

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

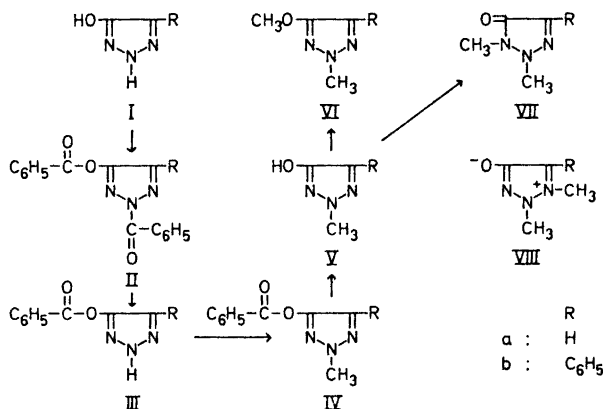
### VI. Preparation of 2-Methyl Substituted 4-Hydroxy-1,2,3-triazoles

MIKAEL BEGRUP

*Polyteknisk Læreanstalt, Organisk-kemisk Laboratorium, Bygning 201, DK-2800 Lyngby, Denmark*

2-Methyl-4-hydroxy-1,2,3-triazole (Va) and its 5-phenyl derivative (Vb) were prepared from the corresponding N-unsubstituted hydroxy-triazoles (I) *via* the dibenzoyl derivatives (II), the monobenzoyl derivatives (III), and the 2-methyl-4-benzoyloxy-1,2,3-triazoles (IV). Methylation of (Va) and (Vb) gave the 2-methyl-4-methoxy-1,2,3-triazoles (VI) and the 1,2-dimethyl-1,2,3-triazolones-5 (VII). The tautomeric structures of (Va) and (Vb) have been investigated.

In previous papers the preparation of 1-substituted-4-hydroxy-1,2,3-triazoles was described.<sup>1,2</sup> 1-Substituted-5-hydroxy-1,2,3-triazoles are readily available.<sup>3</sup> Of the third type of isomer, namely the 2-substituted-4-hydroxy-1,2,3-triazoles, only a few 2-aryl derivatives have been described.<sup>4-6</sup> In the present paper the preparation of 2-methyl-4-hydroxy-1,2,3-triazole (Va) and its 4-phenyl derivative (Vb) is described. The method used would probably be suited for the preparation of other 2-alkyl derivatives as well.



Benzoylation of 4-hydroxy-1,2,3-triazole (Ia) or 4-hydroxy-5-phenyl-1,2,3-triazole (Ib) gave, in high yields, the dibenzoyl compounds (II, a and b). Infrared spectra of the two products (Table 1) indicate that they contain an *N*-benzoyl and an *O*-benzoyl group.<sup>7</sup> It has not been proved whether the *N*-benzoyl group is, in fact, at N-2 as shown in formula (II); but on the basis

Table 1. NMR-spectra in deuteriochloroform with TMS as an internal standard, and infrared absorptions of carbonyl groups.

Compound	IR		NMR					
	cm <sup>-1</sup>		CH ppm	OCH <sub>3</sub> <sup>b</sup> J <sup>13</sup> C-H ppm Hz	NCH <sub>3</sub> J <sup>13</sup> C-H ppm Hz	NCH <sub>3</sub> J <sup>13</sup> C-H ppm Hz		
2-Benzoyl-4-benzoyloxy-triazole (IIa)	1748	1733	—					
2-Benzoyl-4-benzoyloxy-5-phenyl-triazole (IIb)	1765	1723						
4-Benzoyloxy-triazole (IIIa)	1743		—					
4-Benzoyloxy-5-phenyl-triazole (IIIb)	1753							
2-Methyl-4-benzoyloxy-triazole (IVa)	1740		7.77		4.18	144		
2-Methyl-4-benzoyloxy-5-phenyl-triazole (IVb)	1750				4.15	143		
1-Methyl-4-benzoyloxy-triazole <sup>a</sup>	1735		7.88		4.10	143		
1-Methyl-4-benzoyloxy-5-phenyl-triazole <sup>a</sup>	1748				4.07	143		
1-Methyl-5-benzoyloxy-triazole	1748		7.79		4.01	143		
1-Methyl-4-phenyl-5-benzoyloxy-triazole	1748				3.92	143		
2-Methyl-4-hydroxy-triazole (Va)			7.05		4.08	144		
2-Methyl-4-hydroxy-5-phenyl-triazole (Vb)					4.12	143		
2-Methyl-4-methoxy-triazole (VIa)			7.04	3.92	146	4.07	141	
2-Methyl-4-methoxy-5-phenyl-triazole (VIb)				4.03	149	4.03	144	
1,2-Dimethyl-triazolone-5 (VIIa)	1638		7.06		3.62	142	3.53	
1,2-Dimethyl-4-phenyl-triazolone-5 (VIIb)	1630—1650				3.55	142	3.52	
1-Methyl-4-methoxy-triazole <sup>a</sup>			7.15	3.95	146	4.03	142	
1-Methyl-5-methoxy-triazole			7.04	3.95	147		3.77	
1,3-Dimethyl-triazolio-4-oxide <sup>a</sup>	1645		6.67		3.95	143	3.67	

<sup>a</sup> Data have been published previously<sup>8</sup> but are repeated here for comparison.

<sup>b</sup> In cases where both NCH<sub>3</sub> and OCH<sub>3</sub> groups are present the absorptions have been identified through the <sup>13</sup>C—H coupling constants.<sup>8</sup>

of the results obtained by acylation of other 1,2,3-triazole derivatives<sup>8</sup> this seems to be the most likely position.

When (IIa) or (IIb) were heated in an acetone-water mixture, both gave a monobenzoylated product in high yield. From the infrared spectra (Table 1) it is evident that the bands corresponding to the *N*-benzoyl groups have disappeared whereas those attributed to the *O*-benzoyl groups are still present. Therefore, the products must be the two *O*-benzoyl compounds (IIIa and b). This is further verified by the typical C—O stretch ester absorptions in the infrared spectra (see Experimental).

Methylation of (IIIa) with diazomethane gave 2-methyl-4-benzoyloxy-1,2,3-triazole (IVa), the structure of which is derived from the fact that it is different from 1-methyl-4-benzoyloxy-1,2,3-triazole,<sup>1</sup> and from 1-methyl-5-benzoyloxy-1,2,3-triazole, prepared by benzoylation of 1-methyl-5-hydroxy-1,2,3-triazole and shown by infrared data to be an *O*-benzoyl derivative (see Table 1 and Experimental). Similarly, methylation of (IIIb) afforded 2-methyl-4-benzoyloxy-5-phenyl-1,2,3-triazole (IVb), different from 1-methyl-4-benzoyloxy-5-phenyl-1,2,3-triazole,<sup>2</sup> and from 1-methyl-4-phenyl-5-benzoyloxy-1,2,3-triazole, prepared by benzoylation of 1-methyl-4-phenyl-5-hydroxy-1,2,3-triazole.

Finally, hydrolysis of (IVa) and (IVb) gave the 2-methyl-4-hydroxy-1,2,3-triazoles (Va) and (Vb), respectively. The structures of these were proved by methylation with diazomethane. Thus (Va) gave two products, one of which was identical with 2-methyl-4-methoxy-1,2,3-triazole (VIa).<sup>9</sup> The second methylation product was different from any of the previously described isomers.<sup>9,10</sup> An NMR spectrum exhibited two methyl group signals at 3.62 and 3.53  $\delta$ , excluding *C*-methylation. Hence, the structure must be either (VIIa) or (VIIIa), but a choice between these cannot be made at the moment. Methylation of (Vb) gave a mixture of 2-methyl-4-methoxy-5-phenyl-1,2,3-triazole (VIb) and 1,2-dimethyl-4-phenyl-1,2,3-triazolone-5 (VIIb), both of which have been previously described.<sup>11</sup>

NMR data for 2-methyl-4-hydroxy-1,2,3-triazole (Va) and its 5-phenyl derivative (Vb) are presented in Table 1. The infrared spectra of (Va or Vb), in potassium bromide discs or in chloroform solution, showed no absorptions in the carbonyl region above 1600  $\text{cm}^{-1}$ . This indicates that both compounds adopt the hydroxy-structure (V) rather than structures analogous to (VII) or (VIII).

## EXPERIMENTAL

Thin layer and column chromatography was carried out as described previously.<sup>9</sup> NMR spectra were obtained on a Varian A-60 instrument. Position of signals are given in ppm ( $\delta$ -values) relative to tetramethylsilane (Table 1). Deuteriochloroform was used as a solvent. Melting points are uncorrected.

*2-Benzoyl-4-benzoyloxy-1,2,3-triazole (IIa)*. A solution of 4-hydroxy-1,2,3-triazole (Ia) (3.15 g)<sup>12</sup> in pyridine (10 ml) was cooled in an ice-salt bath, and benzoyl chloride (10.2 ml) was added in the course of 2 min. The mixture was allowed to stand at 5° for 24 h. The precipitate was dissolved in methylene chloride (110 ml), and the solution was washed with 4 N acetic acid, water, saturated aqueous sodium hydrogen carbonate, again with water, and finally dried over magnesium sulfate. Removal of the solvent *in vacuo* left the crude product as a yellow mass of crystals. Recrystallization from ethyl acetate-hexane yielded 9.88 g (80 %) of 2-benzoyl-4-benzoyloxy-1,2,3-triazole (IIa) as colourless

crystals, m.p. 118–119°. (Found: C 65.30; H 3.80; N 14.19. Calc. for  $C_{16}H_{11}N_3O_3$ : C 65.51; H 3.78; N 14.32).

*2-Benzoyl-4-benzoyloxy-5-phenyl-1,2,3-triazole (IIb)*. 4-Hydroxy-5-phenyl-1,2,3-triazole (Ib) (4.32 g)<sup>13</sup> was benzoylated, as described above, in pyridine (9.0 ml) with benzoyl chloride (7.5 ml). Recrystallization of the crude product yielded 9.08 g (92 %) of 2-benzoyl-4-benzoyloxy-5-phenyl-1,2,3-triazole (IIb) as colourless crystals, m.p. 146–148°. (Found: C 71.45; H 4.14; N 11.47. Calc. for  $C_{22}H_{15}N_3O_3$ : C 71.54; H 4.10; N 11.38).

*4-Benzoyloxy-1,2,3-triazole (IIIa)*. 2-Benzoyl-4-benzoyloxy-1,2,3-triazole (IIa) (9.28 g) was dissolved in acetone (400 ml). Water (200 ml) was added and the mixture was heated to reflux for 4  $\frac{1}{2}$  h. The solvent was removed *in vacuo* and the residue was washed 3 times with 150 ml of hexane. The remaining 6.46 g of crude product was recrystallized from ether-hexane to give 5.31 g (89 %) of 4-benzoyloxy-1,2,3-triazole (IIIa) as colourless crystals, m.p. 78–80°. (Found: C 57.29; H 3.85; N 22.42. Calc. for  $C_9H_7N_3O_2$ : C 57.13; H 3.73; N 22.21). The infrared spectrum of (IIIa) showed ester absorptions at 1260, 1080, and 1069  $cm^{-1}$ .

*4-Benzoyloxy-5-phenyl-1,2,3-triazole (IIIb)*. 2-Benzoyl-4-benzoyloxy-5-phenyl-1,2,3-triazole (IIb) (2.00 g) was dissolved in acetone (200 ml). Water (80 ml) was added, and the solution was heated to reflux for 11 h. The solvents were removed *in vacuo* leaving a yellow oil which crystallized on cooling. The material was extracted with hexane (4  $\times$  40 ml). This left 1.27 g (89 %) of 4-benzoyloxy-5-phenyl-1,2,3-triazole (IIIb) as colourless crystals, m.p. 122°. Recrystallization from ether-hexane raised the melting point to 126°. (Found: C 67.86; H 4.21; N 15.98. Calc. for  $C_{15}H_{11}N_3O_2$ : C 67.91; H 4.18; N 15.84). The infrared spectrum of (IIIb) showed ester absorptions at 1235–1250, 1070, and 1050  $cm^{-1}$ .

*2-Methyl-4-benzoyloxy-1,2,3-triazole (IVa)*. 4-Benzoyloxy-1,2,3-triazole (IIIa) (751 mg) was methylated with diazomethane by the procedure described previously.<sup>9</sup> The crude product was extracted with hexane (3  $\times$  6 ml). The hexane solution was concentrated to 10 ml and decanted from an impurity which had separated. The 2-methyl-4-benzoyloxy-1,2,3-triazole (IVa) precipitated by cooling of the hexane solution to –30°. Yield 338 mg (42 %) of colourless crystals, m.p. 46–59°. The product was pure enough for synthetic purposes. Further purification could be achieved by column chromatography on silica gel (20 g) with ether-hexane (1:4) as the eluent. First, a minor quantity of methyl benzoate left the column. Then 266 mg of 2-methyl-4-benzoyloxy-1,2,3-triazole, m.p. 64°, was collected. Recrystallization from hexane and cooling in dry ice yielded the pure material, m.p. 68–69°. (Found: C 59.17; H 4.58; N 20.87. Calc. for  $C_{10}H_9N_3O_2$ : C 59.10; H 4.47; N 20.68). The infrared spectrum of (IVa) showed ester absorptions at 1252 and 1087  $cm^{-1}$ . Infrared spectra and melting points showed that the compound was not identical with 1-methyl-4-benzoyloxy-1,2,3-triazole described previously,<sup>1</sup> or with 1-methyl-5-benzoyloxy-1,2,3-triazole. The latter compound was prepared from 1-methyl-5-hydroxy-1,2,3-triazole<sup>12</sup> and benzoyl chloride using the procedure described above for benzoylation of 4-hydroxy-1,2,3-triazole. Yield 93 %. Melting point after recrystallization from ethyl acetate 97–98°. (Found: C 59.13; H 4.37; N 20.61). The infrared spectrum showed ester absorptions at 1235–1255, 1050, and 1070  $cm^{-1}$ . No bands were present between 1600 and 1700  $cm^{-1}$ . This indicates that the compound is *O*-benzoylated. The formation of the benzoyloxy-derivative is in agreement with the formation of 1-benzyl-5-benzoyloxy-1,2,3-triazole from 1-benzyl-5-hydroxy-1,2,3-triazole.<sup>1</sup>

*2-Methyl-4-benzoyloxy-5-phenyl-1,2,3-triazole (IVb)*. In the same way 4-benzoyloxy-5-phenyl-1,2,3-triazole (IIIb), on treatment with diazomethane, yielded a crude product which was extracted with ether (25 ml). Evaporation of the ether left 601 mg of a yellow oil which could be purified by column chromatography on silica gel (75 g) with ether-hexane (1:4) as the eluent. The first fraction contained 368 mg (71 %) of 2-methyl-4-benzoyloxy-5-phenyl-1,2,3-triazole (IVb), a colourless oil which could not be induced to crystallize. For analysis, the material was reprecipitated from hexane by cooling in dry ice. (Found: C 68.63; H 4.68; N 14.92. Calc. for  $C_{16}H_{13}N_3O_2$ : C 68.80; H 4.70; N 15.04). The infrared spectrum of (IVb) showed ester absorptions at 1235, 1255, 1058, and 1070  $cm^{-1}$ . Infrared spectra and melting points showed that the compound was different from 1-methyl-4-benzoyloxy-5-phenyl-1,2,3-triazole,<sup>2</sup> and from 1-methyl-4-phenyl-5-benzoyloxy-1,2,3-triazole. The latter was prepared by benzoylation of 1-methyl-4-phenyl-5-hydroxy-1,2,3-triazole,<sup>13</sup> using the procedure described above, yield 93 %.

Melting point, after recrystallization from ethyl acetate, 159°. (Found: C 68.88; H 4.66; N 14.94). The infrared spectrum showed ester absorptions at 1230 and 1075  $\text{cm}^{-1}$  which, in connection with lack of absorptions between 1600 and 1700  $\text{cm}^{-1}$ , indicate that the compound is *O*-benzoylated.<sup>1</sup>

*2-Methyl-4-hydroxy-1,2,3-triazole (Va)*. 2-Methyl-4-benzoyloxy-1,2,3-triazole (IVa) (510 mg) and 1 N sodium hydroxide (5.4 ml) was heated to reflux for 90 min. The solution was then acidified with 1 N hydrochloric acid to pH 3. After cooling to 0°, the precipitated benzoic acid was filtered off and washed twice with 10 ml of ice cold water. The combined filtrate and washings were evaporated to dryness *in vacuo*, and the residue was extracted with ethyl acetate (4 × 10 ml). The solvent was removed, and the crude product was washed with 60 ml of hexane and recrystallized from ethyl acetate-hexane with cooling in dry ice, yielding 160 mg (64 %) of 2-methyl-4-hydroxy-1,2,3-triazole (Va) as colourless crystals, m.p. 99–100°. (Found: C 36.51; H 5.04; N 42.30. Calc. for  $\text{C}_5\text{H}_8\text{N}_3\text{O}$ : C 36.35; H 5.09; N 42.41). Equiv. weight found by potentiometric titration with 0.1 N aqueous sodium hydroxide: 99.7 (calc. 99.1).  $\text{p}K_a$  in aqueous solution: 9.0. The compound was devoid of absorption in the 1600–1800  $\text{cm}^{-1}$  range, in a potassium bromide disc as well as in chloroform solution.

*2-Methyl-4-hydroxy-5-phenyl-1,2,3-triazole (Vb)*. 2-Methyl-4-benzoyloxy-5-phenyl-1,2,3-triazole (IVb) (2.00 g) and 0.5 N sodium hydroxide (10 ml) was heated to reflux for 3 h. The solution was then acidified with 1 N hydrochloric acid to pH 3. An oil, which soon crystallized, precipitated. The material was filtered off, washed with water (3 × 20 ml) and, after drying, with hexane (5 × 20 ml). This left 2-methyl-4-hydroxy-5-phenyl-1,2,3-triazole (Vb) as colourless crystals, m.p. 150–151°. Yield 905 mg (72 %). Recrystallization from ether-hexane did not raise the melting point. (Found: C 61.80; H 5.20; N 24.13. Calc. for  $\text{C}_9\text{H}_9\text{N}_3\text{O}$ : C 61.70; H 5.18; N 23.98). The compound did not absorb at 1600–1800  $\text{cm}^{-1}$  in infrared.

*Methylation of 2-methyl-4-hydroxy-1,2,3-triazole (Va)*. This compound (167 mg) was dissolved in ether (7 ml) and excess diazomethane was added as previously described.<sup>9</sup> After standing for 24 h at room temperature the ether was cautiously distilled off in a micro distillation apparatus. The oily residue was extracted 3 times with 1 ml portions of hexane. From the hexane extract the solvent was removed in a micro distillation apparatus. This left 137 mg (72 %) of 2-methyl-4-methoxy-1,2,3-triazole (VIa) as a yellow oil which crystallized by standing at –30°, m.p. below 0°. Infrared and NMR-spectra were identical with those of the material described previously.<sup>9</sup>

The oily residue from the hexane extraction was purified by column chromatography on silica gel (20 g) with ethyl acetate as the eluent. The first fraction to leave the column contained a minor amount of 2-methyl-4-methoxy-1,2,3-triazole. The column was then eluted with ethyl acetate-methanol (1:1). Two fractions were collected. The first contained a minor amount of an unidentified compound. The second fraction contained 42 mg (22 %) of 1,2-dimethyl-1,2,3-triazolone-5 (VIIa), (or possibly (VIIIa)), as a nearly colourless oil. Three reprecipitations from ethyl acetate-hexane, with cooling in dry ice, yielded the pure compound which crystallized on standing, m.p. 48–49°. The compound was very hygroscopic and a satisfactory analysis could therefore not be obtained. (Found: C 41.55; H 6.59; N 34.40. Calc. for  $\text{C}_4\text{H}_6\text{N}_3\text{O}$ : C 42.46; H 6.24; N 37.16).

*Methylation of 2-methyl-4-hydroxy-5-phenyl-1,2,3-triazole (Vb)*. This compound (167 mg) was methylated as described above. Evaporation of the solvent left 157 mg of crude product as a colourless oil which was purified by column chromatography on silica gel (20 g) with ether as the eluent. The first fraction contained 116 mg (64 %) of 2-methyl-4-methoxy-5-phenyl-1,2,3-triazole (VIb) as a colourless oil. Infrared and NMR spectra were identical with those of the material described previously.<sup>11</sup> The column was then eluted with ethyl acetate-methanol (1:1) to give a second fraction which contained 33 mg (18 %) of 1,2-dimethyl-4-phenyl-1,2,3-triazolone-5 (VIIb) as a colourless, crystalline mass. Infrared and NMR-spectra were identical with those of the material described previously.<sup>11</sup>

The author is indebted to civilingeniør S. Refn for the infrared spectra. Microanalyses were performed by Dr. A Bernhardt.

## REFERENCES

1. Begtrup, M., Hansen, K. and Pedersen, C. *Acta Chem. Scand.* **21** (1967) 1234.
2. Begtrup, M. and Pedersen, C. *Acta Chem. Scand.* **22** (1968).
3. Benson, F. R. and Savell, W. L. *Chem. Revs.* **46** (1950) 1; Boyer, J. H. *Heterocyclic Compounds*, Wiley, New York 1961, Vol. 7, p. 384.
4. Jagerspacher, C. *Ber.* **28** (1895) 1283.
5. Thiele, J. and Schleussner, K. *Ann.* **295** (1897) 129.
6. Stolle, R. *J. prakt. Chem.* **227** (1928) 275.
7. Bellamy, L. J. *The Infrared Spectra of Complex Molecules*, Methuen, London 1960, p. 212.
8. Birkofer, L. and Wegner, P. *Chem. Ber.* **100** (1967) 3485.
9. Begtrup, M. and Pedersen, C. *Acta Chem. Scand.* **19** (1965) 2022.
10. Begtrup, M. and Pedersen, C. *Acta Chem. Scand.* **20** (1966) 1555.
11. Begtrup, M. and Pedersen, C. *Acta Chem. Scand.* **21** (1967) 633.
12. Pedersen, C. *Acta Chem. Scand.* **12** (1958) 1236.
13. Begtrup, M. and Pedersen, C. *Acta Chem. Scand.* **18** (1964) 1333.

Received December 12, 1968.