

## Studies on Methylated 1,2,3-Triazoles

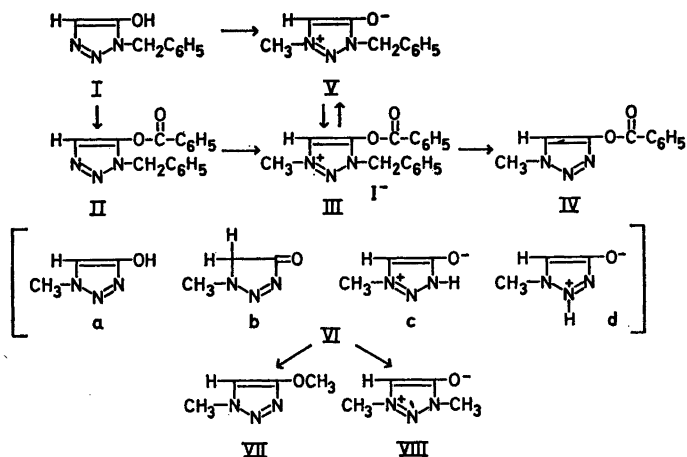
### IV. Preparation of 1-Methyl-4-hydroxy-1,2,3-triazole

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Benzoylation of 1-benzyl-5-hydroxy-1,2,3-triazole (I) gave the *O*-benzoyl derivative (II) which, with methyl iodide, yielded 1-methyl-3-benzyl-4-benzoyloxy-1,2,3-triazolium iodide (III). When (III) was heated with benzoyl chloride it gave 1-methyl-4-benzoyloxy-1,2,3-triazole (IV) which was hydrolysed to 1-methyl-4-hydroxy-1,2,3-triazole (VI). Alternatively, (I) was methylated to give 1-methyl-3-benzyl-1,2,3-triazolio-4-oxide (V) which was converted directly to (IV) by treatment with benzoyl chloride. Methylation of (VI) with diazomethane gave a mixture of *O*-methylated and *N*-methylated products (VII) and (VIII). The tautomeric structure of (VI) has been investigated.

Whereas 1-substituted-5-hydroxy-1,2,3-triazoles are readily available only one 1-substituted-4-hydroxy-1,2,3-triazole has been described, namely 1-phenyl-4-hydroxy-1,2,3-triazole, which Daeniker and Druey prepared by hydrolysis of *N*-*exo*-acetyl-3-phenyl-sydnone imine.<sup>1</sup> In the present paper the preparation of 1-methyl-4-hydroxy-1,2,3-triazole (VI) is described.



Benzoylation of 1-benzyl-5-hydroxy-1,2,3-triazole (I) gave 1-benzyl-5-benzoyloxy-1,2,3-triazole (II). This reaction might also give an *N*-benzoyl-1,2,3-triazole; the infrared spectrum of (II), however, showed ester absorption at 1755, 1240, and 1050  $\text{cm}^{-1}$ , and no absorption in the 1600–1700  $\text{cm}^{-1}$  region which is characteristic of triazolones or triazolio oxides.<sup>2</sup> Treatment of (II) with methyl iodide gave 1-methyl-3-benzyl-4-benzoyloxy-1,2,3-triazolium iodide (III) the structure of which was confirmed by its hydrolysis to 1-methyl-3-benzyl-1,2,3-triazolio-4-oxide (V), a compound which has been described previously.<sup>2</sup> When the triazolium salt (III) was heated with benzoyl chloride it lost benzyl iodide and gave 1-methyl-4-benzoyloxy-1,2,3-triazole (IV) in 68 % yield. Besides, a small amount of 1-methyl-3-benzyl-1,2,3-triazolio-4-oxide (V) was formed by loss of benzoyl iodide. Formation of (V) from (III) is analogous to the conversion of 1,3-disubstituted-4-alkoxy-1,2,3-triazolium salts to 1,3-disubstituted-triazolio-4-oxides with loss of alkyl iodide.<sup>2</sup>

The conversion of (III) into (IV) by treatment with benzoyl chloride suggested that 1-methyl-3-benzyl-1,2,3-triazolio-4-oxide (V) might also be converted into (IV) by the same treatment. This was indeed found to be the case, thereby providing a convenient method for the preparation of (IV) directly from 1-benzyl-5-hydroxy-1,2,3-triazole (I). Thus, methylation of (I) with methyl iodide gave a quantitative yield of (V) which, when boiled with benzoyl chloride, afforded 1-methyl-4-benzoyloxy-1,2,3-triazole (IV) in 70 % yield.

Hydrolysis of (IV) with sodium hydroxide gave a good yield of 1-methyl-4-hydroxy-1,2,3-triazole (VI) which could be reconverted to (IV) by benzoylation. The infrared spectrum of (IV) shows ester group absorptions at 1735, 1252, and 1090  $\text{cm}^{-1}$  which, in connection with lack of absorption between 1600 and 1700  $\text{cm}^{-1}$ , indicate that the compound is *O*-benzoylated.

Methylation of 1-methyl-4-hydroxy-1,2,3-triazole (VI) with diazomethane gave 1-methyl-4-methoxy-1,2,3-triazole (VII) and 1,3-dimethyl-1,2,3-triazolio-

Table 1. NMR spectra in deuteriochloroform.

Compound	$\delta$ -Values			
	OH/NH	CH	CH <sub>2</sub>	CH <sub>3</sub>
1-Benzyl-5-benzoyloxy-1,2,3-triazole (II)			5.55	
1-Methyl-3-benzyl-4-benzoyloxy-1,2,3-triazolium iodide (III)*			5.26	3.98
1-Methyl-4-benzoyloxy-1,2,3-triazole (IV)		7.88		4.12
1-Methyl-4-hydroxy-1,2,3-triazole (VI)	9.20	7.00		4.02
1-Methyl-4-methoxy-1,2,3-triazole (VII)		7.15		4.03, 3.95

\* In deuteriodimethylsulfoxide with TMS as internal standard.

4-oxide (VIII), both of which have been described previously.<sup>3</sup> The formation of (VII) proves the structure of (VI). Daeniker and Druey<sup>1</sup> found that methylation of 1-phenyl-4-hydroxy-1,2,3-triazole gave an *O*-methylated product accompanied by an unidentified compound with infrared absorption at 1660  $\text{cm}^{-1}$ . In view of the results described above this product is probably 1-methyl-3-phenyl-1,2,3-triazolio-4-oxide.

1-Methyl-4-hydroxy-1,2,3-triazole can exist in several tautomeric forms (VIa, b, c, and d). The NMR spectrum in deuteriochloroform (Table 1) shows that no methylene group is present and thus rules out structure (VIb). The infrared spectrum of (VI) in a potassium bromide disk or in chloroform solution shows no absorption at 3100–4000  $\text{cm}^{-1}$ ; a broad absorption band from 2500 to 3100  $\text{cm}^{-1}$  indicates hydrogen bonding. Another strong absorption is found at 1625  $\text{cm}^{-1}$ . Since this is the region where (VIII) and other 1,2,3-triazolio oxides absorb<sup>2-4</sup> it seems likely that (VI) exists preferentially as the structure (VIc) or (VI d), both in the solid state and in solution.

## EXPERIMENTAL

Thin layer and column chromatography was carried out as described previously.<sup>3</sup> NMR spectra were obtained on a Varian A-60 instrument. Position of signals are given in ppm ( $\delta$ -values) relative to tetramethyl silane (Table 1). Deuteriochloroform was used as solvent. Melting points are uncorrected.

*1-Benzyl-5-benzoyloxy-1,2,3-triazole (II)*. To 14.90 g of 1-benzyl-5-hydroxy-1,2,3-triazole<sup>5</sup> in 30 ml of pyridine was added 12.00 ml of benzoyl chloride with stirring and ice-cooling, and the mixture was then left at room temperature for 24 h. Methylene chloride (120 ml) was added and the solution was washed with 4 N acetic acid, saturated aqueous sodium hydrogen carbonate, and water, dried over magnesium sulphate, and filtered through activated carbon. The solvent was evaporated and the residue was recrystallized from ethanol yielding 19.48 g (82 %) of pure product as colourless crystals, m.p. 111°. (Found: C 68.71; H 4.70; N 15.19. Calc. for  $\text{C}_{16}\text{H}_{13}\text{N}_3\text{O}_2$ : C 68.80; H 4.70; N 15.04).

*1-Methyl-3-benzyl-4-benzoyloxy-1,2,3-triazolium iodide (III)*. 1-Benzyl-5-benzoyloxy-1,2,3-triazole (II) (12.91 g), acetonitrile (30 ml), and methyl iodide (30 ml) were refluxed for 5 h. The product was filtered off and washed with four 80 ml portions of chloroform yielding 15.83 g (81 %) of colourless crystals, m.p. 166–167°. After recrystallization from methanol-ether the melting point was 169–170°. (Found: C 48.33; H 3.88; N 9.84; I 29.88. Calc. for  $\text{C}_{17}\text{H}_{16}\text{N}_3\text{O}_2\text{I}$ : C 48.47; H 3.83; N 9.98; I 30.13).

### 1-Methyl-3-benzyl-1,2,3-triazolio-4-oxide (V)

*From 1-methyl-3-benzyl-4-benzoyloxy-1,2,3-triazolium iodide (III)*. To (III) (339 mg) was added barium hydroxide octahydrate (285 mg) and 1 ml of water. The mixture was refluxed for 1 h and the solvent was removed *in vacuo*; the residue was extracted with methanol. The methanol was evaporated leaving a crude product which was purified by column chromatography on silica gel (30 g) using methanol as eluent. The first fraction to come off the column consisted of an iodine containing material. The second fraction gave 238 mg (94 %) of 1-methyl-3-benzyl-1,2,3-triazolio-4-oxide (V), m.p. 85–87°. Infrared and NMR spectra were identical with those of the product described previously.<sup>2</sup>

*From 1-benzyl-5-hydroxy-1,2,3-triazole (I)*. 1-Benzyl-5-hydroxy-1,2,3-triazole (10.01 g) and sodium hydroxide (2.3 g) was dissolved in methanol (20 ml) and methyl iodide (9 ml) was added. The solution was heated under reflux for 3 h. The solvent was then removed and the residue was extracted with boiling chloroform. The extract was washed with saturated aqueous sodium thiosulphate and water and the solution was dried and filtered

through activated carbon. Evaporation of the solvent left 10.89 g (100 %) of (V) as a light brown oil which crystallized on standing, m.p. 87–93°. The product is pure enough for synthetical purposes, but can be recrystallized from ethyl acetate-hexane as described previously.<sup>2</sup>

### 1-Methyl-4-benzoyloxy-1,2,3-triazole (IV)

From 1-methyl-3-benzyl-4-benzoyloxy-1,2,3-triazolium iodide (III). A mixture of (III) (7.50 g) and benzoyl chloride (35 ml) was stirred and heated to 120° for 75 min. After cooling, hexane (250 ml) was added and the precipitate was filtered off and washed with hexane. It was then dissolved in methylene chloride (50 ml) and the solution was washed with saturated aqueous sodium hydrogen carbonate, 10 % aqueous sodium thiosulphate and water, dried and filtered through activated carbon. The solvent was evaporated and the residue was recrystallized from methanol with cooling in carbon dioxide yielding 1.97 g (68 %) of (IV) as colourless crystals, m.p. 122°. (Found: C 59.29; H 4.29; N 20.84. Calc. for C<sub>10</sub>H<sub>9</sub>N<sub>3</sub>O<sub>2</sub>: C 59.10; H 4.47; N 20.68).<sup>1</sup>

The material in the mother liquor was put on a column of silica gel (60 g). By elution with ethyl acetate 349 mg of material was obtained. Recrystallization from ethanol gave 173 mg of (IV), m.p. 122°, bringing the total yield of this compound to 74 %. Further elution of the column with methanol gave three fractions the first two of which consisted of iodine containing materials. The third fraction contained 168 mg of material. Extraction with ethyl acetate and evaporation gave 157 mg (5 %) of (V), m.p. 88–91°. The compound was identified by infrared and NMR spectra.

From 1-methyl-3-benzyl-1,2,3-triazolio-4-oxide (V). Crude (V) (10.89 g) and benzoyl chloride (44 ml) was heated to 115° for 1.5 h in an oil bath. The triazolium oxide (V) dissolved and then a crystalline intermediate precipitated (probably 1-methyl-3-benzyl-4-benzoyloxy-1,2,3-triazolium chloride). Finally, the intermediate dissolved again and a homogeneous solution was formed. After cooling hexane (400 ml) was added and the mixture was allowed to stand at –20° for one day. The crystalline material was then filtered off and washed with hexane leaving 9.96 g of crude product. Recrystallization from ethanol gave 8.20 g (70 %) of pure 1-methyl-4-benzoyloxy-1,2,3-triazole (IV), m.p. 122–123°.

1-Methyl-4-hydroxy-1,2,3-triazole (VI). 1-Methyl-4-benzoyloxy-1,2,3-triazole (IV) (1.95 g) was refluxed for 90 min with two equivalents of 1 N aqueous sodium hydroxide. The pH was then brought to 1 with hydrochloric acid. Benzoic acid was filtered off and washed with water. The filtrate was evaporated to dryness *in vacuo*. The residue was recrystallized from boiling acetone with cooling in carbon dioxide giving 692 mg (73 %) of 1-methyl-4-hydroxy-1,2,3-triazole (VI) as colourless crystals, m.p. 140°. (Found: C 36.43; H 5.21; N 42.52. Calc. for C<sub>5</sub>H<sub>5</sub>N<sub>3</sub>O: C 36.35; H 5.09; N 42.41). Equiv. weight by potentiometric titration with 0.1 N aqueous sodium hydroxide: 99 (calc. 99.1). pK<sub>a</sub> in aqueous solution: 7.4.

Methylation of 1-methyl-4-hydroxy-1,2,3-triazole (VI). Methylation of (VI) (492 mg) with diazomethane, using the procedure described earlier,<sup>3</sup> gave 541 mg of a crude product which was separated into two fractions by column chromatography. The first fraction, which was eluted with ethyl acetate, contained 105 mg (19 %) of 1-methyl-4-methoxy-1,2,3-triazole (VII). Recrystallization from ether-pentane gave the pure compound, m.p. 29–30°. Infrared and NMR spectra were identical with those of the product described earlier.<sup>3</sup>

Elution with methanol gave 387 mg (69 %) of 1,3-dimethyl-1,2,3-triazolio-4-oxide (VIII) as yellowish crystals, m.p. 78–91°. Infrared and NMR spectra proved its identity with the product described earlier.<sup>3</sup>

Benzoylation of 1-methyl-4-hydroxy-1,2,3-triazole (VI). Benzoylation of (VI) (79 mg) using the procedure described above for 1-benzyl-5-hydroxy-1,2,3-triazole gave 161 mg (100 %) of crude 1-methyl-4-benzoyloxy-1,2,3-triazole (IV). Recrystallization from ethanol-ether yielded the pure compound, m.p. 121°, identical with the material described above.

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