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REACTION OF 3-NITRO-1,2,4-TRIAZOLES WITH ALKYLATING AGENTS. 7*. N-MONOALKYLATION BY MONOCYCLIC α-OXIDE POLYMERS

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The N-monoalkylation of 3-nitro, 5-methyl-3-nitro, and 5-ethyl-3-nitro-1,2,4-triazoles by epichlorohydrin polymers and copolymers is nonselective in the presence of base. The reaction products are nitrotriazoles substituted by the polymeric chain in positions 1 or 2 of the heterocycle. The mass fraction of the 2-isomer is 9.6-11.3%. The degree of substitution of the chlorine by the nitrotriazole ring is 98.0-99.5%.

Keywords: N-glycidyl-5-R-3-nitro-1,2,4-triazole, N-alkylation, selectivity.

A specific tendency for N-substitution is revealed when studying the N-alkylation of nitrotriazoles by low molecular weight reagents. The compound yield, N-mono- and full alkylation reaction selectivity, ratio and stability of isomers formed, limits of applicability of the alkylation, and its conditions are basically dictated by the pH of the medium and the activity of the reagents. The N-alkylation and quaternization of nitrotriazoles in the neutral, anionic, and cationic forms have been studied [1-6]. In all cases the reaction products are a mixture of isomers with the exception of certain examples of the selective N-monoalkylation of unsubstituted nitrotriazoles in acidic media [1] and the selective quaternization of 1-alkyl-3-nitro-5-R-1,2,4-triazoles [5].

The aim of this work was to study the N-monoalkylation of nitrotriazoles by polymeric electrophilic agents. In this case, along with revealing the theoretical possibility of the reaction of nitrotriazoles with electrophiles of a similar type it was necessary to resolve those problems associated with the alkylation of a polydentate nucleophile and the polymeric nature of the reagents as search for the temperature-time parameters of the reaction and the choice of solvent.

We have carried out a study of the alkylation and the selectivity of the reaction of 3-nitro-5-R-1,2,4-triazoles (**1**, R = H; **2**, R = Me; **3**, R = Et) with polymeric electrophilic reagents. The polymeric α-monocyclic oxides polyepichlorohydrin (PECH) and the copolymer of epichlorohydrin with ethylene oxide (PECH-C) have been used as the alkylation agent.

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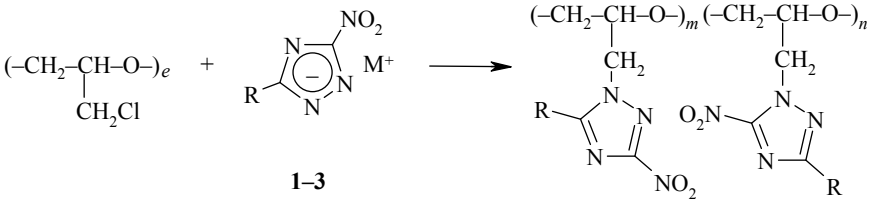
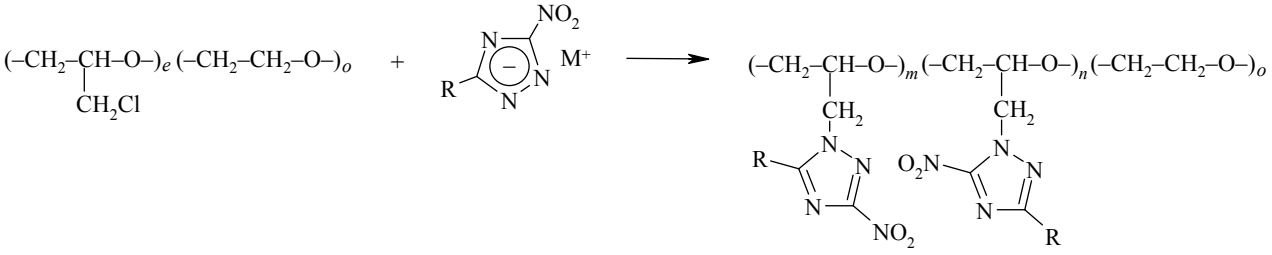
In the processes of N-monoalkylation of the nitrotriazoles **1-3** polyepichlorohydrin shows a markedly lower activity than low molecular weight haloalkanes and dialkyl sulfates [2-4] and this is reflected in the formation of polymers with a lower degree of conversion under conditions similar to the synthesis of low molecular nitrotriazoles. An increase in the conversion results from an increase in the reaction time, heating, and the use of high-boiling polar solvents (e.g. DMF or N-methylpyrrolidone) which quite readily dissolve both the low polarity polymer and also the azole salt. This permits to obtain at 100-130ºC from the nitrotriazoles **1-3** and PECH the N-glycidyl-3-nitro-5-R-1,2,4-triazoles **4-6** with the quantitative conversion (chlorine content 0.1-0.4%, see Table 1):



1–3 **4–6**

4 R = H; **5** R = Me; **6** R = Et

The PECH-C is even less reactive. In analogous conditions to those used for PECH the degree of substitution of halogen in the PECH-C polymer by nitrotriazole rings in the preparation of the copolymer of N-glycidyl-3-nitro-5-R-1,2,4-triazoles and ethylene oxide **7-9** is 10-12% less than with the PECH hence an increase in the degree of conversion needs an increase in the length or temperature of the reaction.

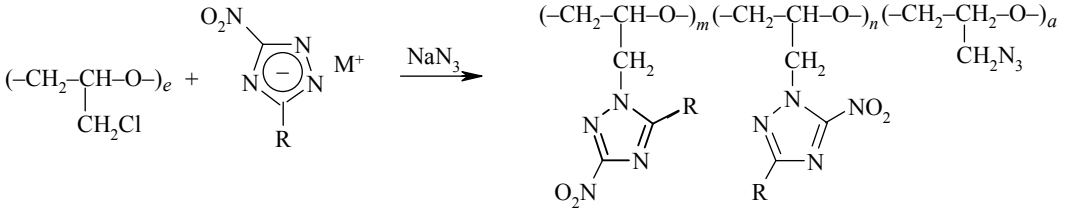


7 R = H; **8** R = Me; **9** R = Et **7–9**

TABLE 1. Elemental Analytical Data and Degree of Substitution in Polymers and Copolymers of N-Glycidylnitrotriazoles **4-12**

Compound	Empirical formula	Found, % / Calculated, %			Degree of substitution, mass %
		C	H	N	
4	$C_5H_6N_4O_3$	35.67 / 35.30	3.61 / 3.55	32.91 / 32.93	99.0
5	$C_6H_8N_4O_3$	40.41 / 39.13	4.12 / 4.38	30.75 / 30.42	98.0
6	$C_7H_{10}N_4O_3$	42.70 / 42.42	5.14 / 5.09	27.87 / 28.27	98.5
7	$C_7H_{10}N_4O_4$	39.64 / 39.25	4.81 / 4.71	25.95 / 26.16	97.6
8	$C_8H_{12}N_4O_4$	42.43 / 42.11	5.38 / 5.26	24.21 / 24.55	98.7
9	$C_9H_{14}N_4O_4$	45.02 / 44.63	6.13 / 5.83	22.78 / 23.15	97.9
10	$C_8H_{11}N_7O_4$	35.95 / 35.69	4.18 / 4.12	36.11 / 36.42	99.5
11	$C_9H_{13}N_7O_4$	38.47 / 38.16	4.74 / 4.63	34.28 / 34.62	99.2
12	$C_{10}H_{15}N_7O_4$	40.78 / 40.40	5.18 / 5.09	32.53 / 32.98	98.8

In addition to the preparation of copolymers with ethylene oxide simultaneous or consecutive alkylation of the corresponding nitrotriazole salts **1-3** and sodium azide with the PECH polymer gave glycidyl azide copolymers with N-glycidyl-3-nitro-5-R-1,2,4-triazoles **10-12**:



10–12

10 R = H; **11** R = Me; **12** R = Et

The ratio of the nitrotriazole and azide components in the copolymers **10-12** is governed within broad limits through the introduction into the reaction mixture of a specific amount of the corresponding nitrotriazole salt and sodium azide.

TABLE 2. Spectroscopic Characteristics of the Polymers of N-Glycidyl-3-nitro-5-R-1,2,4-triazoles **4-6** and Copolymers of N-Glycidyl-3-nitro-5-R-1,2,4-triazoles with Ethylene Oxide **7-9** and Glycidyl azides **10-12**

Compound	IR spectrum, ν, cm^{-1}		^{13}C NMR spectrum, δ, ppm*			
	N(3)	NO_2	C–NO_2	$\underline{C}_{ring}$–R	C_{ring}–$\underline{R}$	Polymer chain
4	—	1550, 1310, 840	163.33	148.22	—	77.8; 69.4; 52.6
5	—	1555, 1310, 845	161.98	157.44	12.5 (CH_3)	78.3; 69.2; 51.5
6	—	1555, 1310, 848	160.52	159.65	18.6 (CH_2); 10.6 (CH_3)	76.7; 68.1; 50.0
7	—	1550, 1308, 835	162.06	147.73	—	77.6; 69.6; 51.9
8	—	1555, 1310, 845	161.86	157.72	12.6	76.2; 69.5; 50.0
9	—	1558, 1310, 850	161.5	159.4	18.5 (CH_2); 10.5 (CH_3)	78.2; 68.1; 50.2
10	2050	1550, 1305, 832	162.15	148.33	—	77.6; 69.6; 51.9
11	2050	1555, 1310, 845	161.91	157.63	12.6	76.2; 69.5; 50.0
12	2050	1558, 1310, 850	160.02	159.05	18.5 (CH_2); 10.7 (CH_3)	79.09; 68.10; 50.18

* Spectra of compounds **4, 6, 7, 9, 12** recorded in DMSO-d_6 and compounds **5, 8, 10, 11** in DMF-d_7.

As in the N-monoalkylation of 3-nitro-5-R-1,2,4-triazoles in the presence of base using low molecular haloalkanes [3] the alkylation reaction of nitrotriazoles by epichlorohydrin polymers and copolymers is non-selective. The reaction products are the nitrotriazoles **1-3** substituted by the polymer chain at positions 1 or 2 in the heterocycle. The polymeric nature of the electrophilic reagent and the associated steric hindrance to attack at position 2 of the heterocycle lead to a marked increase in the selectivity of alkylation of the nitrotriazoles when compared with low molecular weight analogs. As a result of exchange of the alkylating agent the fraction of N-alkylation at atom N(2) when using high molecular reagents (Table 3) is reduced by an average of 20-22% when compared with low molecular reagents [3].

As with low molecular substituents the N(2) substitution fraction with high molecular substituents in the formed polymers **4-12** depends little on the nitrotriazoles **1-3** used (10.7-11.3%).

The need to carry out the alkylation of the nitrotriazoles by the polymeric PECH or PECH-C at increased temperatures and markedly long reaction leads to a small increase in the fraction of the N(1)-isomer. To a greater degree this was displayed with the PECH-C for which a minimum N(2)-isomer content of 9.6% was achieved in the polymeric glycidylnitrotriazoles.

In the region 1120-1125 cm^{-1} the IR spectra of the glycidylnitrotriazoles **4-12** preserved the pattern and absorption frequency of the C–O–C bond in the starting chloropolymers PECH and PECH-C and also showed strong absorption bands typical in frequency of a nitro group bonded to the azole heterocycle (Table 2). As in the previously studied low molecular 3-nitro-5-R-1,2,4-triazole derivatives [3, 7] the absorption bands of the nitro group appear in a narrow spectroscopic range (1558-1550 cm^{-1}, assigned to the symmetrical antiphase stretching vibration), at 1310-1305 (the synphase vibration), and at 832-850 cm^{-1} (C–N deformation vibration). The absorption band at 705 cm^{-1} for the remaining C–Cl bonds from the starting chloropolymers appears only in the intermediate products with low holding times. The azido group in the spectra of the copolymers **10-12** shows a very strong absorption band at 2050 cm^{-1}

The ^{13}C NMR spectra of the synthesized compounds **4-12** show absorption at 160.02-163.33 ppm typical of the nitrotriazole C(3) atom resonance bonded to a nitro group and depends little on the type of substituent on the C(5) atoms. The polymers **4, 7, 10** absorb at 147.73-148.33 ppm for the C(5)–H atom. The introduction into position C(5) of the heterocycle of an alkyl group (methyl in compounds **5, 8, 11** or ethyl in **6, 9, 12**) causes marked low field shifts [3] and the C(5) atoms of these polymers appear at 157.44-159.67 ppm. The products of alkylation of the nitrotriazoles **1-3** with epichlorohydrin polymers and copolymers show a resonance for the chain carbon atoms of the N-glycidyl-3-nitro-5-R-1,2,4-triazole polymers **4-6** and the corresponding copolymers with ethylene oxide **7-9** or glycidyl azide **10-12**: CHO at 76.2-79.1: CH_2O at 68.1-69.6; and CH_2N at 50.0-52.6 ppm.

TABLE 3. Chemical Shifts of the Protons of the C(5) Heterocyclic Substituent and Isomeric Composition of the Alkylation Products of 3-Nitro-5-R-1,2,4-triazoles with Glycidylchloro Polymers

Compound	C(5)–R	C(5)–R, δ, ppm		Isomer content, %	
	R	N(1)	N(2)	N(1) (*m*)	N(2) (*n*)
4	H	8.74	8.25	89.3	10.7
5	CH_3	2.64	2.36	89.0	11.0
6	CH_2–$C\underline{H}_3$	1.26	1.16	88.7	11,3
7	H	8.68	8.15	90.4	9.6
8	CH_3	2.61	2.31	90.2	9.8
9	CH_2–$C\underline{H}_3$	1.25	1.15	90.1	9.9
10	H	8.84	8.17	89.6	10.4
11	CH_3	2.67	2.38	89.3	10.7
12	CH_2–$C\underline{H}_3$	1.27	1.17	88.8	11.2

^{1}H NMR spectroscopy was used to study the selective N-alkylation of the 3-nitro-5-R-1,2,4-triazoles (Table 3). Due to the polymeric nature of the products it should be noted that the proton signals for the ethyl group and methylene chain units of the polymer are broadened and do not have the corresponding triplet and quadruplet forms. Along with this the position of the substituent on the nitrogen atom of the nitrotriazole ring is clearly determined by the nature of the shift of the C(5) atom protons, depending on whether the substituent is found on the N(1) or N(2) atom. The ^{1}H NMR spectra of the 3-nitro-5-R-1,2,4-triazole polymers show a single proton resonance for the ring carbon atom of the 3-nitro-1,2,4-triazole polymers **4, 7, 10** in the form of two singlets at 8.15-8.25 and 8.68-8.84 ppm (Table 3).

By analogy with the known characteristics of N(1) and N(2) proton signals in the isomeric 3-nitro-5-R-1,2,4-triazoles [3, 8] they correspond to the 1-glycidyl-3-nitro- and 1-glycidyl-5-nitro-1,2,4-triazole units of polymers **4, 7, 10**. By analogy with low molecular N-substituted nitrotriazoles [3] the signals for the isomer N(2) protons occur at higher field. In the spectra of polymers having methyl groups on the C(5) ring atom (**5, 8, 11**) two signals were observed for the protons of this substituent which correspond to the isomeric N(1)- and N(2)-substituted nitrotriazole. The signals of the 5-Me protons of N(2)-isomers, when compared with the N(1)-isomers (as in the low molecular nitrotriazoles [3]), occur at high field (in the region 2.61-2.67 ppm for the signals of the 1-substituted unit and 2.31-2.38 ppm for the signals of the isomeric 2-substituted N-glycidyl-5-methyl-3-nitro-1,2,4-triazoles). The position of the substituent in polymers **6, 9, 12** was determined from the nature of the shift of the signals for the alkyl substituent protons in the N(2)-substituted form to high field of the 5-ethyl-N(1)-substituted 3-nitro-1,2,4-triazoles. Specifically, the methyl group of the ethyl substituent at atom C(5) in the 5-ethyl-N(2)-glycidyl-3-nitro-1,2,4-triazoles occurs at 1.15-1.17 ppm and in the N(1)-isomer at 1.25-1.27 ppm. The is confirmed by the synthesis of low molecular N-alkyl-5-ethyl-3-nitro-1,2,4-triazoles.

EXPERIMENTAL

IR spectra were taken on a Perkin-Elmer instrument for KBr tablets and ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-400 spectrometer (400 and 100 MHz respectively) using DMSO-d_6 or DMF-d_7 with the residual solvent signals as internal standard. Elemental analysis was performed on a Flash EA series 1112 element analyzer.

Low molecular models of N-alkyl-5-ethyl-3-nitro-1,2,4-triazoles were prepared according to method [3].

5-Ethyl-1-methyl-3-nitro-1,2,4-triazole. Mp 78-80ºC. ^{1}H NMR spectrum, DMSO-d_6, δ, ppm (*J*, Hz): 1.25 (3H, t, *J* = 7.6, $CH_2C\underline{H}_3$); 2.68 (2H, quin., *J* = 7.6, C_{ring}–CH_2); 4.16 (3H, s, NCH_3). ^{13}C NMR spectrum, δ, ppm: 10.44 ($CH_2\underline{C}H_3$); 18.42 ($\underline{C}H_2CH_3$); 36.04 (NCH_3); 159.59 ($\underline{C}$–C_2H_5); 160.10 (C–NO_2).

3-Ethyl-1-methyl-5-nitro-1,2,4-triazole. ^{1}H NMR spectrum, DMSO-d_6, δ, ppm (*J*, Hz): 1.14 (3H, t, *J* = 7.6, $CH_2C\underline{H}_3$); 2.42 (2H, quin., *J* = 7.6, C_{ring}–CH_2); 3.98 (3H, s, NCH_3). ^{13}C NMR spectrum, δ, ppm: 11.62 ($CH_2\underline{C}H_3$); 21.11 ($\underline{C}H_2CH_3$); 39.26 (NCH_3); 151.93 (C–NO_2); 162.39 ($\underline{C}$–C_2H_5).

Reaction of 3-Nitro-5-R-1,2,4-triazoles with Epichlorohydrin Polymers (General Method). The sodium salt of the nitrotriazole **1-3** (0.15 mol) was added to a solution of the PECH or PECH-C polymer (0.1 mol) in DMF (in the synthesis of the copolymers with glycidyl azide **10-12** sodium azide (0.05 mol) was also added). The product was held for 3-5 h at 100-130ºC. The cooled reaction mixture was poured into water with stirring and the precipitated polymer was filtered off, thoroughly washed with distilled water, and dried *in vacuo*. The properties of the products obtained are given in Tables 1-3.

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