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REACTION OF 1,2,4-TRIAZOLE-3-THIONES WITH 1-CHLORO-2,3-EPOXYPROPANE

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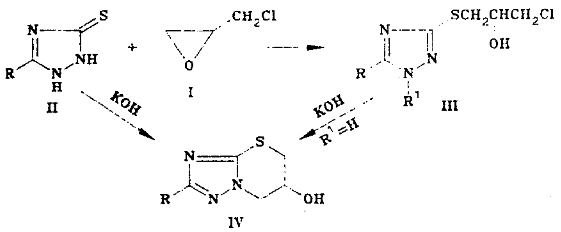
Addition of 1-chloro-2,3-epoxypropane to 1,2,4-triazole-3-thiones depending on the ratio of the reactants leads to the formation of 3-(1-chloro-2-hydroxypropyl)-3-(1-chloro-2-hydroxypropylthio)-1,2,4-triazoles. 3-Hydroxy-1,2,4-triazolo[2,3-b] tetrahydro-1,3-triazines have been synthesized by intramolecular cyclization of the monoadducts.

When five-membered nitrogen-containing heterocyclic compounds are interacted with 1-chloro-2,3-epoxypropane (I), two reaction pathways occur depending on the conditions. Base catalyzed alkylation leads to the formation of glycidyl-substituted azoles [1-3] or opening of the epoxide ring gives 1-chloro-2-hydroxypropyl-substituted azoles [4-7].

In the present work the reaction of 1,2,4-triazole-3-thione and its derivatives (IIa-c) with epoxypropane I has been studied. In the presence of organic bases the process occurs with opening of the epoxide ring to give 3-(1-chloro-2-hydroxypropylthio)-5-R-1,2,4-triazoles (IIIa-c).



II, IV a R=H, b R=CH_3, c R=C_6H_5; III a,d R=H, b,e R=CH_3, c,f R=C_6H_5;
a—c R'=H, d—f R'=$CH_2CHOHCH_2Cl$

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TABLE 1. PMR Spectra of Compounds IIIa-c and IVa-c

Compound	Chemical shifts, ppm (multiplicity)						
	$S{-}C{<}^{H_A}_{H_B}$	CH_X (m)	$Cl{-}C{<}^{H_{A'}}_{H_{B'}}$ (m)	$N{-}C{<}^{H_{A'}}_{H_{B'}}$ (q)	R		
					H (s)	CH_3 (s)	C_6H_5 (m)
IIIa	3,35m	4,18	3,65	—	8,44	—	—
IIIb	3,38m	4,28	3,86	—	—	2,55	—
IIIc	3,48m	4,26	3,80	—	—	—	7,50—8,04
IVa	3,27q 3,39q	4,53	—	4,20 4,29	7,85	—	—
IVb	3,29q 3,40q	4,50	—	4,08 4,17	—	2,23	—
IVc	3,25q 3,35q	4,55	—	4,25 4,33	—	—	7,39—7,96

The effect of the conditions on the yield of the final reaction product has been studied in greater detail using unsubstituted triazolethione IIa as a model. The reaction in dioxane solution in the presence of triethylamine, pyridine, or KOH gives compound IIIa in high yield even at 20°C. When a less basic catalyst such as pyridine is used, in order to complete the reaction it is necessary to increase its duration or heat it to 70°C. Under comparable conditions in benzene the yields of IIIa do not exceed 30%. An increase in polarity of the solvent (ethyl alcohol) makes it possible to obtain propylthiotriazole IIIa in quantitative yield even in the absence of a catalyst.

Introduction of a methyl substituent into the 5-position of the heterocycle lowers the reactivity – product IIIb is isolated only when the reaction is carried out in alcohol or dioxane with heating.

When an excess of epoxypropane I is used, the diadducts 1-(1-chloro-2-hydroxypropyl)-3-(1-chloro-2-hydroxypropylthio)-5-R-1,2,4-triazoles (IIId-f) are synthesized.

In the IR spectra of compounds IIIa-f there are no "thiomide I" absorption bands, which are characteristic of triazolethiones IIa-c (1565, 1600, and 1570 cm^{-1}), and an intense absorption appears in the region 1265-1295 cm^{-1} from a triazole ring which does not have a thioamide fragment in its structure. This indicates that addition of epoxypropane I takes place on the sulfur atom to give monoadducts. In the spectra in solution an absorption band from the unsubstituted NH group is also observed at 3449-3436 cm^{-1}, which is not present in the spectra of the diadducts IIId-f. The absorption bands at 3597-3606 and 3560-3580 cm^{-1} relate to stretching vibrations of the monomeric and bonded OH group respectively. The ratio of intensities of these bands remains constant when the concentration is changed within the limits 0.020-0.001 moles/liter, which indicates the existence in these compounds of intramolecular hydrogen bonding between the proton of the hydroxy group and the chlorine atom.

The structure of compounds IIa-c is confirmed by their PMR spectra (Table 1). The diastereotopic geminal protons of the SCH_2 and CH_2Cl groups in combination with the proton at the asymmetric carbon atom form two three-spin systems of type ABM; this gives rise to a complex pattern in the spectrum which is not amenable to detailed interpretation using known methods for approximation of ABX spin systems [8]. The protons of the methylene group bonded to the surface atom appear at 3.35-3.48 ppm (relative magnetic nonequivalence is $\Delta\delta_{AB} \cong 0.02$ ppm) in the form of a multiplet arising from the overlap of two quartets with vicinal spin-spin coupling constants $J_{AX} \cong 5.5$ and $J_{BX} \cong 2.0$ Hz. The nonequivalence of the protons of the CH_2Cl group (multiplet with center in the region 3.65-3.86 ppm, relative chemical shift $\Delta\delta_{A'B'} \cong 0.05$ ppm) suggests the existence of a preferred conformation of molecule III, which is probably stabilized by the formation of an intramolecular hydrogen bond between the hydroxyl group and the chlorine atom having a relative gauche conformation. This proposal is in agreement with the features of the IR spectra of compounds IIIa-c.

The reaction of triazolethiones II with epoxypropane I in alcohol solution with potassium hydroxide used as catalyst leads to the formation of 3-hydroxy-7-R-1,2,4-triazolo[2,3-b]tetrahydro-1,3-thiazines (IVa-c). Substituted triazolo-1,3-thiazines have been obtained previously by intramolecular cyclization of the adducts of triazolethiones IIa, b with 1-phenyl-2-cyanoacetylene [9]. When epoxypropane I was used, benzimidazo-1,3-thiazines [5] were synthesized.

TABLE 2. Properties of Compounds Synthesized

Compound	T_{mp}, deg C (n_D^{20})	Found, %			Empirical formula	Calculated, %			Yield, %
		Cl	N	S		Cl	N	S	
IIIa	(1,5650)	18,0	21,3	16,1	$C_5H_8ClN_3OS$	18,3	21,7	16,6	97
IIIb	94—95	17,2	20,4	15,4	$C_6H_{10}ClN_3OS$	17,1	20,2	15,4	98
IIIc	106—108	12,8	15,6	11,9	$C_{11}H_{12}ClN_3OS$	13,1	15,6	11,9	75
IIId	(1,5500)	24,9	14,6	11,1	$C_8H_{13}Cl_2N_3O_2S$	24,8	14,7	11,2	93
IIIe	(1,5380)	23,4	14,0	10,5	$C_9H_{15}Cl_2N_3O_2S$	23,6	14,0	10,7	90
IIIf	(1,5820)	19,2	12,0	8,7	$C_{14}H_{17}Cl_2N_3O_2S$	19,6	11,6	8,8	98
Va	193—194	18,3	21,6	17,0	$C_5H_7N_3OS \cdot HCl$	18,3	21,7	16,6	83
Vb	189—190	17,3	20,3	15,8	$C_6H_9N_3OS \cdot HCl$	17,1	20,2	15,4	83
Vc	219—221	13,4	15,6	11,9	$C_{11}H_{11}N_3OS \cdot HCl$	13,1	15,6	11,9	43

TABLE 3. 3-Hydroxy-1,2,4-triazolo[2,3-b]tetrahydro-1,3-triazines

Compound	T_{mp}, deg C	Found, %				Empirical formula	Calculated, %				Yield, %
		C	H	N	S		C	H	N	S	
IVa	155	38,2	4,6	26,6	20,4	$C_5H_7N_3OS$	38,2	4,5	26,7	20,4	63
IVb	169—170	41,9	5,1	24,4	18,6	$C_6H_9N_3OS$	42,1	5,3	24,5	18,7	52
IVc	194—195	56,8	4,8	18,1	13,3	$C_{11}H_{11}N_3OS$	56,6	4,7	18,0	13,7	55

The formation of triazolethiazines IVa-c is due to intramolecular alkylation of the initially formed chloropropylthiotriazoles IIIa-c. For confirmation of this they were treated with alcoholic alkali and as a result compounds IVa-c were isolaed.

In the IR spectra of cyclic compounds IVa-c a pattern similar to that for adducts IIIa-c is observed. The high-frequency absorption bands at 3598-3604 cm^{-1} characterize the free OH group and the lower-frequency bands (3532-3537 cm^{-1}) are due to the formation of intramolecula hydrogen bonding.

As a result of forming the thiazine ring the degree of nonequivalence of the diastereotop protons of the SCH_2 and NCH_2 groups becomes significant — $\Delta\delta_{AB} \cong \Delta\delta_{A'B'} \cong 0.1$ ppm (see Table 1) — which makes a complete analysis of the AB and A'B' subspectra possible using method [8] for an ABX approximation. The resonance from the protons of the SCH_2 group is characterized by two superimposed quartets with the following parameters: $\delta_A = 3.35\text{-}3.40$; $\delta_B = 3.25\text{-}3.29$ ppm $^3J_{AX(trans)} = 4.2$; $^3J_{BX(cis)} = 3.6$; $^2J_{AB} = 13.0$ Hz. The subspectrum of the protons of the NCH_2 fragment has similar characteristics in terms of multiplicity: $\delta_{A'} = 4.08\text{-}4.25$; $\delta_{B'} = 4.17\text{-}4.33$ ppm; $^3J_{A'X(trans)} = 5.8$; $^3J_{B'X(cis)} = 2.6$; $^2J_{A'B'} = 13.0$ Hz.

When treated with hydrogen chloride, triazolethiazines IVa-c readily form the correspondi hydrochlorides Va-c. The IR spectra of these compounds are characterized by a displacement of the stretching vibration bands from the ring to shorter wavelength 1450, 1490-1520, and 1570 cm^{-1}, and by absorption in the region 2400-2600 cm^{-1}.

EXPERIMENTAL

IR spectra wre recorded on a Specord 75-IR instrument as a thin layer, in KBr pellets, an in chloroform solution; PMR spectra were recorded on a Tesla BS-497 instrument (100 MHz) at 20°C in CD_3OD with TMS as internal standard.

3-(1-Chloro-2-hydroxypropylthio)-1,2,4-triazoles (IIIa-c). A mixture of 0.01 mole of triazole II, 0.8 ml (0.01 mole) of epoxypropane I, and 5 drops of triethylamine in 25 ml of dioxane (or methyl alcohol for IIIb) was agitated for 6 h at 20°C. The solvent was distilled off, and the residue was dried under vacuum to give a viscous substance. On standing compounds IIIb, c crystallized out.

1-(1-Chloro-2hydroxypropyl)-3-(1-chloro-2-hydroxypropylthio)-1,2,4-triazoles (IIId-f). A mixture of 0.01 mole of triazole II, 1.8 ml (0.02 mole) of epoxypropane I, and 5 drops of triethylamine in 20 ml of dioxane was heated for 4 h at 95°C, the solvent was distilled off, and a viscous substance was separated. The properties of compounds IIIa-f synthesized are given in Table 2.

3-Hydroxy-1,2,4-triazolo[2,3-b]tetrahydro-1,3-thiazines (IVa-c). A. To a solution of 1.2 g (0.02 mole) of KOH and 0.02 mole of triazole II in 50 ml of methyl alcohol was added dropwise 1.8 ml (0.02 mole) of epoxypropane I; the mixture was agitated for 5 h at 20°C and for 1 h at the boiling point of methyl alcohol. The precipitate of KCl which had formed was filtered off and the filtrate was passed through a layer of Al_2O_3 in order to remove residual KCl. The solvent was distilled off and the residue was extracted with acetone; a crystalline product was separated from the solution of acetone (see Table 3). B. 0.005 mole of propylthiotriazole IIIa-c was added to a solution of 0.3 g (0.005 mole) of KOH in 20 ml of methyl alcohol; the mixture was agitated for 6 h at the boiling point of methyl alcohol and treated according to method A.

Triazolethiazine Hydrochlorides (Va-c). Hydrogen chloride was bubbled through a solution of 0.2 g of triazolethiazine in a mixture of chloroform—methanol (20:1) for 4 h. The crystalline precipitate was filtered off. The properties of compounds Va-c synthesized are given in Table 2.

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