

## The Preparation of Some N-Methyl-1,2,3-Triazoles

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The reaction between diazomethane and cyanogen bromide has been shown to give a mixture of the three N-methyl derivatives of 4-bromo-1,2,3-triazole. The structure of the three products is proved and their reaction with ammonia is studied.

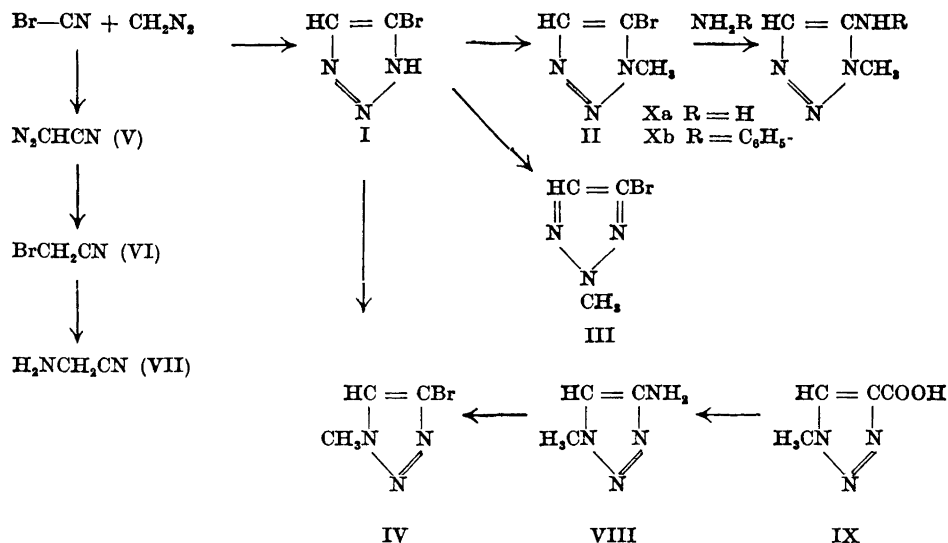
The reaction between cyanogen bromide and diazomethane has been studied by Tamburello and Milazzo<sup>1</sup>. According to these authors the first product of the reaction is 4-bromo-1,2,3-triazole (I) since this compound could be isolated when the reaction was carried out with excess cyanogen bromide. With excess diazomethane present in the reaction mixture I was further methylated and 2-methyl-4-bromo-1,2,3-triazole (III) was isolated.

The methylation of 1,2,3-triazole with dimethyl sulfate has been shown by Huttel and Welzel<sup>2</sup> to give a mixture of 1- and 2-methyl-1,2,3-triazole and in the present paper it is shown that the same two products are obtained when diazomethane is used as the methylating agent.

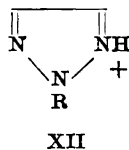
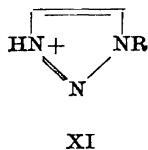
In view of this it would be expected that the methylation of I with diazomethane could give, besides III, two other products, namely 1-methyl-5-bromo-1,2,3-triazole (II) and 1-methyl-4-bromo-1,2,3-triazole (IV) and it was therefore decided to reinvestigate the reaction between diazomethane and cyanogen bromide.

The reaction product, on distillation, gave three fractions (1, 2 and 3, see experimental part) of which the largest and lowest boiling one (1) proved to be a mixture of  $\alpha$ -bromoacetonitrile (VI) and 2-methyl-4-bromo-1,2,3-triazole (III). Treatment of fraction 1 with sodium hydroxide destroyed the bromoacetonitrile and gave pure III. When treated with ammonia the bromoacetonitrile of fraction 1 was converted into  $\alpha$ -aminoacetonitrile (VII) which was isolated as the hydrochloride and identified by comparing its infrared spectrum with that of an authentic sample. Fraction 2 consisted mainly of 1-methyl-5-bromo-1,2,3-triazole (II) and fraction 3 of 1-methyl-4-bromo-1,2,3-triazole (IV).

The assignment of structure to the three isomeric methyl-bromo-triazoles is based on the following. III, in contrast to II and IV, does not form a hydrochloride when treated with hydrogen chloride in ether. A lower basic strength



of 2-substituted 1,2,3-triazoles as compared to the corresponding 1-substituted compounds seems to be a general rule. 2-Methyl-1,2,3-triazole does not form a hydrochloride whereas 1-methyl-1,2,3-triazole does<sup>2</sup>; the 1- and 2-methylbenzotriazoles behave in the same way<sup>3</sup> and so do 1- and 2-phenyl-1,2,3-triazole. This is probably analogous to the difference in basic strength between imidazoles and pyrazoles<sup>4</sup> since a 1-substituted 1,2,3-triazole is likely to be protonated in the 3-position giving an ion of structure XI which is analogous to a protonated imidazole, whereas a 2-substituted 1,2,3-triazole must take up the



proton in position 1- or 3- and give structure XII which is analogous to a protonated pyrazole.

IV has the same melting point as the 1-methyl-4-bromo-1,2,3-triazole described by Huttel and Welzel<sup>2</sup>. Besides, IV was prepared from 1-methyl-4-amino-1,2,3-triazole (VIII) by the Gattermann reaction. The synthesis of VIII is described later in this paper.

II on reaction with aniline gave 1-methyl-5-anilino-1,2,3-triazole (Xb), identical with the compound which Dimroth<sup>5</sup> obtained from 1-methyl-5-chloro-1,2,3-triazole.

The formation of  $\alpha$ -bromoacetonitrile (VI) has probably taken place through diazoacetonitrile (V) which could be formed from diazomethane and cyanogen

bromide by a reaction similar to the formation of diazoketones from acyl halides and diazomethane. The conversion of V into VI by hydrogen bromide can only take place if the reaction mixture at some stage has been deficient in diazomethane since V will react much slower with hydrogen bromide than diazomethane.

The 1-methyl-5-bromo-1,2,3-triazole (II) is the most reactive of the three isomeric methyl-bromo-triazoles. With 10 % ethanolic ammonia at 100° it gives a low yield of 1-methyl-5-amino-1,2,3-triazole (Xa); III and IV do not react, under the same conditions. As shown in the present paper, II reacts with aniline and Dimroth<sup>5</sup> has shown that the corresponding chloro compound also reacts with aniline in contrast to 1-methyl-4-chloro-1,2,3-triazole<sup>2</sup>.

1,2,3-Triazole was obtained by decarboxylation of 4-carboxy-1,2,3-triazole which was prepared in good yield by the reaction of propiolic acid with hydrazoic acid in boiling benzene. Since propiolic acid is easily obtained by oxidation of propargylic alcohol<sup>6</sup> this is probably the most convenient method for the preparation of 1,2,3-triazole. By the corresponding reaction of methyl azide with propiolic acid 1-methyl-4-carboxy-1,2,3-triazole (IX) was prepared. The isomeric 1-methyl-5-carboxy-1,2,3-triazole was not found in the reaction mixture. IX, *via* the chloride, gave the azide which on boiling in ethanol gave 1-methyl-4-carbethoxyamino-1,2,3-triazole. The latter on boiling with dilute sodium hydroxide yielded 1-methyl-4-amino-1,2,3-triazole (VIII).

## EXPERIMENTAL

Melting points are uncorrected.

*4-Carboxy-1,2,3-triazole.* A solution of hydrazoic acid (1.5 mole) and propiolic acid (35 g, 0.5 mole) in benzene (1 200 ml) was refluxed on the steam-bath for 15 h with an effective, water-cooled condenser. Some hydrazoic acid escaped through the condenser during the heating. The product began to separate after a few hours. The mixture was cooled and the product filtered off. Recrystallization from water gave 40 g (71 %) of 4-carboxy-1,2,3-triazole as colourless crystals with m. p. 222–224° (reported<sup>2,7</sup>: 214–215° and 220°).

*1-Methyl-4-carboxy-1,2,3-triazole.* Methyl azide was generated from sodium azide (39 g, 0.6 mole) and dimethyl sulfate (37.5 ml)<sup>8</sup> and passed over anhydrous calcium chloride into a mixture of dry toluene (100 ml) and propiolic acid (14 g, 0.2 mole). The mixture was kept overnight at room temperature and was then heated for 2 h in a pressure-bottle in boiling water. After cooling in ice the crystalline precipitate was filtered off and dried. The product (18.4 g) was recrystallized from water giving 14.6 g (57 %) of 1-methyl-4-carboxy-1,2,3-triazole as colourless crystals with m. p. 218–219° (reported<sup>2</sup>: 224°).

*1,2,3-Triazole.* 4-Carboxy-1,2,3-triazole (40 g) was heated in an oil bath. At a bath-temperature of 220° a vigorous evolution of carbon dioxide took place. The reaction was over in a few minutes and the product was distilled giving 22.8 g (93 %) of 1,2,3-triazole with b. p. 205–206° (760 mm).

*1- and 2-Methyl-1,2,3-triazole.* To an ice-cold solution of 1,2,3-triazole (10.0 g) in ether (100 ml) was added an excess of ethereal diazomethane. The mixture was kept overnight at 0°. Ether and excess diazomethane was distilled off and the residue was distilled through a column of the Podbielniak type giving 5.53 g (46 %) of 2-methyl-1,2,3-triazole with b. p. 102–103° (760 mm) and 5.02 g (42 %) of 1-methyl-1,2,3-triazole with b. p. 223–225° (760 mm).

*Reaction of cyanogen bromide with diazomethane.* To a solution of cyanogen bromide (31.8 g) in dry ether (100 ml) was added an ether solution of diazomethane in portions. At first there was a lively reaction and it was necessary to cool in ice now and then to prevent the solution from boiling. After *ca.* 50 % of the diazomethane had been added the reaction became slower. A total of 3 equiv. of diazomethane was added and the mix-

ture was left overnight at room temperature. Ether and excess diazomethane was distilled off and the residue was distilled through a Podbielniak type column at 16 mm pressure giving 3 fractions:

1. 28.9 g, yellow lachrymatory liquid, b. p. 45–48°.
2. 5.0 g, semi-solid mixture, b. p. 98–100°.
3. 3.9 g, yellow solid, b. p. 140°.

*2-Methyl-4-bromo-1,2,3-triazole.* Fraction 1 (28.9 g) was washed with four 25 ml portions of 2 N sodium hydroxide. The first portion of sodium hydroxide caused heat evolution and a decrease in the volume of the bromo compound. The compound was then dissolved in ether and washed with water and the ether solution was dried with magnesium sulfate and distilled. 2-Methyl-4-bromo-1,2,3-triazole (10.0 g, 21 % based on cyanogen bromide) was obtained as a slightly yellow solid; b. p. 161–162° (760 mm), m. p. 22°. (Found: C 22.35; H 2.46; N 26.14; Br 49.45. Calc. for  $C_3H_4N_3Br$ : C 22.24; H 2.49; N 25.94; Br 49.33.)

*1-Methyl-5-bromo-1,2,3-triazole.* Fraction 2 (5.0 g) was recrystallized from ether-light petroleum (b. p. 40–60°) giving 3.1 g (6.4 %) of colourless crystals with m. p. 37–40°. Two additional recrystallizations gave pure 1-methyl-5-bromo-1,2,3-triazole with m. p. 41–42°. (Found: C 21.95; H 2.55; N 26.23.)

*1-Methyl-4-bromo-1,2,3-triazole.* Fraction 3 (3.9 g) was recrystallized from benzene-light petroleum (b. p. 60–100°) to give 2.7 g (5.5 %) of colourless crystals with m. p. 95–97°. Two additional recrystallizations gave pure 1-methyl-4-bromo-1,2,3-triazole with m. p. 98–99° (reported<sup>2</sup>: 98.5–99°). (Found: C 22.10; H 2.68; N 25.90.)

*$\beta$ -Amino-acetonitrile hydrochloride.* Fraction 1 (5.0 g) was dissolved in liquid ammonia (30 ml) and the mixture was kept in an open flask at room temperature until the ammonia had evaporated. The residue was treated with ether, the ammonium bromide was filtered off, and the ether solution was evaporated to remove excess of ammonia. The residue was again dissolved in ether and dry HCl was passed through the solution giving a white precipitate (1.1 g) which was recrystallized from abs. ethanol. The yield of  $\beta$ -amino-acetonitrile hydrochloride was 0.80 g, m. p. 165–167° (decomp.) (reported<sup>3</sup>: 165°). (Found: C 25.75; H 5.32; N 30.53. Calc. for  $C_2H_5N_2Cl$ : C 25.95; H 5.45; N 30.30.) The infrared spectrum<sup>4</sup> was identical with that of an authentic sample prepared according to Curtius<sup>5</sup>.

The ether solution from which the amino-acetonitrile hydrochloride was precipitated gave, on evaporation, 2-methyl-4-bromo-1,2,3-triazole.

*1-Methyl-4-carbethoxyamino-1,2,3-triazole.* 1-Methyl-4-carboxy-1,2,3-triazole (10 g) and phosphorus pentachloride (16.5 g) were mixed and heated. The mixture melted and a vigorous reaction took place. After a few minutes the reaction was over and phosphorus oxychloride and excess phosphorus pentachloride was removed *in vacuo* at 100°. The crude chloride was dissolved in acetone (125 ml). The solution was cooled in ice and stirred and a solution of sodium azide (15 g) in water (75 ml) was added during a few minutes. The mixture was then stirred for 1 h. Water (500 ml) was added and the colourless precipitate was filtered off, washed with water and dried giving 11.2 g (93 %) of the azide of 1-methyl-4-carboxy-1,2,3-triazole. The azide decomposes at 152–154° with nitrogen evolution and forms a new, colourless compound which melts at 215–217°. This compound is probably the corresponding isocyanate. The azide was not purified further.

The azide (11.2 g) in abs. ethanol (100 ml) was refluxed for 36 h. The solution was then concentrated to 30 ml and cooled yielding 9.1 g (74 %) of colourless crystals with m. p. 114–118°. Two recrystallizations from ethanol gave the pure 1-methyl-4-carbethoxyamino-1,2,3-triazole, m. p. 123–124°. (Found: [C 42.60; H 5.98. Calc. for  $C_6H_{10}N_4O$ : C 42.35; H 5.92.)

*1-Methyl-4-amino-1,2,3-triazole.* The urethane (9.1 g, m. p. 114–118°) and sodium hydroxide (13.3 g, 6 equiv.) in 150 ml of water was boiled for 4 h. The solution was then acidified with conc. HCl and evaporated to dryness *in vacuo*. The residue was extracted with 3 × 50 ml of boiling ethanol, the ethanol solution was concentrated to 30 ml and cooled giving 6.35 g of crude material which was recrystallized from ethanol-ether. Yield 5.1 g (64 %), m. p. 181–184° (decomp.). Two additional recrystallizations from abs.

\* Thanks are due to Mrs. Susanne Refn,<sup>†</sup>M.Sc., for taking the IR-spectra and discussing the evidence thus obtained.

ethanol gave the pure hydrochloride of 1-methyl-4-amino-1,2,3-triazole as colourless crystals with m. p. 182–185°. (Found: C 26.50; H 5.10; N 41.35; Cl 26.45. Calc. for  $C_5H_7N_4Cl$ : C 26.80; H 5.24; N 41.65; Cl 26.35.)

The hydrochloride (1.0 g) was mixed with 5 ml of 40 % sodium hydroxide and extracted continuously with ether for 8 h. The ether was removed and the residue recrystallized from benzene-light petroleum. The yield of 1-methyl-4-amino-1,2,3-triazole was 0.65 g (90 %), colourless crystals, m. p. 88–90°. Recrystallized again, m. p. 88–89°. (Found: C 36.70; H 6.29; N 56.80. Calc. for  $C_5H_7N_4$ : C 36.72; H 6.16; N 57.11.)

*1-Methyl-5-amino-1,2,3-triazole.* 1-Methyl-5-bromo-1,2,3-triazole (1.0 g) was dissolved in 16 ml of 5 % ethanolic ammonia. The solution was heated to 100° in a sealed tube for 10 h. The mixture was then evaporated to dryness and the residue was extracted with ether. The ether solution was treated with dry HCl yielding 0.73 g of a colourless solid which after 2 crystallizations from abs. ethanol gave 0.18 g (22 %) of the hydrochloride of 1-methyl-5-amino-1,2,3-triazole as colourless crystals with m. p. 181–182°. (Found: C 26.90; H 5.27; N 41.90. Calc. for  $C_5H_7N_4Cl$ : C 26.80; H 5.24; N 41.65.)

The 1- and 2-methyl-4-bromo-1,2,3-triazoles did not react with ammonia under the same conditions as above.

*1-Methyl-5-anilino-1,2,3-triazole.* 1-Methyl-5-bromo-1,2,3-triazole (0.5 g) and 0.56 ml (2 equiv.) of aniline was heated on the steam bath for 6 h during which time the mixture solidified. Water was added and the crystalline product was filtered off, washed with water and dried. Yield 0.36 g. Two recrystallizations from benzene-light petroleum (b. p. 60–100°) gave 0.24 g (45 %) of colourless crystals with m. p. 169–171° (Dimroth \* reports 172°).

*1-Methyl-4-bromo-1,2,3-triazole from 1-methyl-4-amino-1,2,3-triazole.* 1-Methyl-4-amino-1,2,3-triazole (0.5 g) was dissolved in 5 ml of constant boiling HBr, cooled in ice, and diazotized with 0.35 g of sodium nitrite. A small amount of copper-bronze was added causing a vigorous nitrogen evolution. After a few minutes the reaction was over and the mixture was heated to the boiling point and cooled again. The colourless crystals which separated were extracted with chloroform (3 × 10 ml). The chloroform solution was concentrated to 10 ml and 50 ml of light petroleum (b. p. 40–60°) was added. On cooling 0.34 g (41 %) of 1-methyl-4-bromo-1,2,3-triazole crystallized out; m. p. 97–99°.

Microanalyses were made by Mr. P. Hansen of The Chemical Laboratory of The University of Copenhagen.

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