# Position of Protonation and of *N*-Methylation in the *s*-Triazolo[1,5-*a*]pyrimidine Ring System

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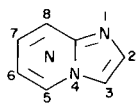
The position of protonation and of *N*-methylation in azaindolizines has been of interest in recent years (2-5). It has been shown (6,7) that all of the diazaindolizines possessing a nitrogen atom at position 1 (**1** and **2**) are protonated on *N*-1. It has also been reported (2,4,6) that the site of protonation (*N*-1) in imidazo[1,2-*a*]pyridine (**3**), imidazo[1,2-*a*]pyrimidine (**4**) and in *s*-triazolo[4,3-*a*]-pyridine (**5**) (in the kinetically controlled methylation only) is also the site of *N*-methylation. Because of reports (8,9) that methylation of *s*-triazolo[1,5-*a*]pyrimidine (**6**) occurs on *N*-4, rather than on *N*-3, as might now be expected, it became of interest to determine the structure of *s*-triazolo[1,5-*a*]pyrimidine methiodide and to compare the position of *N*-methylation with the site of protonation.



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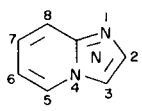

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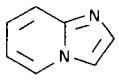

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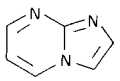

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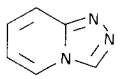

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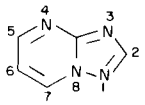

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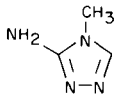
The data summarized in Table I shows that *N*-methylation does not occur on *N*-1, since there is no significant change, due to *peri* interaction (2-5), in the chemical shift of the *N*-methyl protons in the 5,7-dimethyl compound compared with that of the parent *N*-methyl protons, nor is there a significant change in the chemical shift of the 7-methyl protons in the protonated 7-methyl compound when an *N*-methyl group is introduced into the molecule. Therefore, the *N*-methyl group must be on *N*-3 or *N*-4, if it is assumed that methylation of *N*-8 is not likely since it would produce a non-aromatic 8-$\pi$-electron system.

The position of the methyl group was determined by hydrolysis of *s*-triazolo[1,5-*a*]pyrimidine methiodide to yield the known (10) 3-amino-4-methyl-*s*-triazole (**7**) which was identified by melting point and p.m.r. spectroscopy. Therefore, methylation must have occurred on *N*-3 rather than on *N*-4 or *N*-8.

The position of *N*-methylation (*N*-1) of the imidazo-[1,2-*a*]pyrimidine ring system (**4**) was confirmed by a similar degradation of the parent methiodide which afforded the known (11) 1-methyl-2-aminoimidazole (**8**), identified by p.m.r. and mass spectrometry as well as by conversion to the known picrate.



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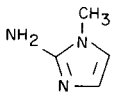

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The position of protonation is clearly (Table I) the same as the position of *N*-methylation in the *s*-triazolo-[1,5-*a*]pyrimidine ring system.

These results consequently negate the reports (8,9) that methylation in *s*-triazolo[1,5-*a*]pyrimidine occurs at *N*-4 rather than on *N*-3 and bring the ring system "in harmony" with the related systems (2-5).

## EXPERIMENTAL

PMR spectra were obtained with Varian A-60 and HA-100 spectrometers. Elemental analyses were done by Mrs. K. Decker of this department. Mass spectra were obtained with a Hitachi-Perkin Elmer RMU-6E mass spectrometer, with an ionization potential of 80 eV and an inlet system temperature of 180°. Melting points are corrected.

Methiodides.

The azaindolizine was dissolved in a minimum amount of acetone and five times the theoretical amount of methyl iodide was added. After standing at room temperature for 12 hours the precipitate was filtered, washed with acetone, and recrystallized from 95% ethanol. Yields, melting points, and analytical data are reported in Table II.

TABLE I

Protonmagnetic Resonance Spectral Data for some *s*-Triazolo[1,5-*a*]pyrimidine in Deuteriosulfuric Acid and their Methiodides in Deuterium Oxide

| Compound | Chemical Shift at Position ($\tau$) | | | | | Coupling Constants (Hz) | | |
|---|---|---|---|---|---|---|---|---|
| | 2 | 3 | 5 | 6 | 7 | $J_{5,6}$ | $J_{6,7}$ | $J_{5,7}$ |
| Parent | 0.69 | - | 0.62 | 2.03 | 0.46 | 4.5 | 6.8 | 1.6 |
| Methiodide | 0.62 | 5.85 (d) | 0.63 | 2.04 | 0.47 | 4.6 | 7.0 | 1.8 |
| 2-Methyl | 7.16 (d) | - | 0.75 | 2.10 | 0.59 | 5.0 | 7.0 | 1.7 |
| Methiodide | 7.14 (d) | 5.95 (d) | 0.69 | 2.06 | 0.55 | 5.0 | 7.0 | 1.5 |
| 5-Methyl (a) | 0.82 | - | 7.05 (d) | 2.30 | 0.70 | 0.0 (b) | 7.0 | 0.0 (b) |
| Methiodide | 0.72 | 5.89 (d) | 7.06 (d) | 2.15 | 0.70 | 0.0 (b) | 7.0 | 0.0 (b) |
| 5,7-Dimethyl | 0.81 | - | 7.18 (d) | 2.31 | 7.03 (d) | 0.0 (b) | 1.0 (b) | 0.0 (c) |
| Methiodide | 0.77 | 5.92 (d) | 7.14 (d) | 2.31 | 7.07 (d) | 0.0 (b) | 0.8 (b) | 0.0 (c) |
| 2,5,7-Trimethyl | 7.20 (d) | - | 7.20 (d) | 2.42 | 7.10 (d) | 0.0 (b) | 0.8 (b) | 0.0 (c) |
| Methiodide | 7.19 (d) | 6.05 (d) | 7.21 (d) | 2.40 | 7.12 (d) | 0.0 (b) | 0.8 (b) | 0.0 (c) |
| 5,6,7-Trimethyl | 0.90 | - | 7.19 (d) | 7.49 (d) | 7.03 (d) | 0.0 (c) | 0.5 (c) | 0.0 (c) |
| Methiodide | 0.87 | 5.95 (d) | 7.17 (d) | 7.50 (d) | 7.07 (d) | 0.0 (c) | 0.5 (c) | 0.0 (c) |

(a) In deuteriotrifluoroacetic acid. (b) $CH_3$-H coupling. (c) $CH_3$-$CH_3$ coupling. (d) Refers to methyl group protons.

Degradation of *s*-Triazolo[1,5-*a*]pyrimidine Methiodide.

To 1.0 g. (3.8 mmoles) of *s*-triazolo[1,5-*a*]pyrimidine methiodide in 5 ml. of water cooled in a methanol-ice bath was added simultaneously with stirring a solution of 1.1 g. of sodium hydroxide in 5 ml. of water and a solution of 2.6 g. of potassium iron (III) cyanide in 10 ml. of water. After standing at room temperature for one hour, the solution was warmed to 60° for five minutes. The solution was then cooled and continuously extracted with chloroform. The chloroform solution was dried over sodium carbonate, filtered, and evaporated to dryness to yield 0.092 g. (25%) of 3-amino-4-methyl-*s*-triazole, m.p. 220-222°, p.m.r. (deuterium oxide): $\tau$ 2.03 (s, one proton) $\tau$ 6.05 (s, three protons); lit. (10) m.p. 222°.

Degradation of Imidazo[1,2-*a*]pyrimidine Methiodide.

This reaction was carried out as above, except that the solution was not warmed above room temperature. Evaporation of the chloroform extract afforded 0.17 g. (46%) of 1-methyl-2-aminoimidazole as a dark red oil which would not crystallize. Mol. wt. (mass spectrometric), 97; p.m.r. (deuteriochloroform): $\tau$ 3.50 (d, one proton, J = 1.5 Hz), $\tau$ 3.62 (d, one proton, J = 1.5 Hz) 5.45 (s, two protons), $\tau$ 6.68 (s, three protons). Treatment with picric acid afforded the picrate, m.p. 207-209°; lit. (11) hygroscopic liquid, picrate m.p. 212°.

TABLE II

Azaindolizine Methiodides

| Compound·$CH_3I$ | Yield % | M.P. °C | | Anal. (%) C | H | N |
|---|---|---|---|---|---|---|
| | | | Calcd.: | C | H | N |
| | | | Found: | C | H | N |
| *s*-Triazolo[1,5-*a*]pyrimidine | 53 | 259-260 | | 27.49 | 2.69 | 21.38 |
| | | | | 27.72 | 2.91 | 21.39 |
| 2-Methyl-*s*-triazolo-[1,5-*a*]pyrimidine | 83 | 249-250 | | 30.45 | 3.29 | 20.29 |
| | | | | 30.67 | 3.32 | 20.00 |
| 5-Methyl-*s*-triazolo-[1,5-*a*]pyrimidine | 58 | 229-230 | | 30.45 | 3.29 | 20.29 |
| | | | | 30.50 | 3.22 | 20.15 |
| 5,7-Dimethyl-*s*-triazolo-[1,5-*a*]pyrimidine | 77 | 235-237 | | 33.11 | 3.82 | 19.31 |
| | | | | 33.47 | 3.89 | 19.49 |
| 2,5,7-Trimethyl-*s*-triazolo-[1,5-*a*]pyrimidine | 85 | 257-259 | | 35.54 | 4.30 | 18.42 |
| | | | | 35.62 | 4.44 | 18.17 |
| 5,6,7-Trimethyl-*s*-triazolo-[1,5-*a*]pyrimidine | 54 | 231-233 | | 35.54 | 4.30 | 18.42 |
| | | | | 35.67 | 4.39 | 18.65 |
| 2,3-Dimethylimidazo-[1,2-*a*]pyrimidine | 97 | 273-275 | | 37.39 | 4.19 | 14.58 |
| | | | | 36.97 | 4.02 | 14.56 |

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