REACTION OF 5-PHENYLTETRAZOLE WITH α-EPOXIDES

S. R. Buzilova, N. I. Kuznetsova, V. M. Shul'gina,
G. A. Gareev, and L. I. Vereshchagin

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A mixture of isomeric 1-(hydroxyethyl)- and 2-(hydroxyethyl)tetrazoles with preponderance of the 1,5 isomer was obtained by alkylation of 5-phenyltetrazole with ethylene oxide in an aqueous alcohol medium in the presence of NaOH. 1,3-Bis(5-phenyl-1-tetrazolyl)-2-propanol is formed from 5-phenyltetrazole and epichlorohydrin under the same conditions. The reaction of 5-phenyltetrazole with epichlorohydrin in acetone in the presence of triethylamine gave 1-(2-hydroxy-3-chloropropyl)-5-phenyltetrazole, the dehydrochlorination of which leads to 1-(2,3-epoxypropyl)-5-phenyltetrazole.

The alkylation of α oxides by various NH acids of the heterocyclic series has been studied quite thoroughly [1-6]. It has been established that the reaction depends to a significant degree on the acidity of the azole used and in the case of elevated pK_a values may occur even without a catalyst [1]. However, the literature does not contain any information relative to the reaction of α-oxides with tetrazoles, which, as compared with other azoles, have the maximum acidities.

In order to study the reaction of tetrazoles with α-oxides we selected 5-phenyltetrazole (I) as a model azole, inasmuch as it is the most accessible compound and, in contrast to tetrazole, is quite soluble in organic solvents. However, despite its relatively high acidity, 5-phenyltetrazole (pK_a 4.53) [7] does not react with ethylene oxide and epichlorohydrin in the absence of a catalyst in aprotic and proton-donor solvents. The reaction becomes possible only under the influence of catalysts with basic character. Thus 5-phenyltetrazole reacts with ethylene oxide in an aqueous alcohol medium in the presence of sodium hydroxide to give isomeric 1- and 2-(β-hydroxyethyl)tetrazoles (IIa, b) with preponderance of the 1,5 isomer. According to the PMR spectrum, in which the signals of the methylene groups of the hydroxyethyl fragment of the isomers are well resolved, the amount of the 1,5 isomer reaches 95%. The IR spectra of these substances contain, in addition to absorption bands of the double bonds of aromatic ring (1600-1610 cm^{-1}), broad absorption bands of a hydroxy group at 3200-3250 cm^{-1}.

At the same time, 1,3-bis(5-phenyl-1-tetrazolyl)-2-propanol (IVa) was isolated instead of the expected chlorocarbinol III in the alkylation of 5-phenyltetrazole with epichlorohydrin and an equimolar amount of sodium hydroxide. Two successive reactions, viz., the formation of chlorocarbinol and its subsequent reaction with the unchanged sodium tetrazolate, are evidently observed in this case. This assumption is confirmed by the successive synthesis of chlorohydrin III by reaction of epichlorohydrin with 5-phenyltetrazole in the presence of a mildly active alkylation catalyst, viz., triethylamine in an aprotic solvent, and by reaction of the resulting tetrazolylchlorohydrin III with 5-substituted sodium tetrazolates VIa-e. The constants of carbinol IVa are in agreement with those of the carbinol obtained by direct condensation of epichlorohydrin with phenyltetrazole in an alkaline medium. The structure of chlorohydrin III is confirmed by the characteristic absorption bands of the bonds of the hydroxy (3250 cm^{-1}) and chloromethyl (760 cm^{-1}) groups. In addition to signals of the protons of a phenyl ring (7.45 and 8.02 ppm), signals of the protons of a chlorohydrin grouping (3.77, 4.53, and 4.87 ppm) are present in the PMR spectrum. The band of the vibrations of a hydroxy group at 3200 cm^{-1} show up most intensely in the IR spectrum of ditetrazolylpropanol IV.

In addition to this pathway, one might have expected the conversion of chlorocarbinol III to epoxide V and its reaction with sodium phenyltetrazolate. However, this scheme is unlikely, since the alkylation is carried out in the presence of an equimolar amount of alkali, and

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A. A. Zhdanov Institute of Petrochemical and Coal-Tar Chemical Synthesis, A. A. Zhdanov Irkutsk State University, Irkutsk 664033. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 119-121, January, 1983. Original article submitted April 20, 1982.

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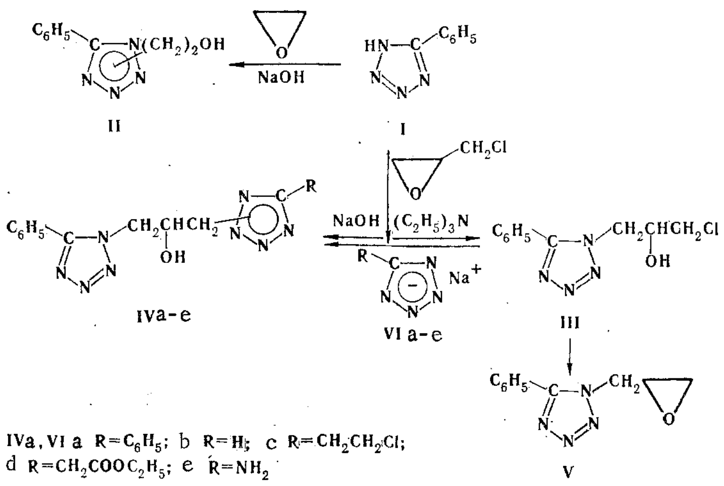
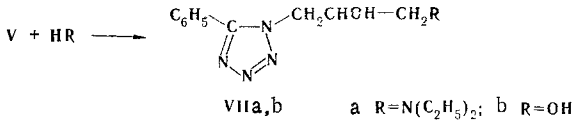
experiments demonstrated that the step involving the dehydrochlorination of chlorohydrin III requires excess alkaline reagent.



Signals of the protons of an epoxypropyl grouping (2.90, 3.55, and 4.78 ppm) and of an aromatic ring (7.35 and 7.95 ppm) are observed in the PMR spectrum of epoxypropyltetrazole V, which was obtained by treatment of chlorohydrin III with sodium hydroxide in acetone. The epoxide ring of this substance has properties that are characteristic for α-epoxy compounds. Thus it readily undergoes ring opening under the influence of diethylamine and water to give the corresponding amino alcohol and glycol (VIIa, b).



EXPERIMENTAL

The IR spectra were recorded with a UR-20 spectrometer. The PMR spectra were obtained with a Varian H-100 spectrometer with hexamethyldisiloxane as the internal standard.

1-(β-Hydroxyethyl)-5-phenyltetrazole (II). A mixture of 5 g (0.034 mole) of 5-phenyltetrazole, 1.2 g (0.03 mole) of sodium hydroxide, and 3.1 g (0.07 mole) of ethylene oxide in 50 ml of 80% ethanol was maintained at room temperature in a sealed volume for 4 h. When pH 7.5-8.0 was reached, the reaction mass was diluted with water to twice its original volume, the ethanol was evaporated, and the residue was extracted with ether. The extract was dried over $MgSO_4$, the solvent was removed, and the residue was recrystallized from ethanol to give 4 g (70%) of a product with mp 65-67°C. PMR spectrum (in acetone): 4.16 (2H, CH_2OH); 4.80 (2H, CH_2); 7.45, 8.05 ppm (5H, C_6H_5). Found, %: C 56.8; H 5.4; N 30.0. $C_9H_{10}N_4O$. Calculated, %: C 56.8; H 5.3; N 29.4.

1-(2-Hydroxy-3-chloropropyl)-5-phenyltetrazole (III). A 9.2-g (0.1 mole) sample of epichlorohydrin was added to a solution of a 5-phenyltetrazole salt prepared from 10.2 g (0.07 mole) of 5-phenyltetrazole and 10 g (0.1 mole) of triethylamine in 100 ml of acetone, and the reaction mixture was maintained at room temperature for 10 h. The acetone was removed, 10 ml of water was added to the residue, and the precipitated crystals were removed by filtration, washed with water, and recrystallized from ethanol to give 11.7 g (70%) of a product with mp 90-92°C. IR spectrum (in CCl_4): 760 (C—Cl) and 3250 cm^{-1} (OH). PMR spectrum (in CCl_4): 4.87 (2H, CH_2); 3.77 (2H, CH_2Cl); 4.53 (1H, CH); 7.45, 8.02 ppm (5H, C_6H_5). Found, %: C 50.6; H 4.5; Cl 14.4; N 23.4. $C_{10}H_{11}ClN_4O$. Calculated, %: C 50.4; H 4.6; Cl 14.7; N 23.5.

1-3-Bis(5-phenyltetrazolyl)-2-propanol (IVa). A mixture of 3.8 g (0.026 mole of 5-phenyltetrazole, 1.06 g (0.026 mole) of sodium hydroxide, and 4.9 (0.52 mole) of epichlorohydrin was placed in a 50-ml volumetric flask and diluted to the mark with 80% ethanol. The reaction mixture was maintained at room temperature for 3-4 h, after which the precipitated IVa was removed by filtration. The filtrate was evaporated to a volume of 10 ml, 10 ml of water was added, and an additional amount of bistetrazole IVa was isolated to give a total of 3 g (66.6%) of a product with mp 195-196°C (from ethanol). IR spectrum (in CCl_4). 1590 (phenyl ring) and 3250 cm^{-1} (OH). Found, %: C 58.7; H 4.5; N 32.4. $C_{17}H_{15}N_8O$. Calculated, %: C 58.6; H 4.5; N 32.1.

1-[5-Phenyl-1(2)-tetrazolyl]-3-[1(2)-tetrazolyl]-2-propanol (IVb). A mixture of 2.1 g (0.03 mole) of tetrazole, 2 g of NaOH, and 7.2 g (0.03 mole) of chlorocarbinol III in 70 ml of 80% ethanol was heated at 50°C for 3 h, after which the solvent was evaporated to a volume of 7-10, 15 ml of water was added, and the precipitated crystals of carbinol IVb were removed by filtration to give 7.5 g (93%) of a product with mp 96-97°C. Found, %: C 49.1; H 4.2; N 39.6. $C_{11}H_{12}N_8O$. Calculated, %: C 48.5; H 4.4; N 41.1.

Carbinol IVc, with mp 98-100°C (from ethanol), was similarly obtained in 72% yield by the reaction of 1-(2-hydroxy-3-chloropropyl)-5-phenyltetrazole (III) with 5-(β-chloroethyl)-tetrazole salt VIc. IR spectrum: 1590 (phenyl ring) and 3250 cm^{-1} (OH). Found, %: C 47.0; H 4.8; Cl 10.7; N 33.3. $C_{13}H_{15}ClN_8O$. Calculated, %: C 46.6; H 4.5; Cl 10.6; N 33.5.

Carbinol IVd, with mp 132-133.5°C (from ethanol), was obtained in 56% yield from ethyl 5-tetrazolylacetate sodium salt (VId). IR spectrum: 1613 (phenyl ring), 1743 (COOH) [sic], and 3255 cm^{-1} (OH). Found, %: C 47.0; H 4.6; N 33.8. $C_{13}H_4N_8O_3$. Carbonol IVe, with mp 209°C (from ethanol), was obtained in 65% yield from 5-aminotetrazole sodoim salt VIe. Found, %: C 46.6; H 4.7; N 42.7. $C_{11}H_{19}N_9O$. Calculated, %: C 45.9; H 4.6; N 43.9.

Carbinol IVa, with mp 195-196°C, was obtained in 83% yield from 5-phenyltetrazole.

1-(2,3-Epoxypropyl)-5-phenyltetrazole (V). A solution of 3.6 g (0.09 mole) of NaOH in 10 ml of water was added in small portions to a solution of 14.3 g (0.06 mole) of chlorocarbinol III in 130 ml of acetone, and the mixture was stirred at room temperature for 2 h. The NaCl was removed by filtration, the filtrate was evaporated, 20 ml of water was added to the residue, and the mixture was extracted with ether. The ether solution was dried over $MgSO_4$, the solvent was evaporated, and the residue was recrystallized from ethanol to give 10 g (83%) of a product with mp 49-50°C. IR spectrum: 868 and 1270 cm^{-1} (epoxide ring). Found, %: C 59.2; H 5.1; N 27.8. $C_{10}H_{10}N_4O$. Calculated, %: 59.4; H 4.9; N 27.7.

1-(2-Hydroxy-3-diethylaminopropyl)-5-phenyltetrazole (VIIa). A solution of 1.2 g (0.006 mole) of epoxide V and 1 g (0.01 mole) of diethylamine in 10 ml of 80% ethanol was heated at 60°C for 1.5-2 h, after which the solution was evaporated, 5 ml of water was added to the residue, and the aqueous mixture was extracted with ether. The extract was dried over $MgSO_4$, and the solvent was removed to give a product with mp 54-56°C (from ethyl acetate) in 88% yield. Found, %: C 60.9; H 7.6; N 25.3. $C_{14}H_{21}N_5O$. Calculated, %: C 61.1; H 7.6; N 25.4.

1-(2,3-Dihydroxypropyl)-5-phenyltetrazole (VIIb). A 2-g (0.01 mole) sample of epoxide V was dissolved in 50 ml of 80% ethanol, 1 ml of concentrated H_2SO_4 was added, and the mixture was refluxed for 1 h. The solvent was removed, and the residue was recrystallized from petroleum ether to give VIIb, with mp 82-83°C, in 45% yield. IR spectrum: 3290, 3365 cm^{-1} (OH). Found, %: C 54.2; H 5.9; N 25.9. $C_{10}H_{12}N_4O_2$. Calculated, %: C 54.5; H 5.4; N 22.4.

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