HETEROCYCLIC NITRO COMPOUNDS

VII.* REPLACEMENT OF NITRO GROUPS BY CHLORINE AND BROMINE IN NITRO DERIVATIVES OF 1,2,4-TRIAZOLE

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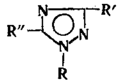
The reaction of 3(5)-nitro-1,2,4-triazole with hydrogen halides (HCl and HBr) leads to replacement of the nitro group by chlorine and bromine. In 1-methyl-3,5-dinitro-1,2,4-triazole the nitro group in the 5 position is replaced. Nucleophilic substitution of halogen in 1-methyl-3-nitro-5-halotriazoles leads to the formation of the corresponding 1-methyl-3-nitro-5-substituted 1,2,4-triazoles.

In extending our investigation of the reaction of nitro derivatives of 1,2,4-triazole with nucleophilic reagents [1-3] we have studied the action of hydrogen chloride and hydrogen bromide on several 3(5)-nitro-1,2,4-triazoles. The replacement of the nitro group by halogen by the action of hydrogen halides and phosphorus chlorides has been described for nitro compounds of the benzene series [4]. This sort of reaction was observed during attempts to esterify 3-nitro-5-carboxy-1,2,4-triazole in the presence of hydrogen chloride and during its reaction with phosphorus pentachloride [6] as well as for 3-nitrotriazol-5-one derivatives [3,6,7].

Triazoles I-V were selected for further investigation.



I $R=R''=H$ $R'=NO_2$; II $R=CH_3$ $R'=H$ $R''=NO_2$;
III $R=H$ $R'=R''=NO_2$; IV $R=CH_3$ $R'=R''=NO_2$;
V $R=CH_3$ $R'=NO_2$ $R''=NH_2$; VI $R=R''=H$ $R'=Cl$;
VII $R=H$ $R'=NO_2$ $R''=Cl$; VIII $R=H$ $R'=R''=Cl$;
IX $R=CH_2CH_2NO_2$ $R'=NO_2$ $R''=Cl$; X $R=R''=H$ $R'=Br$;
XI $R=CH_3$ $R'=H$ $R''=Br$; XII $R=CH_3$ $R'=NO_2$ $R''=Cl$;
XIII $R=CH_3$ $R'=NO_2$ $R''=Br$; XIV† $R=CH_3$ $R'=NO_2$ $R''=OH$;
XV $R=CH_3$ $R'=NO_2$ $R''=NHCH_3$; XVI $R=CH_3$ $R'=NO_2$ $R''=N(CH_3)_2$;
XVII $R=CH_3$ $R'=NO_2$ $R''=N(CH_3)NH_2$; XVIII $R=CH_3$ $R'=NO_2$ $R''=OCH_3$;
XIX $R=CH_3$ $R'=NO_2$ $R''=OC_2H_5$; XX $R=CH_3$ $R'=NO_2$ $R''=OC_6H_5$;
XXI $R=CH_3$ $R'=Cl$ $R''=NH_2$.

The reaction was carried out either in ether with bubbling through gaseous hydrogen chloride or by refluxing in concentrated hydrohalic acids.

Compound I reacted slowly with hydrogen chloride in ether, and the yield of VI did not exceed 15-20%. III in ether reacted with HCl to form products of substitution of one or both nitro groups (VII and VIII); the reaction proceeds more readily due to the additional activating effect of the nitro group. VII could not be

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*See [1] for Communication VI.

†The compound has the 1-methyl-3-nitro-1,2,4-triazol-5-one structure.

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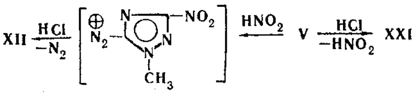
isolated in pure form but was identified in the form of the product of reaction with nitroethylene as 1-β-nitroethyl-3-nitro-5-chloro-1,2,4-triazole (IX).

It was found to be more convenient to carry out the substitution of the nitro group in the mononitrotriazoles by refluxing them in hydrohalic acids. Thus, the corresponding halo derivatives (VI, X, and XI) were obtained in good yields by heating I and II in hydrochloric and hydrobromic acids. When this method was applied to IV, products of substitution by halogen of one of the nitro groups (XII and XIII) were synthesized. XII and XIII were subjected to reaction with nucleophilic reagents (hydroxyl and alkoxide ions and amines) to prove the structure of the compounds obtained. XIV-XX were identical to compounds synthesized by means of appropriate nucleophilic substitution reactions with IV [1-3]. It was thereby proved that the substitution of a nitro group by halogen in IV occurs at the 5-position as in the substitution by other nucleophilic groups [1-3].

The reaction of V with hydrochloric acid resulted in the formation of the compounds: the expected XXI and side product XII. The formation of XII can be explained by the fact that amine V is diazotized by the nitrous acid evolved during substitution of the nitro group with subsequent substitution of the diazo group by halogen. This is confirmed by the increased yield of XII in the absence of urea in the reaction mixture.



Thus the reaction of nitro derivatives of 1,2,4-triazole with hydrohalic acids turned out to be a convenient method for the synthesis of chloro- and bromotriazoles containing other functional groups in addition to halogen in the ring.

EXPERIMENTAL

3-Chloro-1,2,4-triazole (VI). A. Compound I [0.8 g (0.007 mole)] was suspended in 60 ml of ether, hydrogen chloride was bubbled through the suspension for 8 h, and the mixture was then allowed to stand in a stopped flask for 4 days. The resulting precipitate was filtered and extracted with hot benzene (three 20-ml portions). Cooling of the extract precipitated 0.1 g (14%) of crystals of VI with mp 165-166 deg (166 deg [5]). The compound did not depress the melting point of an authentic sample of VI. The benzene-insoluble residue was starting I.

B. I [1 g (0.0088 mole)] was refluxed for 8 h in 20 ml of concentrated hydrochloric acid, 80 ml of water was added, and the mixture was extracted with ethyl acetate. The solvent was evaporated, and the residue was crystallized from benzene to give 0.55 g (61%) of a product with mp 166 deg. The product was identical to the product obtained via method A.

3-Bromo-1,2,4-triazole (X). This was obtained in 50% yield in the same way as VI (method B) by refluxing I in hydrobromic acid and had mp 187 deg (from benzene) (187-188 deg [6]). The compound did not depress the melting point of an authentic sample of X.

1-Methyl-5-bromo-1,2,4-triazole (XI). This was obtained from II in 55% yield and had mp 49-50 deg (49-50 deg [6]) [8].

Reaction of III with Hydrogen Chloride. Hydrogen chloride was bubbled through a solution of 8.5 g (0.0535 mole) of III in 50 ml of ether for 4 h. The solution was evaporated to 10 ml and cooled to −20 deg to precipitate 3 g (40%) of VIII with mp 147 deg (two recrystallizations from benzene). The product did not depress the melting point of sample of VIII previously obtained in [9]. Nitroethylene (3 g) was added to the ether solution after precipitation of VIII. After 24 h the solution was filtered,* the filtrate was evaporated to dryness, and the residue was recrystallized three times from ethanol to give 0.2 g of IX with mp 100-101 deg. Found %: C 22.0; H 1.7; Cl 16.0; N 31.3; mol. wt. 223. $C_4H_4ClN_5O_4$. Calc. %: C 21.7; H 1.8;

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*The precipitate on the filter was a mixture of β-nitroethyl derivatives III and VIII, from which 1-(β-nitroethyl)-3,5-dinitro-1,2,4-thiazole with mp 146 deg was isolated [10].

Cl 16.0; N 31.5; mol wt. 221.5. IR spectrum: 1550, 1310 cm^{-1} (heterocyclic nitro group), 1365 cm^{-1} (aliphatic nitro group), 750 cm^{-1} (C-Cl).*

1-Methyl-3-nitro-5-chloro-1,2,4-triazole (XII). Compound IV [1 g (0.0058 mole)] was heated for 3 h with 30 ml of concentrated hydrochloric acid at 103-105 deg. The acid was then evaporated to dryness on a water bath, and the residue was crystallized from benzene to give 0.7 g (74%) of a product with mp 88-89 deg. Found %: C 21.9; H 2.0; Cl 21.7; N 33.9; mol. wt. 164. $C_3H_3ClN_4O_2$. Calc. %: C 22.1; H 1.8; Cl 21.8; N 34.3; mol wt. 162.5. IR spectrum: 1555, 1315 cm^{-1} (nitro group), 720 cm^{-1} (C–Cl).

1-Methyl-3-nitro-5-bromo-1,2,4-triazole (XIII). This was obtained in 86% yield by heating IV with hydrobromic acid and had mp 89-90 deg (from benzene). Found %: C 17.2; H 1.4; Br 38.1; N 26.7; mol. wt. 202. $C_3H_3BrN_4O_2$. Calc. %: C 17.3; H 1.4; Br 38.6; N 27.0; mol. wt. 207. IR spectrum: 1555, 1315 cm^{-1} (nitro group), 645, 675 cm^{-1} (C-Br).

Reaction of XII and XIII with Nucleophilic Reagents.† A. Compound XII or compound XIII (2 g) was heated for 20 min in 30 ml of 10% sodium hydroxide, the mixture was cooled, and the solution was acidified to pH 1. It was then extracted with ethyl acetate, and the ethyl acetate was evaporated from the extract to give 1 g (72%) (from XII) or 1.2 g (69%) (from XIII) of XIV with mp 229 deg (dec., from ethanol). The product was identical to 1-methyl-3-nitro-1,2,4-triazol-5-one [2].

B. Compound XII or XIII (1 g) was added to a solution of 0.3 g of sodium in 25 ml of absolute methanol. The solution was heated for 3 h at 65-70 deg, filtered, and the filtrate was evaporated. The residue was washed with water, and dried to give 38-40% of XVIII with mp 145.5 deg.

C. The reaction was carried out in the same way as experiment B using sodium ethoxide to give 44% of XIV with mp 72-73 deg.

D. Phenol (1.5 g), 0.3 g of sodium, and 1 g of XII or XIII were dissolved in 35 ml of absolute dioxane. The mixture was heated at 90-95 deg for 4 h, the solvent was evaporated, and the residue was washed with water and crystallized from ethanol to give 1.02 g (74%) of XX with mp 126.5 deg.

E. Compound II or XIII (1 g) was heated with 25 ml of 25% aqueous methylamine at 90 deg for 3 h. Cooling of the mixture gave a precipitate which was filtered, washed with water, and recrystallized twice from ethanol to give 0.6 g (62%) of XV with mp 205-206 deg.

F. The reaction was carried out in the same way as experiment E using dimethylamine to give 60% of XVI with mp 109 deg (from ethanol).

G. Compound XII or XIII (1 g) was heated in 30 ml of dioxane with 1 g of methylhydrazine at 90 deg for 3 h. The solvent was then evaporated, and the residue was washed with water and crystallized from water to give 0.6 g (56%) of XVII with mp 162 deg.

1-Methyl-3-chloro-5-amino-1,2,4-triazole (XXI). A mixture of 7 g (0.049 mole) of V and 10 g of urea was refluxed for 6 h with 90 ml of concentrated HCl, after which the solution was evaporated to dryness in vacuo, and the residue was extracted with hot benzene (80 ml). The benzene was evaporated, and the residue was crystallized from benzene–hexane (1:2) to give 0.8 g of a product with mp 90 deg which did not depress the melting point of an authentic sample of 1-methyl-3-nitro-5-chloro-1,2,4-triazole (XII). The benzene-insoluble product was extracted with boiling ethyl acetate (three 100-ml portions); the solvent was evaporated and XXI was crystallized from toluene with added activated charcoal to give 2.9 g of a product with mp 157-158 deg. Found %: C 27.2; H 3.8; Cl 26.7; N 42.4; mol. wt. 133. $C_3H_5ClN_4$. Calc. %: C 27.2; C 27.2; H 3.8; Cl 26.8; N 42.3; mol. wt. 132.5. IR spectrum: 3425, 3320 cm^{-1} (amino group valence vibrations), 1650 cm^{-1} (amino group deformation vibrations), 740 cm^{-1} (C–Cl).

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*The IR spectra of films of the compounds were obtained with a UR-10 spectrometer.

† The products in experiments A-G were identified from their melting points, melting-point depressions of mixtures with authentic samples, and IR spectra.

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