HETEROCYCLIC NITRO COMPOUNDS

III. Reactions Of Nitro-1, 2, 4-Triazoles With Aliphatic Amines*

L. I. Bagal, M. S. Pevzner, and V. Ya. Samarenko

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Reaction of 1-methyl-3, 5-dinitro-1, 2, 4-triazole with aliphatic amines results in the replacement of the nitro group in the 5-position of the triazole ring by the amino group. Some reactions of the compounds obtained have been investigated.

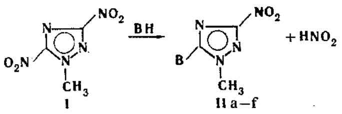
Nucleophilic replacement reactions of the aromatic nitro group by amino, hydroxy, and alkoxy groups have been fairly widely investigated in the benzene series [2, 3]. In the heterocyclic series, this reaction has been investigated mainly in the nitropyridines [4–6] and a few other nitrogeneous heterocycles [7].

The reaction of nitrotriazoles with nucleophiles has not, as yet, been investigated, although we had previously encountered isolated examples [8] of this type of reaction in the attempted esterification of 3-nitro-5-carboxy-1, 2, 4-triazole with methanol in presence of hydrogen chloride, and in its reaction with phosphorus pentachloride, both of which reactions led to the replacement of the nitro group by chlorine.

This paper deals with the reaction of 1-methyl-3, 5-dinitro-1, 2, 4-triazole (I) with aliphatic amines. Reaction of I with ammonia and primary and secondary amines results in the facile replacement of one of the nitro groups.

In order to combine with the liberated nitrous acid, an excess of amine was used. Water and dioxane were used as solvents.

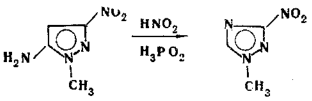
Reaction of I with triethylamine in aqueous dioxane resulted in the replacement of the nitro group by hydroxyl, giving 1-methyl-3-nitro-1, 2, 4-triazol-5-one (III):



Compound III was also obtained as a by-product in the reaction of I with ammonia.

Reaction of I with nucleophiles can give two isomers (replacement of the nitro group in the 3- or 5-position). Thin layer chromatography of the reaction products on alumina showed the presence of one isomer only in all cases. The purity of the compounds obtained was also confirmed by their sharp mp's. In order to determine the position of the nitro group which was replaced, the products were converted into compounds of known structure.

Deamination of IIa gave 1-methyl-3-nitro-1, 2, 4-triazole (IV), showing that replacement of the nitro group in I occurred at the 5-position:



The amine IIa was acetylated and diazotized. It is interesting that the reaction with nitrous acid in acid solution gave not the diazonium salt but the stable nitrosoamine VI.

The structure of the alkylamino compounds IIb and IId was proved by their conversion into 1-methyl-5-substituted triazoles VIIIb and VIIId:

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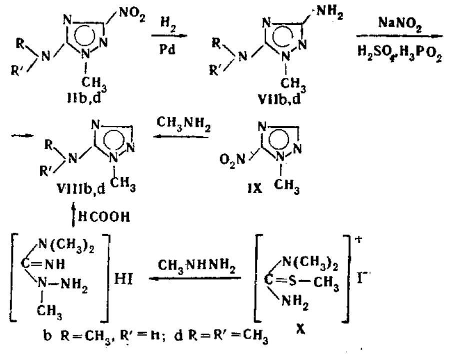
*For part II, see [1].



The presence of the ethylene imine group in IIf was confirmed by fission of the ethylene imine ring by treatment with hydrochloric acid to give 1-methyl-3-nitro-5-β-chloroethylamino-1, 2, 4-triazole (XI). The properties of the triazole derivatives are given in the table. In all cases, the nitro group in the 5-position of the triazole ring was replaced.

Our experimental results confirm the increased nucleophilic reactivity of the 5-position of the 1, 2, 4-triazole ring which is indicated by MO LCAO calculations [9, 10].

EXPERIMENTAL

I-Methyl-3-nitro-5-amino-1, 2, 4-triazole (IIa). Four grams (0.023 mole) of I [1] in 100 ml of 25% aqueous ammonia was heated in an autoclave at 70–80° C for 4 hr. The mixture was cooled, and the product which separated was filtered off and washed with water. Thin-layer chromatography on alumina (solvent system dioxane–hexane, 2 : 3) indicated the homogeneity of the compound.

1-Methyl-3-nitro-5-acetamido-1, 2, 4-triazole (V). One gram (0.007 mole) of amine IIa was heated in 15 ml of acetic anhydride for 4 hr, and the mixture concentrated in vacuo until crystallization began, when benzene was added and the mixture filtered.

1-Methyl-3-nitro-5-nitrosoamino-1, 2, 4-triazole (VI). To 1.2 g (0.0085 mole) of amine IIa in 25 ml of 10% H_2SO_4 at 0° C was added dropwise a solution of 0.65 g of sodium nitrite in 10 ml of water. The mixture was stirred for 30 min, the precipitate filtered off, and the solid washed with water and dried in a vacuum desiccator. The compound exhibited acidic properties, and gave a positive Liebermann reaction, showing the presence of an N-nitroso group.

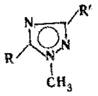
Deamination of IIa. To 70 ml of conc H_2SO_4 was added in small portions with stirring and cooling (0° C) 3 g of sodium nitrite, followed by the dropwise addition of a solution of 29 g of sodium hypophosphite in 50 ml of 30% H_2SO_4. To this mixture was added a suspension of 3 g (0.021 mole) of amine IIa in 200 ml of glacial acetic acid. After 24 hr at 0° C, the mixture was poured onto ice and extracted with ethyl acetate. The extract was washed with water and sodium carbonate solution, and dried over calcium chloride. The solvent was removed, and the residue recrystallized from ethanol, giving 0.5 g (22%), mp 62–63° C. The compound was identical in its properties (mp, mixed mp, IR spectrum, R_f) with 1-methyl-3-nitro-1, 2, 4-triazole (IV) [1].

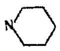
1-Methyl-3-nitro-5-methylamino-1, 2, 4-triazole (IIb). To 1 g (0.0115 mole) of I in 25 ml of dioxane at 20° C was added 3.6 ml of a 20% aqueous solution of methyl amine. After heating for 1 hr at 75–80° C, the mixture was cooled, and the reaction product which separated was filtered off. A further quantity of product was obtained by concentrating the filtrate. Thin-layer chromatography on alumina (solvent system dioxane–hexane, 3 : 2) showed that the compound was homogeneous.

The amino compounds IIc, d, e and g were obtained similarly to IIb, by reaction of the corresponding amines with I in aqueous dioxane.

1-Methyl-3-nitro-5-ethyleneimino-1, 2, 4-triazole (IIf). To solution of 2.4 g (0.0139 mole) of I in 30 ml of dioxane was added dropwise 1.7 ml of ethylene imine. The temperature of the mixture rose to 40–45° C, and gas was

1, 2, 4-Triazoles



Compound	R′	R	Mp, °C (solvent for crystallization)	IR spectra [11], cm^{-1}				Molecular formula	Found				Calculated			
				ν_{NO_2}	ν for amino groups: Valency vibrations	ν for amino groups: Deformational vibrations	Other		C, %	H, %	N, %	M	C, %	H, %	N, %	M
IIa	NO_2	NH_2	254-256 Ethanol	1510 1320	3445; 3300—3180	1660		$C_3H_5N_5O_2$	25.10	3.42	49.19	140	25.15	3.49	48.90	143
IIb	NO_2	$NHCH_3$	207-208 Ethanol	1520 1310	3420	1600		$C_4H_7N_5O_2$	29.90	4.65	44.45	159	30.50	4.47	44.65	157
IIc	NO_2	$NH\text{-}CH{=}CH_2$	68-69 (ether-hexane, 2 : 1, at -70°)	1533 1313	3240—3380	1570	1644—1650 (C=C)	$C_6H_9N_5O_2$	39.60	4.97	38.57	193	39.33	4.92	38.24	183
IId	NO_2	$N(CH_3)_2$	109 (Ethanol)	1550 1315	—	—	1600 (not assigned)	$C_5H_9N_5O_2$	35.20	5.39	41.02	176	35.10	5.26	40.93	171
IIe	NO_2	$N(C_2H_5)_2$	47.5-48 (ether-light petroleum, -70° C)	1560 1315	—	—		$C_7H_{13}N_5O_2$	42.55	6.44	35.45	197	42.21	6.53	35.18	199
IIf	NO_2		114-115 (Ethanol)	1550 1315	—	—		$C_5H_7N_5O_2$	35.10	4.25	41.38	175	35.50	4.14	41.40	169
IIg	NO_2		120.5-121.5 (carbon tetrachloride-heptane, 1 : 3)	1553 1315				$C_8H_{13}N_5O_2$	—	—	32.88	218	—	—	33.15	211
V	NO_2	$NHCOCH_3$	172-173 (Ethanol)	1530 1313			1795 (C=O)	$C_5H_7N_5O_3$	32.20	3.95	37.72	180	32.45	3.79	37.90	185
VI	NO_2	NHNO	78 (Ethanol)	1570 1320			1450; 1085 (−N=O)	$C_3H_4N_6O_3$	20.90	2.20	49.05	182	20.90	2.33	48.80	172
VIIb	NH_2	$NHCH_3$	170 (isopropanol-light petroleum, 5 : 1)	—	3300; 3180	1660; 1560		$C_4H_9N_5$	37.78	7.86	55.24	132	37.80	7.10	55.10	127
VIId	NH_2	$N(HC_3)_2$	136.5 (light petroleum-chloroform, 5 : 1)	—	3320; 3180	1640; 1580	—	$C_5H_{11}N_5$	42.35	8.29	49.72	145	42.55	7.80	49.65	141
VIIIb*	H	$NHCH_3$	211-212 (Ethanol)	—	—	—	—	$C_4H_8N_4{\cdot}C_6H_3N_3O_7$	34.85	3.46	28.90	—	35.20	3.23	28.73	—
VIIId*	H	$N(CH_3)_2$	152-153 (benzene-ethanol, 6 : 1)	—	—	—	—	$C_5H_{10}N_4{\cdot}C_6H_3N_3O_7$	37.12	3.95	27.78	—	37.20	3.66	27.62	—
XI	NO_2	$NHCH_2CH_2Cl$	130 (Ethanol)	1540 1315	3290		720 (C−Cl)	$C_5H_8ClN_5O_2$**	—	—	33.91	—	—	—	34.10	—

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*Picrate.

**Found, %: Cl 17.16. Calculated, %: Cl 17.35.

evolved. After 1 hr, the mixture was filtered, the dioxane removed, and the residue crystallized from ethanol.

1-Methyl-3-amino-5-methylamino-1, 2, 4-triazole (VIIb). A 3.7 g (0.0236 mole) amount of the methylamino compound IIb, dissolved in 200 ml of ethanol, was placed in a hydrogenation flask with 1.5 g of catalyst (palladium on charcoal). Air was displaced from the flask with carbon dioxide gas, and hydrogen was introduced from a gasometer while the flask was shaken continuously. When uptake of hydrogen had ceased, the solution was filtered, the alcohol removed, and the residue crystallized from isopropanol–light petroleum (5: 1).

1-Methyl-3-amino-5-dimethylamino-1, 2, 4-triazole (VIId) was obtained in a similar way to VIIb.

1-Methyl-5-methylamino-1, 2, 4-triazole (VIIIb) picrate. A) To a solution of 2 g (0.0158 mole) of 1-methyl-3-amino-5-methyl-amino-1, 2, 4-triazole (VIIb), 8.35 g of sodium hypophosphite, and 9.8 ml of conc H_2SO_4 in 40 ml of water was added at room temperature 2.4 g of sodium nitrite in 6 ml of water. The mixture was kept for 30 min at 20° C, 1 hr at 40° C, and allowed to stand overnight. The acid was neutralized with NaOH solution, the mixture evaporated to dryness on the water bath, the residue dried and extracted with dichloroethane. The solvent was removed, and the residue was dissolved in 20 ml of isopropanol. The solution was treated with a solution of 3.2 g of picric acid in isopropanol. The picrate of VIIIb which separated was filtered off, washed with benzene and dried to give 2 g (37.3%), mp 211–212° C (from ethanol).

B) To a solution of 1.28 g (0.01 mole) of 1-methyl-5-nitro-1, 2, 4-triazole (IX) [12] in 15 ml of dioxane was added 25 ml of 25% aqueous methyl amine. The mixture was heated for 10 hr at 70–75° C, kept overnight, the dioxane evaporated, the residue evaporated with isopropanol (to remove water), and dried in a vacuum desiccator. The residue was dissolved in 15 ml of isopropanol, and a solution of 2.66 g of picric acid in isopropanol was added. The picrate which separated was filtered off to give 1.65 g (48.5%), mp 211–212° C (from ethanol). The material gave no depression of mp on admixture with the product obtained by method (A), and was identical with it by elemental composition and IR spectrum.

1-Methyl-5-dimethylamino-1, 2, 4-triazole (VIIId) picrate. A) Obtained similarly to VIIIb from 1-methyl-3-amino-5-dimethylamino-1, 2, 4-triazole (VIId) (method a), mp 152–153° C (from benzene–ethanol, 6: 1).

B) (a) **S-Methyl-N, N-dimethylisothiourea hydriodide (X).** 13.1 g (0.14 mole) of N, N-dimethylthiourea [13] was boiled in 75 ml of absolute ethanol with 24 ml of methyl iodide for 2 hr, the alcohol removed in vacuo, and the residue crystallized from a mixture of ether and alcohol, giving 27.5 g (89%), mp 97–98° C. Found, %: N 11.09; mol wt 249. Calculated for $C_4H_{10}N_2S \cdot HI$, %: N 11.38; mol wt 246.

(b) **1, 1, 3-Trimethyl-3-aminoguanidine hydriodide and 1-methyl-5-dimethylamino-1, 2, 4-triazole (VIIId) picrate.** 27 g (0.115 mole) of X and 5.6 g of methylhydrazine were boiled in 100 ml of absolute ethanol for 16 hr, and the alcohol removed in vacuo. The resulting 1, 1, 3-trimethyl-3-aminoguanidine hydriodide was used without further purification for the cyclization. The salt (5.2 g) and 5.6 ml of 88% formic acid were heated for 40 hr at 105–110° C. The mixture was then evaporated on the water bath, the residue dissolved in hot isopropanol, and a hot solution of 5 g of picric acid in isopropanol added. The picrate of VIIId which separated on cooling was recrystallized from benzene-ethanol (6: 1) to give 6 g (79%), mp 152–153° C. The compound was identical (mp, mixed mp, IR spectrum) with the compound prepared by method (A).

1-Methyl-3-nitro-5-β-chloroethylamino-1, 2, 4-triazole (XI). A 0.3 g (0.00178 mole) amount of IIf was dissolved in 5 ml of dioxane, and 1 ml of conc H_2SO_4 added. After 1 hr, the solvent was removed, and the residue crystallized from ethanol.

1-Methyl-3-nitro-1,2,4-triazol-5-one (III). A) To a solution of 1 g (0.0058 mole) of I in 10 ml of aqueous dioxane was added 0.9 ml of triethylamine, and the mixture heated at 75–80° C for 4 hr. The dioxane was removed, and the residue treated with 25 ml of cold (0° C) H_2SO_4. The crystals which separated were filtered off and washed with cold water, mp 229° C (decomp., from ethanol) (this compound was obtained [14] after this paper had gone to press). Yield 0.4 g (48%). Found, %: C 24.80; H 2.87; N 38.94; mol wt 148. Calculated for $C_3H_4N_4O_3$, %: C 25.00; H 2.78; N 38.90; mol wt 144. IR spectrum, cm^{-1}: 1690–1710 (C=O group); 1550, 1360–1340 (nitro group) [11].

B) The filtrate after isolation of the amine IIa, obtained by reaction of I with aqueous ammonia, was evaporated to dryness, treated with 5% H_2SO_4, and the resulting precipitate filtered off, mp 229° C (decomp., from ethanol). The compound was identical (mp, IR spectrum, analysis) with the compound obtained by method (A).

Chromatography was carried out on thin layers of "chromatography" grade alumina. No binder was used. The solvent systems were dioxane-hexane (2 : 3) and acetone–heptane (1 : 1). The chromatograms were visualized in UV light (Brumberg ultrachemiscope).

IR Spectra were recorded on a UR-10 instrument, as films or as vaseline oil suspensions.

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Lensovet Leningrad Technological Institute.