until the solution was completely homogeneous. The product was extracted with six 20-ml portions of methyl acetate, and the extract was dried over magnesium sulfate. The residue remaining after removal of the solvent was crystallized from chloroform to give a product with mp 69-70° in 81% yield. The product was identical to diol V.

LITERATURE CITED

1. T. P. Kofman, V. I. Manuilova, T. N. Timofeeva, and M. S. Pevzner, Khim. Geterotsikl. Soedin., No. 5, 705 (1975).

2. T. P. Kofman, G. A. Zykova, V. I. Manuilova, T. N. Timofeeva, and M. S. Pevzner, Khim. Geterotsikl. Soedin., No. 7, 997 (1974).
3. L. I. Bagal and M. S. Pevzner, Khim. Geterotsikl. Soedin., No. 4, 558 (1970).
4. C. E. Kröger and W. Freiberg, Z. Chem., 5, 381 (1965).
5. V. F. Shvets and N. N. Lebedev, Tr. Mosk. Khim. Tekh. Inst., 42, 79 (1969).
6. R. Stolle and K. Krauch, J. Prakt. Chem., 88, No. 2, 306 (1913).