

## The Methylation of Some 5-Hydroxy-1,2,3-triazoles

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Methylation of 1-methyl-5-hydroxy-1,2,3-triazole with diazomethane gives a mixture of 1-methyl-5-methoxy-1,2,3-triazole and 1,2-dimethyl-1,2,3-triazolone-5. The two products have been separated and their structure proved. Methylation of 1-methyl-4-carbomethoxy-5-hydroxy-1,2,3-triazole gave similar products. 5-Hydroxy-1,2,3-triazole yielded four dimethylated products which were separated and identified. Methylation of 4-carbomethoxy-5-hydroxy-1,2,3-triazole gave only three products. Reaction of 1-methyl-4-carbomethoxy-5-methoxy-1,2,3-triazole with methyl iodide unexpectedly gave 1,2-dimethyl-4-carbomethoxy-1,2,3-triazolone-5.

Methylation of 1-substituted-5-hydroxy-1,2,3-triazoles may give a mixture of two methylated products. Thus Scarpati<sup>1</sup> found that methylation of 1,4-diphenyl-5-hydroxy-1,2,3-triazole with diazomethane gave a mixture of 1,4-diphenyl-2-methyl-1,2,3-triazolone-5 and 1,4-diphenyl-5-methoxy-1,2,3-triazole. Dimroth<sup>2</sup> treated the sodium salt of the same compound with methyl iodide and isolated the N-methylated compound only. Dimroth<sup>2</sup> also treated the silver salt of 1-phenyl-4-carbomethoxy-5-hydroxy-1,2,3-triazole with ethyl iodide and isolated a compound which he believed to be the O-ethylated product.

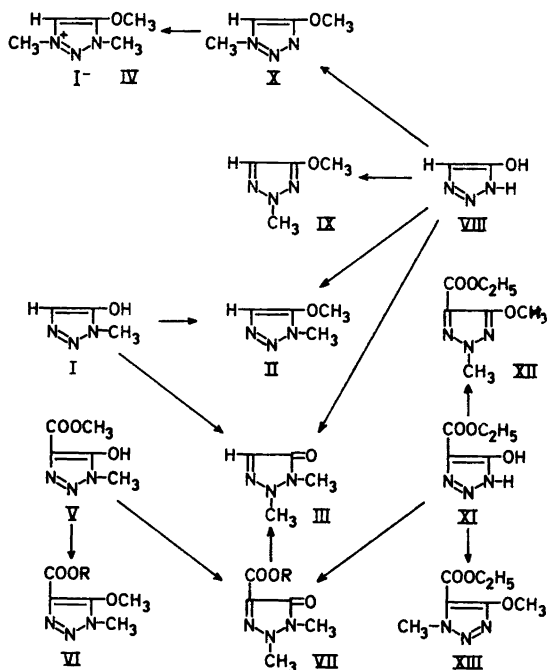
5-Hydroxy-1,2,3-triazoles without substituents on nitrogen may exist in several tautomeric forms\* and therefore may give several different products on methylation. However, no examples of the methylation or alkylation of such compounds have been recorded. In the present paper the methylation of some simple 5-hydroxy-1,2,3-triazoles is described.

Methylation of 1-methyl-5-hydroxy-1,2,3-triazole (I) with diazomethane gave a mixture of two products which could be separated by distillation. 1-Methyl-5-methoxy-1,2,3-triazole (II) was further purified by column chromatography. The 1,2-dimethyl-1,2,3-triazolone-5 (III) is very hygroscopic and it was therefore isolated as its hydrochloride. The structures of (II) and (III) are proved by their infrared spectra since (III) shows a carbonyl absorption which is not found in (II). Treatment of (II) with methyl iodide gave a methio-

\* The tautomeric structures which are used for hydroxy-1,2,3-triazoles in the present paper are arbitrary. The tautomerism of these compounds is being studied.

dide which must have the structure (IV).<sup>3</sup> Theoretically C-methylation of (I) might be possible, but this would give 1,4-dimethyl-5-hydroxy-1,2,3-triazole which would react with excess diazomethane to take up a second methyl group and this has not been observed.

Methylation of 1-methyl-4-carbomethoxy-5-hydroxy-1,2,3-triazole (V) gave nearly equal amounts of the O-methylated product (VI, R = CH<sub>3</sub>) and the N-methylated product (VII, R = CH<sub>3</sub>). The structure of (VI) was shown by its identity with the compound obtained by Dimroth<sup>4</sup> from the reaction of 1-methyl-4-carbomethoxy-5-chloro-1,2,3-triazole with sodium methoxide. The structure of (VII) was proved by its conversion into (III).



Methylation of 5-hydroxy-1,2,3-triazole (VIII) gave four products which were separated by a combination of distillation and chromatography. The N,N'-dimethylated triazolone (III) was obtained in 38 % yield as the highest boiling fraction and 1-methyl-5-methoxy-1,2,3-triazole (II) was isolated in very low yield. A third compound which was obtained in low yield was easily shown to be 1-methyl-4-methoxy-1,2,3-triazole (X) since it gave the same methiodide (IV) as (II). The fourth product of which 43 % was isolated would then be expected to be 2-methyl-4-methoxy-1,2,3-triazole (IX) since this is the only remaining product that can arise from methylation of (VIII). The structure of (IX) has not been proved but its properties are consistent with those of a 2-substituted triazole. Thus (IX) does not react with methyl iodide and it does not form a salt with hydrogen chloride in dry ether in agreement with the low basicity found in 2-substituted 1,2,3-triazoles.<sup>5</sup>

Methylation of 4-carbethoxy-5-hydroxy-1,2,3-triazole (XI) may give four dimethylated products, but only three of these were found. The N,N'-dimethylated derivative (VII, R = C<sub>2</sub>H<sub>5</sub>) was obtained in 27 % yield and its structure was proved by hydrolysis to (III). Two other products were obtained in 15 and 52 % yield, but structures could not be assigned to these compounds which are assumed to be 2-methyl-4-carbethoxy-5-methoxy-1,2,3-triazole (XII) and 1-methyl-4-methoxy-5-carbethoxy-1,2,3-triazole (XIII). It was expected that (XIII) would react with methyl iodide as opposed to (XII); however, none of the two compounds could be induced to react with methyl iodide. Attempts to convert them into (IX) or (X) by saponification and decarboxylation were also unsuccessful. 1-Methyl-4-carbethoxy-5-methoxy-1,2,3-triazole (VI, R = C<sub>2</sub>H<sub>5</sub>) was not obtained by the methylation of (XI), but it was prepared from the corresponding methylester (VI, R = CH<sub>3</sub>). Treatment of (VI, R = C<sub>2</sub>H<sub>5</sub>) with methyl iodide was expected to give a quaternary salt but, unexpectedly, 1,2-dimethyl-4-carbethoxy-1,2,3-triazolone-5 (VII, R = C<sub>2</sub>H<sub>5</sub>) was formed by this treatment. This reaction is being further studied.

Attempts to monomethylate 5-hydroxy-1,2,3-triazole or its carbethoxy derivative (XI) by treatment with one molar equivalent of diazomethane gave dimethylated products only. Methylation of sodium or silver salts of the hydroxytriazoles described above with methyl iodide gave N,N'-dimethylated products in high yields. No O-methylated products could be detected.

#### EXPERIMENTAL

The purity of all products was checked by thin layer chromatography on silica gel HF<sub>254</sub> (Merck). Spots were detected in U.V.-light and with iodine vapor. For column chromatography was used silica gel (Merck) (0.05–0.2 mm) to which was added 2 % of a fluorescent indicator (Riedl De Haën Leuchtpigment ZS Super). The silica gel was packed as a chloroform suspension in a tube of clear quartz. The zones could then be visualized by illumination with a 254 m $\mu$  U.V.-lamp.

*1-Methyl-4-carbomethoxy-5-hydroxy-1,2,3-triazole* was prepared according to Dimroth,<sup>4</sup> but instead of heating the reaction mixture in a sealed tube it was heated on a water bath in a flask equipped with an efficient condenser. The bath temperature was raised to 70° in the course of 5 h. Yield 25 %, m.p. 135–136°.

*1-Methyl-5-hydroxy-1,2,3-triazole*. The carbomethoxy compound (8.4 g) was boiled for 3 h in water (50 ml) containing 6.4 g of sodium hydroxide. The pH of the solution was then brought to ca. 3 with conc. hydrochloric acid and the mixture was boiled for a few minutes. The water was removed *in vacuo* and the residue was extracted several times with boiling ethanol. The ethanol was removed and the residue was recrystallized from ethanol yielding 4.1 g (77 %) of 1-methyl-5-hydroxy-1,2,3-triazole, m.p. 166–167° (recorded<sup>7</sup> 168–170°).

*5-Hydroxy-1,2,3-triazole* was prepared according to Pedersen.<sup>8</sup> To ensure complete saponification the alkaline solution should be boiled for 3 h instead of 1 h.

*4-Carbethoxy-5-hydroxy-1,2,3-triazole*. The corresponding potassium salt<sup>6</sup> was dissolved in water and acidified with conc. hydrochloric acid. The water was removed *in vacuo* and the residue was extracted with boiling ethanol. Evaporation of the ethanol gave the product which was recrystallized from water, yield 83 %, m.p. 128–130° (recorded<sup>7</sup> m.p. 130°).

#### Methylations

Methylations were carried out by adding excess of distilled ethereal diazomethane to a cooled solution of the hydroxytriazole in methanol. The mixture was then kept over night at room temperature and the solvent was evaporated with a stream of air leaving a crude product which was worked up as described in the following.

*1-Methyl-5-hydroxy-1,2,3-triazole.* This compound (9.63 g) was methylated as described above and the product was distilled in a 45 cm Podbielniak column<sup>8</sup> giving 2.46 g (22 %) of 1-methyl-5-methoxy-1,2,3-triazole as a colourless oil, b.p. 122–137° (19 mm) and 7.85 g (71 %) of 1,2-dimethyl-1,2,3-triazolone-5 as yellowish crystals, b.p. 148° (0.9 mm).

Thin layer chromatography of the 1-methyl-5-methoxy-1,2,3-triazole showed that it contained small amounts of the higher boiling material. A sample was further purified by column chromatography using ethyl acetate as eluant. The product was finally recrystallized from ether-pentane, m.p. 32°. (Found: C 42.75; H 6.26. Calc. for  $C_4H_7N_3O$ : C 42.46; H 6.24). An infrared spectrum showed no carbonyl absorption.

The 1,2-dimethyl-1,2,3-triazolone-5 melted at 90–97°. The compound is very hygroscopic and a satisfactory analysis could therefore not be obtained. An infrared spectrum showed a strong carbonyl band at 1645  $cm^{-1}$ . A hydrochloride was prepared by precipitation with ether from a solution of the triazolone in ethanolic hydrogen chloride. The hydrochloride was recrystallized from ethanol-ether, m.p. 135°. (Found: C 31.85; H 5.55; N 28.22. Calc. for  $C_4H_7N_3O \cdot HCl$ : C 32.05; H 5.39; N 28.10. Equiv. wt. found by titration with 0.1 N sodium hydroxide: 152. Calc.: 150). The hydrochloride was hygroscopic and took up one mole of water on standing in air. After recrystallization from acetone the monohydrate melted at 50°. (Found: C 28.11; H 6.08; N 24.84. Calc. for  $C_4H_9N_3O_2 \cdot HCl$ : C 28.66; H 6.01; N 25.07).

*1-Methyl-4-carbomethoxy-5-hydroxy-1,2,3-triazole.* Methylation of 247 mg of this compound gave a crude product which showed two spots on thin layer chromatography. The two components were separated by column chromatography using ethyl acetate-methanol (1:1) as eluant.

The fastest moving fraction on evaporation of the solvent gave 145 mg (54 %) of 1-methyl-4-carbomethoxy-5-methoxy-1,2,3-triazole as colourless crystals, m.p. 81–83°. Recrystallization from pentane did not change the melting point. The product was shown by infrared spectrum and mixed melting point to be identical with an authentic sample prepared according to Dimroth.<sup>4</sup>

The slower moving fraction gave 121 mg (45 %) of 1,2-dimethyl-4-carbomethoxy-1,2,3-triazolone-5 as colourless crystals, m.p. 129–130°. Recrystallization from ethyl acetate raised the melting point to 132°. The compound was hygroscopic and a correct analysis could not be obtained. A sample of this compound (132 mg) was boiled for 2.5 h with 2 ml of 50 % aqueous potassium hydroxide. The solution was acidified with conc. hydrochloric acid and boiled for a few minutes. The water was removed *in vacuo* and the residue was extracted with hot ethanol. Removal of the ethanol gave 39 mg of colourless crystals, m.p. 46–48°. Infrared spectra and mixed melting point showed that the product was the monohydrate of 1,2-dimethyl-1,2,3-triazolone-5, hydrochloride.

*5-Hydroxy-1,2,3-triazole.* The crude product obtained by methylation of 9.82 g of 5-hydroxy-1,2,3-triazole was distilled in a Podbielniak column. Three fractions were collected.

The first fraction was almost pure 2-methyl-4-methoxy-1,2,3-triazole, b.p. 28° (44 mm), yield 5.64 g (43 %). The product was redistilled at ordinary pressure, b.p. 152°. (Found: C 42.62; H 6.43; N 38.27. Calc. for  $C_4H_7N_3O$ : C 42.46; H 6.24; N 37.15). The product did not react with boiling methyl iodide.

The second fraction (2.48 g, b.p. 88–106° (0.9 mm)) was a mixture of two compounds. These were separated on a column using ethyl acetate as eluant thereby giving 2 % of 1-methyl-5-methoxy-1,2,3-triazole, identical with the material described above, and 5 % of 1-methyl-4-methoxy-1,2,3-triazole. The latter was recrystallized from ether-pentane, m.p. 27–28°. It was converted into the methiodide by treatment with methyl iodide (see later). NMR-spectra of 1-methyl-5-methoxy- and 1-methyl-4-methoxy-1,2,3-triazole were taken. They both showed the presence of two methyl groups and a single proton; the chemical shift of the single proton differed for the two compounds.

The third fraction obtained from the distillation consisted of 4.94 g (38 %) of 1,2-dimethyl-1,2,3-triazolone-5 with m.p. 90–97°. The product was chromatographically pure and its infrared spectrum was identical with that of the material obtained above.

*4-Carbomethoxy-5-hydroxy-1,2,3-triazole.* Methylation of 289 mg of this compound gave a crude product which was separated into three compounds by two successive chromatographic operations using ethyl acetate-methanol (1:1) and ether as eluants.

Chromatography with ethyl acetate-methanol separated the mixture into two fractions. The slow running fraction consisted of 94 mg (27 %) of 1,2-dimethyl-4-carbomethoxy-

1,2,3-triazolone-5, m.p. 118°. Recrystallization from pentane gave the pure compound, m.p. 122°. (Found: C 45.37; H 6.04; N 23.03. Calc. for  $C_7H_{11}N_3O_3$ : C 45.39; H 5.99; N 22.69). Hydrolysis of this product as described above for the corresponding methyl ester gave 81 % of the monohydrate of 1,2-dimethyl-1,2,3-triazolone-5, hydrochloride, m.p. 46–48°. An infrared spectrum proved its identity with the material prepared above.

The fast running fraction obtained by chromatography with ethyl acetate-methanol was rechromatographed using ether as eluant and thereby separated into two fractions.

The fraction which came off the column first gave 177 mg (52 %) of a compound with m.p. 59°. Recrystallization from pentane gave a pure product, m.p. 64°. (Found: C 45.80; H 6.04; N 22.46. Calc. for  $C_7H_{11}N_3O_3$ : C 45.39; H 5.99; N 22.69).

The second fraction to come off the column gave 51 mg (15 %) of an isomeric compound, m.p. 57–58°. Recrystallization from ether-pentane raised the melting point to 59°. (Found: C 45.60; H 5.62; N 22.76). The two latter compounds did not react with boiling methyl iodide.

*1,3-Dimethyl-4-methoxy-1,2,3-triazolium iodide.* 1-Methyl-5-methoxy-1,2,3-triazole (65 mg) was dissolved in 2 ml of methyl iodide and the solution was kept at room temperature for 48 h. The precipitate (99 mg, m.p. 98°) was recrystallized from methanol-ether giving 78 mg (53 %) of pure 1,3-dimethyl-4-methoxy-1,2,3-triazolium iodide, m.p. 110°. (Found: C 23.79; H 4.04; N 16.50; I 49.75. Calc. for  $C_8H_{10}N_3OI$ : C 23.55; H 3.95; N 16.47; I 50.09).

When the methyl iodide solution was boiled an unidentified compound with the formula  $C_8H_{15}N_6O_3I$  was formed, m.p. 128–130°. (Found: C 27.17; H 4.26. Calc.: C 27.13; H 4.27).

1-Methyl-4-methoxy-1,2,3-triazole (40 mg) was kept in methyl iodide for 6 days. The product was recrystallized from methanol-ether, yield 18 mg (20 %), m.p. 108°. Mixed melting point and infrared spectra proved its identity with the 1,3-dimethyl-4-methoxy-1,2,3-triazolium iodide described above.

*1-Methyl-4-carbomethoxy-5-methoxy-1,2,3-triazole.* 1-Methyl-4-carbomethoxy-5-methoxy-1,2,3-triazole<sup>4</sup> (184 mg) and 1 ml of a solution of 0.20 g of sodium in 5 ml of ethanol was boiled for a few minutes. The ethanol was removed and the residue was extracted with methylene chloride. Evaporation of the solvent gave the product as a yellow oil, yield 140 mg (71 %). Column chromatography with ethanol as eluant gave the pure product as an oil which crystallized on cooling, m.p. ca. 0°. (Found: C 45.40; H 6.30; N 22.50. Calc. for  $C_8H_{11}N_3O_3$ : C 45.39; H 5.99; N 22.69).

1-Methyl-4-carbomethoxy-5-methoxy-1,2,3-triazole (102 mg) was kept in 2 ml of methyl iodide for 48 h at room temperature. The methyl iodide was evaporated and the residue was recrystallized from ethyl acetate-pentane giving, besides unchanged starting material, 11 % of 1,2-dimethyl-4-carbomethoxy-1,2,3-triazolone-5, m.p. 118°. A mixed melting point and an infrared spectrum proved its identity with the material described above.

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*Note added in proof:* After the completion of this work evidence has been found that the structures assigned to the N,N'-dimethylated products in the present paper are erroneous. It will be shown in a forthcoming paper that these products probably are 1,3-dimethyl-1,2,3-triazolones-4.

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