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Studies on Methylated 1,2,3-Triazoles. II

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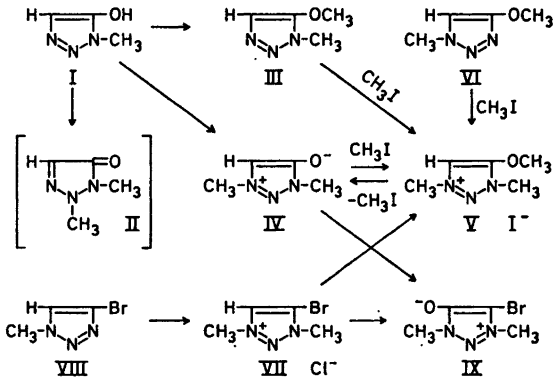
Reaction of 1-methyl-5-methoxy-1,2,3-triazole with methyl iodide gave 1,3-dimethyl-4-methoxy-1,2,3-triazolium iodide; this compound could also be prepared by treatment of 1,3-dimethyl-1,2,3-triazolone-4 with methyl iodide or from the reaction of 1,3-dimethyl-4-bromo-1,2,3-triazolium iodide with sodium methoxide. When 1,3-dimethyl-4-methoxy-1,2,3-triazolium iodide was heated or kept at room temperature in chloroform solution it lost methyl iodide and gave 1,3-dimethyl-1,2,3-triazolone-4. Treatment of 1,3-dimethyl-4-bromo-1,2,3-triazolium chloride with sodium hydroxide gave a compound which is believed to be 1,3-dimethyl-5-bromo-1,2,3-triazolone-4. The latter compound was also made by bromination of 1,3-dimethyl-1,2,3-triazolone-4.

In a previous paper[1] (number I of this series) the methylation of some 5-hydroxy-1,2,3-triazoles was described and it was found that methylation of 1-methyl-5-hydroxy-1,2,3-triazole (I) with diazomethane gave a mixture of 1-methyl-5-methoxy-1,2,3-triazole (III) and a *N*-methylated compound. The latter compound was assumed to be 1,2-dimethyl-1,2,3-triazolone-5 (II) on the basis that its infrared spectrum shows the presence of a carbonyl group and because it corresponds to one of the tautomeric forms in which 1-methyl-5-hydroxy-1,2,3-triazole may be written.



It will be shown in the present paper that the structure (II), which was proposed for the *N*-methylated product, is erroneous and that this compound is actually 1,3-dimethyl-1,2,3-triazolone-4 (IV), that is, a compound with a mesoionic or betaine structure. That the structure (II), assigned to the dimethylated triazolone, is erroneous was first indicated by the fact that when this compound was treated with boiling methyl iodide it gave an almost quantitative yield of 1,3-dimethyl-4-methoxy-1,2,3-triazolium iodide (V). This seemed a very unlikely reaction of (II) and it indicated that one of the structures, (II) or (V), was wrong.

The triazolium iodide (V) had been prepared previously by the reaction of 1-methyl-5-methoxy-1,2,3-triazole (III) or 1-methyl-4-methoxy-1,2,3-triazole (VI) with methyl iodide.[1] The structure of (III) must be correct since it is the only *O*-methylated product that can arise from the methylation of (I) and since 1-substituted-1,2,3-triazoles are known to give 1,3-disubstituted-triazolium salts by alkylation.[2,3] Hence (V) would be expected to be a 1,3-dimethyl derivative.

Furthermore, (V) was prepared from 1-methyl-4-bromo-1,2,3-triazole (VIII), a compound the structure of which has been proved.[4,5] Reaction of (VIII) with methyl iodide gave a triazolium iodide which was rather unstable; but by treatment with silver chloride it yielded the stable 1,3-dimethyl-4-bromo-1,2,3-triazolium chloride (VII). Treatment of (VII) with sodium methoxide gave a solution which was shown by NMR spectroscopy to contain the 1,3-dimethyl-4-methoxy-1,2,3-triazolium salt (V). However, because of the instability of (V) (see below) only traces of this compound could be isolated and the main product which was isolated from the treatment of (VII) with sodium methoxide was 1,3-dimethyl-1,2,3-triazolone-4 (IV).

With the structure of 1,3-dimethyl-4-methoxy-1,2,3-triazolium iodide (V) proved, the structure (II), which was proposed for the dimethyl-triazolone obtained by methylation of (I), becomes very unlikely and therefore this compound is now proposed to be 1,3-dimethyl-1,2,3-triazolone-4 (IV). Although no direct proof of the structure (IV) has been found, this structure is in good agreement with the formation of (V) by treatment with methyl iodide. Furthermore, it was found that a solution of (V) loses methyl iodide at room temperature with the formation of (IV). The conversion of (V) into (II) under these conditions would be highly unlikely.

The latter reaction was followed by NMR spectroscopy. 1,3-Dimethyl-4-methoxy-1,2,3-triazolium iodide was dissolved in deuteriochloroform and the solution was kept at room temperature while NMR spectra were taken at intervals. The freshly prepared solution gave the spectrum of (V) (see Table 1). After 0.5 h the signals corresponding to (IV) appeared and at the same time the signal of methyl iodide at δ 2.26 appeared. These signals grew at the expense of the signals of (V) and after 4 days the latter signals could not be seen. Evaporation of the solvent then gave a quantitative yield of (IV). Integration of the NMR spectra gave a quantitative picture of the reaction as shown in Fig. 1 where curve a represents the disappearance of (V) and curve b the formation of (IV). The first part of both curves represent a first order reaction with the velocity constant calculated to 1.33×10^{-1} h^{-1}.

Table 1. NMR spectra in deuteriochloroform.

Compound	Chemical shift, δ-values		
	C—H	CH_3	CH_2CH_3
1-Methyl-4-methoxy-1,2,3-triazole	7.06	4.02, 3.95	
1-Methyl-5-methoxy-1,2,3-triazole	7.07	3.98, 3.82	
1,3-Dimethyl-1,2,3-triazolone-4	6.74	3.97, 3.70	
1,3-Dimethyl-4-methoxy-1,2,3-triazolium iodide	9.29	4.46, 4.36, 4.13	
1,3-Dimethyl-4-ethoxy-1,2,3-triazolium chloride	10.1	4.50, 4.10	4.68, 1.57
1,3-Dimethyl-4-bromo-1,2,3-triazolium chloride [a]	8.72	4.30, 4.35	
1-Methyl-4-bromo-1,2,3-triazole	7.63	4.12	

[a] In deuterium oxide solution.

When the chloroform solution of (V) was heated to 70° the decomposition to (IV) was completed in 30 min.

When 1,3-dimethyl-1,2,3-triazolone-4 (IV) was boiled with ethyl iodide a high yield of 1,3-dimethyl-4-ethoxy-1,2,3-triazolium iodide was formed; the compound was isolated as the corresponding chloride after treatment with silver chloride. This ethoxy analogue of (V) is much more stable than (V). Thus a chloroform solution of the ethoxy compound was unchanged after standing for 4 days at room temperature and when the solution was heated to 80° for 1 h only 26 % of the 1,3-dimethyl-4-ethoxy-1,2,3-triazolium chloride

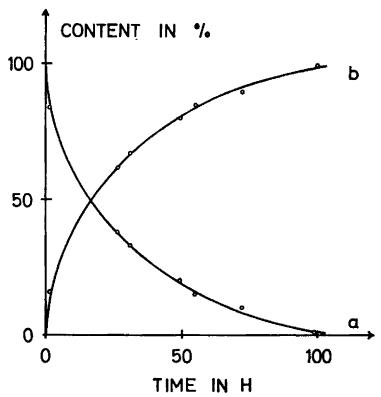


Fig. 1. The conversion of 1,3-dimethyl-4-methoxy-1,2,3-triazolium iodide (curve a) to 1,3-dimethyl-1,2,3-triazolone-4(curve b).

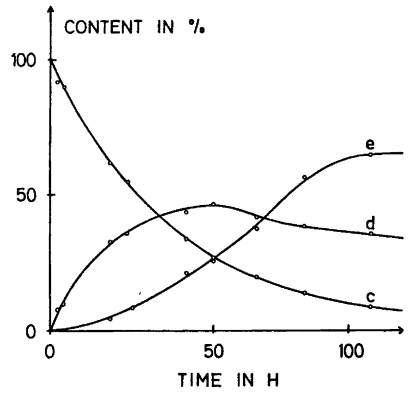


Fig. 2. Reaction of 1-methyl-5-methoxy-1,2,3-triazole with methyl iodide. Curve (c) shows content of 1-methyl-5-methoxy-1,2,3-triazole; curve (d) that of 1,3-dimethyl-4-methoxy-1,2,3-triazolium iodide and curve (e) 1,3-dimethyl-1,2,3-triazolone-4.

was converted to 1,3-dimethyl-1,2,3-triazolone-4 as seen by the NMR spectrum. Treatment of 1,3-dimethyl-4-bromo-1,2,3-triazolium chloride (VII) with sodium ethoxide gave a 71 % yield of 1,3-dimethyl-4-ethoxy-1,2,3-triazolium chloride, identical with the material prepared from (IV).

It was described earlier [1] that 1-methyl-5-methoxy-1,2,3-triazole (III) or 1-methyl-4-methoxy-1,2,3-triazole (VI) both gave (V) on treatment with methyl iodide. However, because of the tendency of (V) to lose methyl iodide its isolation should be carried out under mild conditions. As a matter of fact, 1-methyl-5-methoxy-1,2,3-triazole can be converted to 1,3-dimethyl-1,2,3-triazolone-4 in almost quantitative yield by treatment with methyl iodide. This is illustrated in Fig. 2 which shows the course of the reaction of (III) with methyl iodide in deuteriochloroform at room temperature. The reaction was followed by NMR spectroscopy; integration gave the relative proportions of the compounds present in the reaction mixture at various intervals. A NMR spectrum of the freshly prepared solution gave the signals of (III) only (see Table 1). After 2.5 h four new signals corresponding to 1,3-dimethyl-4-methoxy-1,2,3-triazolium iodide (V) appeared in the spectrum and these signals reached a maximum corresponding to a 47 % content of (V) in the course of 50 h. When the reaction was interrupted at this stage a 53 % yield of crude (V) could be isolated. If the reaction mixture was kept further the signals from 1,3-dimethyl-1,2,3-triazolone-4 (IV) appeared in the spectrum and after 6 weeks at room temperature the signals of (III) and (V) could not be seen. At this stage a 83 % yield of (IV) could be isolated.

The rearrangement of the methoxy compound (III) to the triazolone (IV) is analogous to the rearrangement of methoxypyrimidines to *N*-methylpyrimidones in the presence of methyl iodide as described by Hilbert and Johnson.[6,7] These authors also observed that a quaternary salt was an intermediate in the rearrangement. The *O*-alkylation of 1,3-dimethyl-1,2,3-triazolone-4 (IV) to give a quaternary salt is a less common type of reaction [8] which may be favoured in the present case by the betaine structure of (IV) since a negative charge on the oxygen atom would be expected to facilitate *O*-alkylation.

The conversion of (III) to (IV) with methyl iodide explains why methylation of 1-methyl-5-hydroxy-1,2,3-triazole (I) with methyl iodide gave (IV) as the only product.[1]

Since 1,3-dimethyl-4-bromo-1,2,3-triazolium chloride (VII) could be converted to the methoxy compound (V) by treatment with sodium methoxide it would be expected that reaction of (VII) with sodium hydroxide would give 1,3-dimethyl-1,2,3-triazolone-4 (IV). This was, however, not the case. When (VII) was heated with aqueous sodium hydroxide a product was formed which contained bromine and which is believed to be 1,3-dimethyl-5-bromo-1,2,3-triazolone-4 (IX) on the basis of its analysis and spectra. The infrared spectrum of (IX) shows a carbonyl group at 1640 cm^{-1}, consistent with a structure analogous to (IV) which has a carbonyl band at 1645 cm^{-1}. The NMR spectrum of (IX) showed two signals at δ 3.97 and 3.77 corresponding to the two methyl groups. The mechanism of the formation of (IX) is not known. (IX) was also prepared by bromination of 1,3-dimethyl-1,2,3-triazolone-4, thereby confirming its structure.

EXPERIMENTAL

Thin layer and column chromatography was done as described earlier.[1] NMR spectra were taken on a Varian A-60 instrument. Position of signals are given in ppm (δ values) relative to tetramethyl silane.

1,3-Dimethyl-4-bromo-1,2,3-triazolium chloride (VII). A mixture of 1-methyl-4-bromo-1,2,3-triazole [4,5] (417 mg) and methyl iodide (2.5 ml) was heated in a sealed tube to 100° for 6 h. Evaporation of the methyl iodide left 1,3-dimethyl-4-bromo-1,2,3-triazolium iodide as dark coloured crystals which were rather unstable. This product was dissolved in ethanol and stirred for 2 h with an excess of freshly prepared silver chloride. The silver salts were then filtered off and the solvent was removed *in vacuo*. The residue was recrystallized from ethanol-ether to give 440 mg (81 %) of 1,3-dimethyl-4-bromo-1,2,3-triazolium chloride as colourless crystals, m.p. 193°. (Found: C 22.25; H 3.49; N 19.62. Calc. for $C_4H_7N_3BrCl$: C 22.60; H 3.32; N 19.80).

Reaction with sodium methoxide. To 98 mg of 1,3-dimethyl-4-bromo-1,2,3-triazolium iodide was added a solution of sodium (8.0 mg) in methanol (3.5 ml) and the mixture was heated to 75° for 2 h. Sodium iodide (70 mg) was added and the mixture was stirred for 15 min and filtered. The solvent was removed *in vacuo* and the residue was extracted with chloroform. A NMR spectrum showed the presence of 1,3-dimethyl-4-methoxy-1,2,3-triazolium iodide and 1,3-dimethyl-1,2,3-triazolone-4.

The chloroform was removed *in vacuo* at room temperature and the residue was recrystallized several times from methanol-ether yielding 3 mg (3 %) of 1,3-dimethyl-4-methoxy-1,2,3-triazolium iodide. An infrared spectrum proved its identity with the product described earlier.[1]

The mother liquors were combined and the solvent evaporated. The residue consisted of 35 mg (96 %) of 1,3-dimethyl-1,2,3-triazolone-4, identified by infrared and NMR spectra.

Reaction with sodium ethoxide. To 1,3-dimethyl-4-bromo-1,2,3-triazolium chloride (70 mg) was added 0.17 ml of a solution of 220 mg of sodium in 5 ml of ethanol and the mixture was heated to 70° for 3 h. (No reaction took place at room temperature). The mixture was then neutralized with carbon dioxide, the solvent was removed *in vacuo* at room temperature and the residue was extracted with chloroform. Evaporation of the chloroform left 89 mg of an oil which was dissolved in ethanol and stirred with freshly prepared silver chloride for 1 h. Filtration and evaporation of the solvent gave 63 mg (71 %) of 1,3-dimethyl-4-ethoxy-1,2,3-triazolium chloride as a yellow oil which was very hygroscopic. Infrared and NMR spectra showed that the product was identical with the material described below.

1,3-Dimethyl-4-methoxy-1,2,3-triazolium iodide (V). 1,3-Dimethyl-1,2,3-triazolone-4 (217 mg) was boiled under reflux with methyl iodide (2 ml) for 3 h. Removal of the methyl iodide left 455 mg (94 %) of yellow crystals, m.p. 99—100°. Three recrystallizations from methanol-ether gave the pure product, m.p. 111°. Infrared and NMR spectra proved its identity with the product described earlier.[1]

1,3-Dimethyl-4-ethoxy-1,2,3-triazolium chloride. 1,3-Dimethyl-1,2,3-triazolone-4 (30 mg) was heated to 75° with ethyl iodide (2 ml) for 3 h. Removal of the ethyl iodide left 74 mg of a product which was dissolved in ethanol and stirred for 1 h with an excess of freshly prepared silver chloride. Filtration and removal of the solvent *in vacuo* at room temperature gave 49 mg (99 %) of a yellowish oil which was purified by reprecipitation from ethanol-ether. The compound did not crystallize. It was very hygroscopic and therefore a correct analysis could not be obtained. (Found: C 39.63; H 6.76; N 23.65. Calc. for $C_6H_{12}N_3OCl$: C 40.57; H 6.76; N 23.65). A sulphate was prepared, but this was equally hygroscopic. Attempts to prepare a picrate were unsuccessful.

Decomposition of 1,3-dimethyl-4-methoxy-1,2,3-triazolium iodide (V). 1,3-Dimethyl-4-methoxy-1,2,3-triazolium iodide (19 mg) was dissolved in deuteriochloroform (0.5 ml) in a NMR sample tube and the solution was allowed to stand at room temperature. NMR spectra were taken at intervals. After four days the signal of the starting material could not be seen; the solution gave a spectrum of 1,3-dimethyl-1,2,3-triazolone-4 and methyl iodide. Removal of the solvent gave 9 mg (100 %) of 1,3-dimethyl-1,2,3-triazolone-4 (IV), m.p. 78—85° (because of the hygroscopic nature of this compound a sharp melting point cannot be obtained [1]). Its infrared spectrum was identical with that of an authentic sample.

Decomposition of 1,3-dimethyl-4-ethoxy-1,2,3-triazolium chloride. A chloroform solution of this triazolium salt was unchanged after standing for 4 days at room temperature. The solution was then heated to 80° for 1 h. A NMR spectrum showed that 26 % of the chloride was converted to 1,3-dimethyl-1,2,3-triazolone-4. The signals of ethyl chloride at δ 3.22 and 1.88 could also be seen in the spectrum.

Reaction of 1-methyl-5-methoxy-1,2,3-triazole (III) with methyl iodide. 1-Methyl-5-methoxy-1,2,3-triazole [1] (50 mg) was dissolved in deuteriochloroform (0.5 ml) and methyl iodide (0.10 ml) was added. The solution was kept at room temperature in a NMR sample tube and spectra were taken at intervals. After standing for 6 weeks only the signals of 1,3-dimethyl-1,2,3-triazolone-4 could be seen in the spectrum. Evaporation of the solvent then left 44 mg (83 %) of this compound. m.p. 78—85°. Its infrared spectrum was identical with that of an authentic sample.

In another experiment the solvents were removed after 48 h when the signals of 1,3-dimethyl-4-methoxy-1,2,3-triazolium iodide had reached a maximum and this compound could then be isolated in 53 % yield using the procedure described earlier.[1]

Reaction of 1,3-dimethyl-4-bromo-1,2,3-triazolium chloride (VII) with sodium hydroxide. A solution of the triazolium salt (92 mg) in 4 ml of 1 N sodium hydroxide was heated to 100° for 16 h in a sealed tube. The solution was then neutralized with 1 N hydrochloric acid, the water was evaporated *in vacuo* and the residue was extracted with acetone. Removal of the acetone left an oil which crystallized. The product was purified by chromatography on a column of silica gel (20 g) using methanol as the eluant. After elution of an impurity the main component was eluated. Removal of the solvent gave 22 mg (27 %) of 1,3-dimethyl-5-bromo-1,2,3-triazolone-4 as colourless crystals, m.p. 141°. (Found: C 25.16; H 3.06; N 20.27; O 8.30; Br 41.34. Calc. for $C_4H_6N_3OBr$: C 25.02; H 3.15; N 21.89; O 8.33; Br 41.62).

Bromination of 1,3-dimethyl-1,2,3-triazolone-4 (IV). To an ice-cold solution of 1,3-dimethyl-1,2,3-triazolone-4 (112 mg) in chloroform (1 ml) was added an ice-cold solution of bromine (0.05 ml) in chloroform (5 ml). The precipitate which rapidly formed was filtered off after 10 min. It was dissolved in water and stirred for 1 h with an excess of Amberlite IR-4B. The ion exchange resin was then filtered off, the water was removed *in vacuo* and the residue was extracted with chloroform. Evaporation of the chloroform gave 84 mg of 1,3-dimethyl-5-bromo-1,2,3-triazolone-4, m.p. 141°.

The material in the mother liquor from the bromination was treated with ion exchange resin as described above. Evaporation of the chloroform extract gave 68 mg of product which was separated into two fractions by chromatography on a column of silica gel (30 g) using methanol as eluant.

The first fraction from the column contained 48 mg of 1,3-dimethyl-5-bromo-1,2,3-triazolone-4, m.p. 141°, bringing the total yield of this compound to 132 mg (70 %). Mixed melting point, infrared and NMR spectra proved its identity with the material described above.

The second fraction to come off the column contained 21 mg of unchanged starting material.

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