HETEROCYCLIC NITRO COMPOUNDS. 25.* 1-HYDROXYMETHYL-3-NITRO-1,2,4-TRIAZOLES AND THEIR DERIVATIVES

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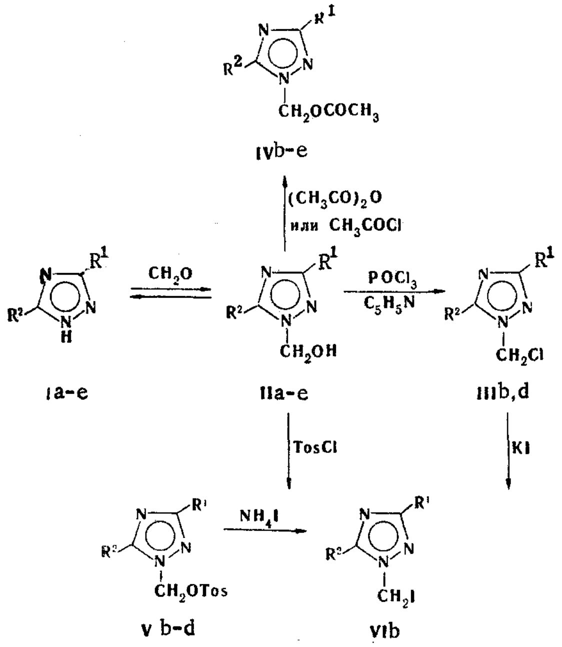
1-Hydroxymethyl derivatives of tetrazoles were obtained by the reaction of 1,2,4-triazole and 3-nitro-5-substituted triazoles with formaldehyde in water. The hydroxy groups were replaced by chlorine, and the hydroxymethyltriazoles were acetylated and tosylated. The chloro and tosyl groups are readily replaced by iodine by the action of potassium and ammonium iodide in acetone.

The available literature data on the reaction of 1,2,4-triazole derivatives with formaldehyde are limited [2, 3]. 3-Hydroxymethyltriazoles were obtained by the reaction of 1,2,4-triazole and 1-benzyl-1,2,4-triazole with formaldehyde [2].

3-Alkylthio- and alkylsulfonyl-1,2,4-triazoles give 1-hydroxymethyl derivatives [3]. However, it was not clear whether 1-hydroxymethyltriazoles that contain acceptor substituents in the ring exist. With this in mind, we subjected 1,2,4-triazole and 3-nitro-5-substituted 1,2,4-triazoles (Ia-e) to reaction with formaldehyde, as a result of which we obtained 1-hydroxymethyl-1,2,4-triazoles IIa-e (Table 1).

The hydroxymethylation of triazoles is reversible, and in alkaline media the equilibrium is shifted to favor the formation of the starting compounds. Absorption maxima corresponding to the anions of the triazoles were observed in the UV spectra of alkaline solutions of hydroxymethyl derivatives. In the case of dinitrotriazole Ie the equilibrium is shifted to



I, II a $R^1=R^2=H$; b $R^1=NO_2$, $R^2=H$; c $R^1=NO_2$, $R^2=CH_3$; d $R^1=NO_2$, $R^2=Br$; e $R^1=R^2=NO_2$; III, IV, V b $R^1=NO_2$, $R^2=H$; c $R^1=NO_2$, $R^2=CH_3$; d $R^1=NO_2$, $R^2=Br$; e $R^1=R^2=NO_2$; VI b $R^1=NO_2$, $R^2=H$

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*See [1] for communication 24.

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TABLE 1. 1-Hydroxymethyl-1,2,4-triazoles and Their Derivatives

Compound	mp, °C (crystallization solvent)	IR spectrum, cm^{-1}	PMR spectrum, δ, ppm	Found				Empirical formula	Calc.,				Yield, %
				C, %	H, %	N, %	*M*		C, %	H, %	N, %	*M*	
IIa	70—71 (chloroform)	3120 (OH), 1520, 1400, 1270, 1200, 1130, 1080, 1040, 970, 900 (ring)	8,10 (C_3—H), 8,70 (C_5—H), 5,75 (CH_2), 6,90 (OH)	34,9	4,3	40,9	105	$C_3H_5N_3O$	34,4	5,6	40,5	99	90
IIb	80—81 (dichloroethane)	3360 (OH), 1560, 1310 (NO_2), 1520, 1450, 1410, 1380, 1290, 1220, 1180, 1110, 1050, 1010, 980, 880, 840 (ring)	8,90 (C_5—H), 5,90 (CH_2), 6,60 (OH)	25,2	2,8	39,0	145	$C_3H_4N_4O_3$	25,0	2,8	38,9	144	81
IIc	134—135 (dichloroethane)	3230 (OH), 1560, 1310 (NO_2), 1520, 1490, 1400, 1380, 1220, 1150, 1090, 1020, 850 (ring)	2,60 (CH_3), 5,73 (CH_2), 7,40 (OH)	30,1	4,0	35,3	161	$C_4H_6N_4O_3$	30,4	3,8	35,5	158	84
IId	131—132 (dichloroethane)	3230 (OH), 1560, 1310 (NO_2), 680 (C—Br), 1500, 1420, 1220, 1110, 980, 850 (ring)	5,80 (CH_2), 7,20 (OH)	15,9	0,9	25,3	225	$C_3H_3N_4O_3Br^a$	16,3	1,3	25,1	223	92
IIIb	30—31 (benzene)	1560, 1310 (NO_2), 1520, 1440, 1220, 1100, 980, 850	6,40 (CH_2), 9,10 (C_5—H)	23,6	1,5	35,0	160	$C_3H_3N_3O_3Cl^b$	23,2	1,8	34,5	161,5	62
IIId	106 (chloroform)	1560, 1310 (NO_2), 1510, 1430, 1200, 1100, 970, 840 (ring)	6,30 (CH_2)	14,6	0,5	23,2	247	$C_3H_2N_4O_2ClBr$	15,0	0,8	23,2	241,5	82
IVb	—	1760 (C=O), 1570, 1310 (NO_2), 1520, 1450, 1430, 1240, 1220, 1060	8,98 (C_5—H), 6,40 (CH_2). 2,15 (CH_3)	31,8	2,8	29,9	186	$C_5H_6N_4O_4$	32,3	3,2	30,1	186	34 (A), 38 (B)
IVc	49—50 (water)	1770 (C=O), 1560, 1320 (NO_2), 1540, 1490, 1470, 1400, 1210 (ring)	6,32 (CH_2), 2,15 ($COCH_3$), 2,72 (ring CH_3)	35,6	3,7	28,6	202	$C_6H_8N_4O_4$	36,0	4,0	28,0	200	57

IV d	89—90 (ethyl acetate)	1770 (C=O), 1560, 1310 (NO_2), 770 (C—Br), 1490, 1450, 1415, 1225, 1200, 1060 (ring)	6,38 (CH_2), 2,15 (CH_3)	22,7	1,7	21,1	255	$C_5H_5N_4O_4Br$[c]	22,7	1,9	21,1	265	30
IVe	—	1770 (C=O), 1580, 1520, 1320 (NO_2), 1460, 1420, 1370, 1340, 1220, 1150, 1100, 1050, 1010, 980, 860, 830	6,75 (CH_2), 2,15 (CH_3)	26,3	2,9	30,0	237	$C_5H_5N_5O_6$	26,0	2,2	30,3	231	22
Vb	140 (acetone–ethanol)	1570, 1300 (NO_2), 1520, 1430, 1370, 1240, 1210, 1190, 1180, 1090, 1040, 1010, 990, 890, 840, 820	8,90 (C_5—H), 6,45 (CH_2), 2,40 (phenyl CH_3)	40,0	3,1	18,6	300	$C_{10}H_{10}N_4O_5S$[d]	40,3	3,4	18,8	298	59
Vc	152 (acetone–ethanol)	1570, 1310 (NO_2), 1500, 1410, 1380, 1280, 1210, 1190, 1110, 1040, 1000, 870, 850, 840	6,50 (CH_2), 2,65 (triazole CH_3) 2,45 (phenyl CH_3)	42,3	3,7	17,9	320	$C_{11}H_{12}N_4O_5S$[e]	42,3	3,8	18,0	312	32
Vd	135 (acetone–ethanol)	1570, 1300 (NO_2), 1500, 1450, 1420, 1400, 1380, 1250, 1210, 1180, 1110, 1020, 990, 840, 820	6,38 (CH_2), 2,45 (phenyl CH_3)	31,6	2,1	14,2	—	$C_{10}H_9N_4O_5BrS$[f]	31,8	2,3	14,8	387	42
VI b	69 (ethanol)	1550, 1300 (NO_2), 1510, 1440, 1390, 1210, 1200, 820, 680	9,10 (C_5—H), 6,43 (CH_3)	14,6	1,4	21,8	246	$C_3H_3N_4O_2I$	14,8	1,2	22,1	259	75 (A) 87 (B)

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[a] Found, %: Br 35.3. Calculated, %: Br 35.8. [b] Found, %: Cl 21.3. Calculated, %: Cl 21.5. [c] Found, %: Br 29.8. Calculated, %: Br 30.2. [d] Found, %: S 10.2. Calculated, %: S 10.8. [e] Found, %: S 9.9. Calculated, %: S 10.3. [f] Found, %: Br 19.7. Calculated, %: Br 20.6.

favor the starting compounds even in aqueous solution. The formation of 1-hydroxymethyl-3,5-dinitrotriazole (IIe) was established by means of the PMR spectrum in the reaction of dinitrotriazole with a suspension of paraformaldehyde in ether; however, we were unable to isolate IIe in pure form. Decomposition of IIe to the starting components occurred at 0°C in vacuo. Hydroxymethyltriazoles IIa-d remained unchanged after 1-2 months at room temperature. Gradual decomposition with splitting out of formaldehyde to give the starting triazoles occurred upon more prolonged storage. Cleavage to give the starting components also occurred during chromatography of the 1-hydroxymethyl derivatives on Silufol.

Absorption bands at 3100-3400 cm^{-1}, which correspond to the vibrations of a hydroxy group, were observed in the IR spectra of IIa-d along with a group of bands at 800-1600 cm^{-1}, which are characteristic for triazole rings with the corresponding substituents. The position of the 1-hydroxymethyl group was established by examination of the PMR spectra (Table 1). The presence of two different signals of C_3—H and C_5—H protons in the PMR spectrum of IIa constituted evidence that the hydroxymethyl group is attached to the N_1 atom.

In the PMR spectrum of IIb the signal of the protons of the methylene group (NCH_2OH, 5.90 ppm) is shifted to weaker field as compared with IIa to the extent of only 0.15 ppm. This made it possible to assign the 1-hydroxymethyl-3-nitro-1,2,4-triazole structure to IIb. The shift of this signal to weak field would have been more significant (0.4-0.5 ppm) in the case of attachment of the hydroxymethyl group to the N_2 or N_4 atom. Proceeding from similar considerations, we also assigned the corresponding 1-hydroxymethyl-3-nitro-1,2,4-triazole structures to IIc and IId.

The combination in 1-hydroxymethyl-3-nitrotriazoles of a relatively easily cleaved hydroxymethyl group, nitrogen atoms that are capable of protonation, and a nitro group that is sensitive to the action of nucleophilic agents led to certain peculiarities and anomalies in the reactivities of these compounds. Thus, in the case of attempts to replace the hydroxy group by halogen by the action of ordinary chlorinating agents ($SOCl_2$, PCl_5, and $POCl_3$) we detected 3-nitro-1,2,4-triazole and 3-chloro-1,2,4-triazole in the reaction mixture instead of the expected 1-chloromethyl derivative. We were able to accomplish replacement of the hydroxy group by chlorine in IIb and IId by reaction of the hydroxmethyltriazoles with the pyridine—$POCl_3$ (PCl_5) complex in dry ethyl acetate.

In the reaction of N-hydroxymethyltriazoles with acetic anhydride, in addition to acylation (products IVb-e), we observed cleavage at the N—CH_2OH bonds to give the starting triazoles. Moreover, replacement of the nitro group in the 3 position of the ring by halogen, which was established in the case of 1-hydroxymethyl-3-nitrotriazole (IIb), is possible under the influence of acetyl chloride. 1-Acetoxymethyl-3,5-dinitrotriazole (IVe) was obtained by the action of acetic anhydride on an ether solution of hydroxymethyl derivative IIe.

1-(p-Tosyl)methyl-3-nitro-1,2,4-triazoles (Vb-d) were obtained by the reaction of the 1-hydroxymethyl derivatives with p-toluenesulfonyl chloride in the presence of pyridine or by fusion with the addition of anhydrous ferric chloride.

The chlorine in III and the tosyl group in Vb are readily replaced by iodine by the action of potassium or ammonium iodide in acetone.

Since 1-hydroxymethyl-3-nitro-1,2,4-triazoles can be regarded as vinylogs of 1-hydroxymethylnitramines, we assumed that the hydroxymethyl derivatives of triazole would behave similarly in the reactions that are characteristic for hydroxymethylnitramines. It is known that 1-hydroxymethylnitramines form ethers of hydroxymethylnitramines or methylenebis(nitramines) under the influence of H_2SO_4, depending on the acid concentrations [5-7]. The key step in the mechanism of these reactions is protonation of the oxygen atom of the hydroxymethyl group with subsequent splitting out of water and further transformations of the carbonium-immonium ions [7].

A study of the behavior of 1-hydroxymethyltriazoles IIa-d in 60-95% sulfuric acid showed that IIa-d do not form two-ring products, whereas the starting triazoles were isolated in the case of dilution. The absorption maxima characteristic for protonated nitrotriazoles (220-250 nm) [8] were observed in the UV spectra of the sulfuric acid solutions. No substantial shift of the signal of the methylene protons was observed in the PMR spectra of these solutions. Protonation of the 1-hydroxymethyltriazoles in sulfuric acid evidently occurs at the N_4 atom rather than at the oxygen atom of the hydroxymethyl group, and the mechanism of the subsequent transformations of IIa–d at the hydroxymethyl group is consequently not realized.

EXPERIMENTAL

The IR spectra of films of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of solutions of the compounds in hexadeuteroacetone were recorded with a Perkin–Elmer R-12 spectrometer (60 MHz). The UV spectra were recorded with an SF-16 spectrophotometer.

1-Hydroxymethyl-1,2,4-triazoles (IIa–d). A 0.07-mole sample of 37% formalin was added to a solution (or suspension) of 0.05 mole of triazole Ia–d in 30 ml of water, and the mixture was stirred for 5 h. The reaction products were extracted with ethyl acetate (IIa–d) or removed by filtration (IIb). The yields and properties of these and the following compounds are presented in Table 1.

1-Chloromethyl-3-nitro-1,2,4-triazoles (IIIb, d). A 2.9-g (0.02 mole) sample of hydroxymethyl derivative IIb was added at 0°C to a solution prepared from 3.4 g (0.02 mole) of phosphorus oxychloride and 1.74 g (0.02 mole) of pyridine in 20 ml of ethyl acetate, and the mixture was heated slowly to 70°C and stirred at this temperature for 3 h. The solution was cooled, the solvent was removed by distillation in vacuo, and the residual oil was washed to neutrality with water. It was then dissolved in ether, and the ether solution was dried with magnesium sulfate. The ether was removed by distillation, and the residue was crystallized from benzene to give 2.0 g (62%) of IIIb. Compound IIId was similarly obtained in 80% yield.

1-Acetoxymethyl-3-nitro-5-R-1,2,4-triazoles (IVb–d). A) Acetylation with Acetyl Chloride. A 3-g sample of 1-hydroxymethyl-3-nitrotriazole (IIb) was maintained at 20°C in 45 ml of freshly distilled acetyl chloride for 24 h. After 24 h, the precipitate (0.1 g) was removed by filtration and identified as 3-chloro-1,2,4-triazole from IR and PMR spectral data and the results of TLC and a mixed-melting-point determination. The excess acetyl chloride was removed by distillation in vacuo, and the residual oil was dissolved in methylene chloride. The solution was washed with sodium bicarbonate solution and water and dried with magnesium sulfate, and the solvent was removed by distillation. The residue (an oil) was evacuated at 70°C and 10 mm for 5-6 h, and the product, with n_D^{20} 1.5030, was found to be a chromatographically individual substance. 3-Nitrotriazole and 3-chlorotriazole were detected in the bicarbonate solution by TLC.

B) Acetylation with Acetic Anhydride. A 2-g sample of IIb was heated in 20 ml of acetic anhydride at 50°C for 10 h, after which the excess acetic anhydride was removed by distillation in vacuo. The residue was then worked up as in method A. Compounds IVc, d were similarly obtained by method B.

1-Acetoxymethyl-3,5-dinitro-1,2,4-triazole (IVe). A 10-ml sample of an ether solution of the dinitrotriazole containing 2.05 g of product Ie (determined by titration) was stirred with 2 g of paraformaldehyde for 4 days. An intense signal at 6.28 ppm, which was assigned to the protons of the methylene group of hydroxymethyl derivative IIe, was observed in the PMR spectrum of the solution. The precipitated paraformaldehyde was removed by filtration, 3 ml of acetic anhydride was added to the filtrate, and the mixture was maintained at 20°C for 3 days. The ether was removed by distillation, and the excess acetic anhydride was removed by distillation in vacuum. The residue was dissolved in methylene chloride, and the solution was washed with sodium bicarbonate and water and dried with magnesium sulfate. The solvent was removed by distillation.

Substance IVe was isolated in the form of an oil that was undistillable in vacuo (1 mm) but was a chromatographically individual substance.

1-Tosylmethyl-3-nitro-1,2,4-triazoles (Vb–d). A) A 6.7-g sample of freshly crystallized p-toluenesulfonyl chloride was added at –5°C to a solution of 5 g of the hydroxymethyl derivative (IIb, c) in 18 ml of dry pyridine, and the mixture was stirred at 0°C for 1 h. It was then poured into 150 ml of 10% hydrochloric acid, and the precipitate was removed by filtration, washed with 5% hydrochloric acid and water, and dried. Products Vb, c were crystallized.

B) A 0.2-g sample of anhydrous ferric chloride and 2 g of hydroxymethyl derivative IId were added to fused p-toluenesulfonyl chloride (1.7 g), and the mixture was heated at 90°C until hydrogen chloride evolution ceased (1.5 h). It was then cooled and treated with water, and the aqueous mixture was filtered. The solid material was washed to neutrality with water and dissolved in acetone. The acetone solution was filtered, the solvent was removed from the filtrate by evaporation, and the residue was crystallized to give 1.4 g (42%) of tosyl derivative Vd.

1-Iodomethyl-3-nitro-1,2,4-triazole (VIb). A) From Chloromethyl Derivative IIIb. A mixture of 2 g of IIIb and 2.04 g of potassium iodide in 50 ml of acetone was refluxed for 3 h, after which the solvent was removed by evaporation, and the residue was washed with petroleum ether until it solidified. The solid was crystallized from ethanol.

B) From Tosylate Vb. A mixture of 1.5 g of Vb and 1.46 g of ammonium iodide in 100 ml of acetone was refluxed for 10 h, after which it was filtered, and the solvent was removed by evaporation. The residue was dissolved in ethyl acetate, and the solution was washed with 5% sodium thiosulfate solution and water. The ethyl acetate was removed by evaporation, and the residual oil was triturated with petroleum ether until it solidified. The solid was recrystallized from ethanol.

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HETEROCYCLIC NITRO COMPOUNDS. 26.* REACTION OF 1-SUBSTITUTED 3,5-DINITRO-1,2,4-TRIAZOLES WITH ANIONS OF HETEROCYCLIC NH ACIDS

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1-Substituted 3-nitro-5-(N-azolyl)-1,2,4-triazoles mixed with 1-substituted 3-nitro-1,2,4-triazol-5-ones are obtained in the reaction of 1-substituted 3,5-dinitro-1,2,4-triazoles with anions of heterocyclic NH acids (1,2,4-triazole, 1,2,3-triazole, pyrazole, benzotriazole, benzimidazole, and indazole derivatives). 1-Methyl-3-nitro-5-amino-1,2,4-triazole is formed instead of the expected 5-tetrazolyl derivative in the reaction of 1-methyl-3,5-dinitro-1,2,4-triazole with tetrazole in alkaline media.

The use of anions of heterocyclic NH acids in nucleophilic aromatic substitution reactions has been described in the case of the reaction of pyrazole [2, 3], imidazole [2-4], 1,2,3- [5] and 1,2,4-triazoles [2, 6, 7], benzimidazole [2], and benzotriazole [8] with halodinitro- and trinitrobenzenes. Analogous reactions in the heterocyclic series have been

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*See [1] for communication 25.

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