SYNTHESIS OF N-HYDROXYMETHYL DERIVATIVES OF 5-SUBSTITUTED TETRAZOLES

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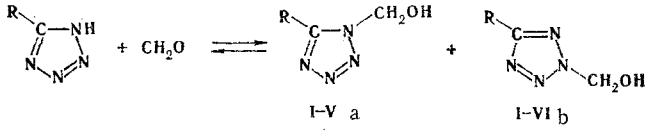
UDC 547.796.1:542.953.1:543.422

Mixtures of isomeric 1- and 2-hydroxymethyl derivatives are formed in the reaction of tetrazole and 5-alkyltetrazoles with formaldehyde in aqueous media, while only one isomer is formed from 5-phenyl- and 5-trifluoromethyltetrazoles. The structures and ratios of the isomers were determined by PMR spectroscopy.

The literature data on the addition of formaldehyde to NH acids of the heterocyclic series are quite limited [1-3]. The hydroxymethylation of derivatives of the 1,2,4-triazole series has been studied in greater detail [1, 2]. Thus a series of N-hydroxymethylation products has been obtained by the reaction of 1,2,4-triazole and 3-nitro-5-substituted 1,2,4-triazoles with formaldehyde. Information relative to the reaction of tetrazole derivatives with formaldehyde is currently limited to data on the hydroxymethylation of 1-substituted tetrazolinethiones, which takes place at the nitrogen atom in the 4 position of the ring [3].

It seemed of interest to subject 5-substituted tetrazoles to hydroxymethylation in order to obtain previously unknown N-hydroxymethyl derivatives of the tetrazole series. We selected tetrazoles with various substituents in the 5 position as the subjects of this investigation. The reaction of the examined compounds with excess formaldehyde in water led to the formation of the expected N-hydroxymethyl derivatives (I-VI) in 55-80% yields (Table 1).



I-V a I-VI b

I R=H; II R=CH_3; III R=C_2H_5; IV R=$C_6H_5CH_2$; V R=C_6H_5; VI R=CF_3

The hydroxymethylation of unsubstituted tetrazole and 5-methyl- and 5-ethyltetrazoles was carried out in the presence of catalytic amounts of sodium hydroxide at pH 5 (reaction medium). In view of the low solubility of 5-phenyl- and 5-benzyltetrazoles in water their sodium salts were subjected to the reaction. 5-Trifluoromethyltetrazole was used in the form of the free NH acid.

Mixtures of the corresponding isomeric 1- and 2-hydroxymethyl derivatives (Ia,b-IVa,b) were obtained as a result of hydroxymethylation of unsubstituted tetrazole and 5-methyl-, 5-ethyl-, and 5-benzyltetrazoles, whereas the primary formation of one of the possible isomers was observed in the reaction of 5-phenyl- and 5-trifluoromethyltetrazoles with formaldehyde. The compounds obtained were identified from their IR and PMR spectra and from the results of elementary analysis. Stretching, stretching-deformation, and deformation vibrations of the tetrazole ring at 1510-1530, 1400-1480, 1260-1310, 990-1100, 900-960, and 700-720 cm^{-1}, as well as stretching vibrations of an OH group at 3100-3350 cm^{-1}, appear distinctly in the IR spectra of all of the compounds.

The structures and quantitative ratios of the synthesized products were determined by PMR spectroscopy (Table 1). The chemical shifts in the PMR spectra of isomers Ia,b-IVa,b were assigned on the basis of the principle observed in the tetrazole series, viz., the signal of the protons of the alkyl groups in the 1 position is located at a stronger field (by 0.1-0.3 ppm) than in the spectra of the 2-substituted isomers [4]. Thus two signals of protons of

Lensovet Leningrad Technological Institute, Leningrad 198013. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 415-418, March, 1983. Original article submitted July 19, 1982.

0009-3122/83/1903-0341$07.50

TABLE 1. 1- and 2-Hydroxymethyl-5-R-tetrazoles

Compound	mp,[a] °C	IR spectrum,[b] cm^{-1}	PMR spectrum, δ, ppm	Found, %			Empirical formula	Calc., %			Yield, %
				C	H	N		C	H	N	
Ia	—[c]	3100 (OH), 1520, 1440, 1430, 1260, 1100, 1010, 960, 710 (ring)	6,00 (1-CH_2), 9,30 (5-H)	23,9	4,1	56,1	$C_2H_4N_4O$	24,0	4,0	56,0	48,5
Ib			6,08 (2-CH_2), 8,75 (5-H)								16,5
IIa	74	3200 (OH), 1530, 1470, 1400, 1270, 1230, 1100, 1010, 900, 710 (ring)	2,60 (CH_3), 5,85 (1-CH_2), 6,80 (OH)	30,9	5,0	49,7	$C_3H_6N_4O$	31,6	5,3	49,1	40,5
IIb	62		2,55 (CH_3), 5,95 (2-CH_2), 6,40 (OH)								13,5
IIIa	97	3100 (OH), 1530, 1480, 1450, 1260, 1060, 1020, 970, 900, 700 (ring)	1,35 (CH_3), 3,00 (5-CH_2), 5,75 (1-CH_2), 6,40 (OH)	37,1	6,2	44,1	$C_4H_8N_4O$	37,5	6,2	43,8	60
IIIb	66		1,30 (CH_3), 2,95 (5-CH_2), 5,90 (2-CH_2), 6,50 (OH)								20
IVa	100	3200 (OH), 1510, 1460, 1420, 1260, 1210, 1080, 930, 720 (ring)	7,30 (C_6H_5), 5,70 (1-CH_2), 4,38 (5-CH_2)	56,3	5,4	30,0	$C_9H_{10}N_4O$	56,8	5,3	29,5	40
IVb	85		7,30 (C_6H_5), 5,85 (2-CH_2), 4,25 (5-CH_2)								20
V	212	3250 (OH), 1530, 1470, 1450, 1300, 1080, 990, 720 (ring)	7,70 (C_6H_5), 6,10 (N—CH_2), 5,80 (OH)	55,0	4,1	30,9	$C_8H_8N_4O$	54,5	4,54	31,82	75
VIb	—[d]	3350 (OH), 1530, 1470, 1420, 1310, 1050, 1020 (ring), 1100	6,25 (2-CH_2), 7,90 (OH)	20,5	2,4	34,8	$C_3H_3F_3N_4O$[e]	21,4	1,8	33,3	80

[a]The compounds were recrystallized: IIa, IIIa, IVb, and V from chloroform, IIb and IIIb from petroleum ether—chloroform, and IVa from chloroform—ethanol.
[b]The spectra of mixtures of isomers are presented.
[c]The mixture of isomers Ia,b had n_D^{20} 1.4712.
[d]This compound had n_D^{20} 1.3941.
[e]Found: F 33.7%. Calculated: F 33.9%.

N-methylene groups with chemical shifts of 6.00 and 6.08 ppm, which were assigned to isomers Ia and Ib, respectively, were observed in the PMR spectrum of the mixture of hydroxymethyl derivatives of unsubstituted tetrazole. A similar assignment of the signals of the N-methylene protons was also made in the PMR spectra of IIa,b-IVa,b (Table 1). An analysis of the PMR spectra of products IIa,b-IIIa,b also showed that the signals of the protons of the C-methyl groups of IIa and IIIa (2.60 and 1.35 ppm) are shifted somewhat to weaker field as compared with the signals of isomers IIb and IIIb (2.55 and 1.30 ppm).

The ratios of isomers Ia-IIIa and Ib-IIIb estimated from the integral intensities of the signals of the protons of the 1- and 2-CH_2 groups were ∿3:1, as compared with 2:1 for IVa and IVb. Individual isomers IIa-IVa and IIb-IVb were isolated from the mixtures of N-hydroxymethyl derivatives IIa,b-IVa,b by fractional crystallization from organic solvents. We were unable to separate the mixture of isomeric alcohols Ia,b by fractional crystallization or fractional distillation, since cleavage of the N–CH_2OH bonds to give the starting tetrazole was observed upon prolonged heating.

Only one signal of N-methylene protons (6.10 and 6.25 ppm, respectively) was present in the PMR spectra of products V and VI, and this made it possible to conclude that only one of the possible isomers was formed as a result of hydroxymethylation. In the literature it is noted that the introduction of strong electron-acceptor substituents in the 5 position of the ring gives rise to primary reaction of tetrazolate anions with electrophilic reagents at the $N_{(2)}$ atom [5, 6]. It may therefore be assumed that primarily the 2,5-substituted isomer (VIb) is formed in the hydroxymethylation of 5-trifluoromethyltetrazole. It is still impossible to unambiguously determine the position of the hydroxymethyl group in product V. Additional study is necessary to solve this problem.

EXPERIMENTAL

The IR spectra of solutions of the compounds in acetone were recorded with an IKS-22 spectrometer. The PMR spectra of solutions in d_6-acetone were recorded with a Perkin-Elmer R-12 spectrometer (60 MHz) with hexamethyldisiloxane as the internal standard.

5-Substituted Tetrazoles. These compounds were obtained by the methods in [7, 8].

1- and 2-Hydroxymethyl-5-R-tetrazoles (Ia,b-IVa,b, V, and VIb; Table 1). A 2.6-ml (0.03 mole) sample of aqueous formalin was added with stirring at 20°C to a solution of 0.01 mole of the 5-substituted tetrazole in 100 ml of water containing 0.04 g (0.001 mole) of sodium hydroxide in the case of unsubstituted tetrazole and 5-methyl- and 5-ethyltetrazoles or 0.4 g (0.01 mole) of sodium hydroxide in the case of 5-methyl- and 5-ethyltetrazoles or 0.4 g (0.01 mole) of sodium hydroxide in the case of 5-phenyl- and 5-benzyltetrazoles, and the mixture was maintained at room temperature for 3 days. At the end of this time product V was isolated by acidification of the reaction mixture to pH 2 with 10% sulfuric acid with subsequent separation of the precipitate and crystallization from chloroform. Products Ia,b-IVa,b and VIb were extracted from the reaction mixture with ethyl acetate; prior to extraction of the isomeric alcohols IVa,b the reaction mixture was acidified to pH 2 with 10% sulfuric acid. The extracts were dried with magnesium sulfate, and the solvent was removed by distillation. The mixtures of isomers IIa,b-IVa,b were separated by fractional crystallization from organic solvents (Table 1). Compound VIb and the mixture of isomeric alcohols Ia,b were purified by dissolving in a heated (to the boiling point) mixture of chloroform and petroleum ether (3:1) with subsequent cooling of the resulting solution, separation of the liberated oil, and evacuation of the latter at a residual pressure of 30-40 mm at 40°C for 1 h.

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