

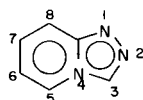
The Syntheses and Thermal Rearrangement of some Methiodides of *s*-Triazolo[4,3-*a*]pyridines

William W. Paudler and Richard J. Brumbaugh

Clippinger Laboratories, Department of Chemistry, Ohio University

It has been shown that the *N*-methylation, with methyl iodide, of *s*-triazolo[4,3-*a*]pyridines affords a mixture of the N-1 and the N-2 methiodides. The N-2 methiodides can be thermally rearranged to the N-1 methiodides. The 8-methyl N-1 methiodides exhibit *peri* interaction between the two methyl groups. This interaction is reflected in greater stability of the N-2 methiodide vs. the N-1 compound.

The *N*-methylation of *s*-triazolo[4,3-*a*]pyridine (I) has recently been described by Potts and coworkers (1). *N*-Methylation of these compounds can occur, of course, either on N-1, N-2 or N-4. Since we have previously (2) shown that *N*-methylation in imidazo[1,2-*a*]pyridines



I

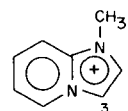
occurs at N-1 and not at N-4, we might well expect that N-1 and/or N-2 will be the preferred site(s) of *N*-methylation in the *s*-triazolo[4,3-*a*]pyridines. Molecular orbital calculations (1) indicate a higher charge density on N-1 than on N-2. Thus, 1-methylation would be predicted to occur preferentially over N-2 methylation. The methiodides described by Potts were indeed identified to be the 1-methyl compounds.

It appeared feasible that, under suitably mild conditions, there might be formed a mixture of the 1-methyl, as well as the 2-methyl compounds. Methylation of the parent (I) with methyl iodide affords a slightly yellow, crystalline material whose pmr spectrum shows two distinct methyl group proton signals ( $\tau$  5.67 and 5.58, respectively), with a relative area ratio of 67 to 33.

Fractional crystallization from absolute ethyl alcohol, along with alumina chromatography, separated these two isomers into the pure components. Similarly, mixtures of two isomeric methiodides were obtained from the 3-, 5-, 7-, 8-, and the 3,8-dimethyl-*s*-triazolo[4,3-*a*]pyridines. Table I records the relative amounts of these isomers.

The question as to which isomer corresponds to the 1-methyl and which to the 2-methyl derivative now needs to be considered.

We have shown (2,3) that H-2 and H-3 as well as H-5 of the N-1 methiodides of imidazo[1,2-*a*]pyridines (II) are



II

subject to facile protium-deuterium exchange in deuterium oxide. This exchange occurs on carbon atoms which are adjacent to a "positive" nitrogen atom. Thus, we might expect that H-3 would be subject to very facile protium-deuterium exchange in the N-2 methiodides of *s*-triazolo[4,3-*a*]pyridine, while it would be less readily replaced by deuterium in the N-1 methiodides. The pmr spectra (Table II) in deuterium oxide of those methiodides where the *N*-methyl group resonates at  $\tau$  5.6  $\pm$  0.04, all show a rapidly exchanging tremendously deshielded ( $\tau$  approximately -0.4) singlet due to H-3. The *N*-methyl protons of the other methiodides all resonate at approximately  $\tau$  5.7 (with the exception of the 8-methyl derivative (see below)). The proton on C-3 of these methiodides appears at a much more shielded position ( $\tau$  0.5) than in the former series. These observations identify the former set of methiodides as the N-2 methyl and the latter as the N-1 methyl derivatives.

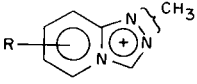
The *N*-methyl protons of the N-1 methiodides of the 8-methyl and of the 3,8-dimethyl-*s*-triazolo[4,3-*a*]pyridines resonate at a more deshielded position ( $\tau$  5.43), than do those of the parent and the other C-methyl N-1 methiodides.

This steric effect is also reflected in the large difference between the chemical shifts of the C-methyl protons in the 8-methyl and in the 3,8-dimethyl N-1 methiodides ( $\tau$  7.08) and the N-2 methiodides ( $\tau$  7.33).

Furthermore, the *peri* interaction between the N-1 methyl and the C-8 methyl groups is apparent from the

TABLE I

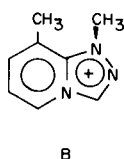
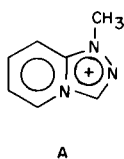
Relative Amounts of 1-Methyl and of 2-Methyl-*s*-triazolo[4,3-*a*]pyridinium Iodides Obtained by *N*-Methylation of the Free Bases

Compound	1-Methyl (percent)	2-Methyl (percent)
		
R		
H	67	33
3-methyl	71	29
5-methyl	60	40
7-methyl	70	30
8-methyl	41	59
3,8-dimethyl	42	58

chemical shifts of the N-1 methyl group protons, which are more deshielded with respect to the N-2 methyl group protons in the 8-methyl methiodides, while the reverse is true for the other methiodides.

We have previously shown (2) that the same difference ( $\Delta \tau$  0.27) prevails in the N-1 methiodides of the imidazo[1,2-*a*]pyridines. The question arises whether this *peri* interaction sufficiently alters the  $sp^2$  hybridization of N-1 to cause a deformation of the otherwise planar ring system. If this is the case, one would expect H-3 to become more shielded in the 1,8-dimethyl compound than it is in any of the other 1,*X*-dimethyl iodides. This is expected since such a deformation would alter the ring current and would thus cause decreased deshielding of the ring protons (4). The data reported in Table II clearly demonstrates that there is *no significant*, if any, *disruption* of coplanarity of the ring system. The same conclusion is reached when the chemical shifts of the C-3 methyl group protons in the 1,3-dimethyl compound are compared with the corresponding ones in the 1,3,8-trimethyl derivative. Again, no change in the chemical shifts of the C-3 methyl protons are observed, as would be expected if a change in ring-current had taken place.

We can consequently suggest with some certainty, that the *peri* interaction is relieved by a movement *out of the plane* of the ring system of the N-1 methyl group without significantly affecting the planarity of the ring system. Structures A and B are an attempt to picture these

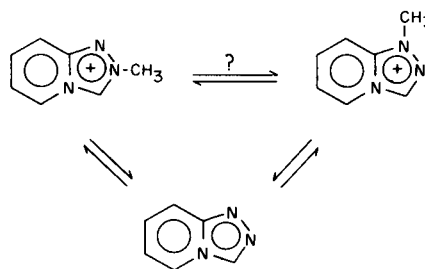


considerations for the parent and the 8-methyl N-1 methiodides, respectively.

Thermal Rearrangement of the *N*-Methiodides of Some *s*-triazolo[4,3-*a*]pyridines.

The mass spectra of the N<sub>1</sub> and of the N<sub>2</sub> methiodides of a given *s*-triazolo[4,3-*a*]pyridine are essentially superimposable. Thus, one might suggest that a thermal dequaternization takes place in the mass spectrometer. This process has been observed many times (5) for other quaternary methiodides.

In the present case it is feasible that any one of the following processes is operative:



The thermal dequaternization of the N-1 and of the N-2 methiodides of *s*-triazolo[4,3-*a*]pyridine at 235° affords the free base only. If the reaction is not allowed to go to completion, the remaining methiodide is the N-1 compound only. Thus, we can suggest that either, the N-2 methiodide is less stable than the N-1 methiodide and decomposes to the free base and methyl iodide faster than the N-1 compound, or that a rearrangement of the N-2 methiodide to the N-1 methiodide takes place with ease.

If the thermal dequaternization of the N-2 methiodide of the parent compound is done in a sealed tube, all of it is converted to the N-1 methiodide. The reverse process, N-1 methiodide to N-2 methiodide transformation, does not take place.

Crossover products are obtained when the N-1 methiodide of the parent is heated with the 8-methyl-*s*-triazolo[4,3-*a*]pyridine. The ratio of N-1 to N-2 methiodide of the 8-methyl compound obtained in this reaction is the same as the ratio (60:40) of these isomers obtained from the thermal rearrangement of the 8-methyl-*s*-triazolo[4,3-*a*]pyridine N-1 and N-2 methiodides. The thermal rearrangement of the 3-, 5-, and 7-methyl-*s*-triazolo[4,3-*a*]pyridine N-2 methiodides to the corresponding N-1 methiodides also occurs quantitatively (see Table III).

The thermal rearrangement of the 8-methyl and of the 3,8-dimethyl-*s*-triazolo[4,3-*a*]pyridine N-1 and N-2 methiodides does *not* afford the N-1 methiodide as readily as do the other derivatives. Under conditions where the other compounds are quantitatively converted to the N-1

TABLE II

NMR Spectral Data of Some *s*-Triazolo[4,3-*a*]pyridine Methiodides (a)

Compound:



R(d)	CH <sub>3</sub> N (position)	Proton Chemical Shifts ( $\tau$ ) Position						R	CH <sub>3</sub> N-
		3	5	6	7	8	8		
H	1	0.53 (0.13)	1.20 (0.92)	2.42(c) (2.25)(c)	1.87(c) (1.96)(c)	1.82(c) (1.58)(c)	—	(—)	5.67 (5.67)
H	2	-0.43(b) (-0.78)	1.33 (1.00)	2.53(c) (2.25)(c)	2.10(c) (1.96)(c)	2.10(c) (1.58)(c)	—	(—)	5.58 (5.58)
3-CH <sub>3</sub>	1	—	1.37 (1.00)	2.20(c) (2.33)(c)	1.82(c) (2.03)(c)	1.82(c) (1.66)(c)	7.08 (7.08)	7.08 (7.08)	5.70 (5.70)
3-CH <sub>3</sub>	2	—	1.50 (1.12)	2.20(c) (2.33)(c)	1.82(c) (2.03)(c)	1.82(c) (1.66)(c)	6.87 (6.83)	6.87 (6.83)	5.63 (5.67)
5-CH <sub>3</sub>	1	0.53 (0.04)	—	2.60 (2.50)	2.18(c) (2.07)(c)	1.92 (1.75)	7.08 (7.09)	7.08 (7.09)	5.68 (5.67)
5-CH <sub>3</sub>	2	-0.23(b) (-1.03)	—	2.62 (2.52)	2.18(c) (2.07)(c)	1.92 (1.75)	7.18 (7.18)	7.18 (7.18)	5.56 (5.58)
7-CH <sub>3</sub>	1	0.63 (0.24)	1.28 (1.03)	2.50 (2.42)	—	2.04 (1.67)	7.30 (7.32)	7.30 (7.32)	5.71 (5.73)
7-CH <sub>3</sub>	2	-0.33 (-0.68)	1.40 (1.13)	2.62 (2.60)	—	2.28 (2.13)	7.42 (7.46)	7.42 (7.46)	5.58 (5.60)
8-CH <sub>3</sub>	1	0.60 (0.16)	1.37 (1.06)	2.52(c) (2.46)(c)	2.20(c) (1.94)	—	7.08 (7.08)	7.08 (7.08)	5.43 (5.46)
8-CH <sub>3</sub>	2	-0.40 (-0.80)	1.37 (1.16)	2.52(c) (2.46)(c)	2.20(c) (2.12)	—	7.33 (7.42)	7.33 (7.42)	5.52 (5.52)
3,8-di-CH <sub>3</sub>	1	—	1.59 (1.29)	2.53(c) (2.63)(c)	2.20(c) (2.30)(c)	—	7.08 (7.08)	7.08 (7.08)	5.43 (5.52)
3,8-di-CH <sub>3</sub>	2	—	1.59 (1.29)	2.53(c) (2.63)(c)	2.20(c) (2.30)(c)	—	7.08 (7.11)	7.08 (7.11)	5.62 (5.68)
							8CH <sub>3</sub>		
							3CH <sub>3</sub>		
							8CH <sub>3</sub>		
							3CH <sub>3</sub>		

(a) In deuterium oxide numbers in parentheses refer to solutions in DMSO-d<sub>6</sub>. (b) Proton exchanges very rapidly (~5 minutes at room temperature) in deuterium oxide. (c) Center of a complex multiplet. (d) With the exception of the parent methiodides, all of the 2-methyl methiodide spectra were analyzed from the mixtures of the 1-methyl and the 2-methyl methiodides.

TABLE III

Thermal Rearrangement of the Methiodides of Some *s*-Triazolo[4,3-*a*]pyridines

Methiodide	Temp.	Time, min.	Percent	
			N-1 Methiodide	N-2 Methiodide
N-1 parent	225	30	100	0
N-2 parent	225	30	100	0
N-1 (67%) N-2 (33%) parent	225	30	100	0
N-1 (71%) N-2 (29%) 3-methyl	220	90	97	3
N-1 (60%) N-2 (40%) 5-methyl	270(a)	90	100	0
N-1 (70%) N-2 (30%) 7-methyl	230	30	100	0
N-1 (41%) N-2 (59%) 8-methyl	220 250	60 300	60 60	40 40
N-1 (42%) N-2 (58%) 3,8-dimethyl	225 250	60 300	43 43	57 57

(a) No significant rearrangement at lower (225°) temperature for 90 minutes.

TABLE IV

Analytical Data For the N-1 and N-2 Methiodide Mixtures Obtained  
By *N*-Alkylation of Some *s*-Triazolo[4,3-*a*]pyridines (a)

Starting Material	N-1, N-2 Methiodide Mixture total percent yield	Elemental Analyses					
		Calculated			Found		
		C	H	N	C	H	N
parent	75	32.20	3.09	16.10	32.25	3.00	16.18
3-methyl	81	34.93	3.66	15.27	35.18	3.69	15.34
5-methyl	70	34.93	3.66	15.27	34.80	3.61	15.32
7-methyl	72	34.93	3.66	15.27	35.18	3.74	15.42
8-methyl	75	34.93	3.66	15.27	35.18	3.67	15.16
3,8-dimethyl	78	37.38	4.18	14.53	37.50	4.14	14.56

(a) Tables I and II list the chemical shifts of the N-CH<sub>3</sub> protons and the relative amounts of the methiodides formed. The amounts were determined by comparison of the area ratio of the N-CH<sub>3</sub> group singlets.

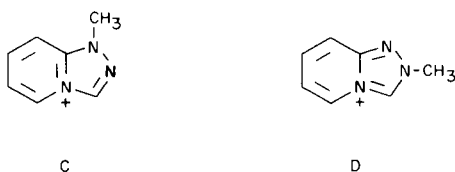
methiodides, the 8-methyl and the 3,8-dimethyl N-2 methiodides are not. This again reflects the *peri* interaction which decreases the ease of formation of the N-1 methiodides. The *peri* interaction is even more severe in the 3,8-dimethyl-*s*-triazolo[4,3-*a*]pyridine N-1 methiodide. This is evident from the observation that the ratio of N-1

to N-2 methiodides is not altered under conditions where even the 8-methyl N-2 methiodide rearranges to some extent. This can be explained by the existence of *two peri*-type interactions in the 3,8-dimethyl-*s*-triazolo[4,3-*a*]pyridine N-1 methiodide which involves H-3 and C-8 methyl interaction in addition to the N-1/C-8 methyl

interaction.

While these data do not absolutely preclude a direct rearrangement of the N-2 methiodides to the N-1 methiodides, we feel strongly that a dealkylation-realkylation process occurs under these heterogeneous thermal conditions.

A comparison of the major resonance contributing structures, C and D, of the N-1 and the N-2 methiodides, clearly explains the greater stability of the N-1 compounds, since we are comparing a "benzenoid" system (C) with a less stable *ortho*-quinoid structure (D).



### EXPERIMENTAL

#### Preparation of N-1 and N-2 Methiodides of Some *s*-Triazolo[4,3-*a*]pyridines.

The appropriate *s*-triazolo[4,3-*a*]pyridine derivative (0.5 g.) was dissolved in 2 ml. of methanol and 1 ml. of methyl iodide was then added. The resulting solution was allowed to stand at room temperature for 24 hours. The addition of about 30 ml. of ether precipitated a slightly off-white solid. This solid was washed with anhydrous ether and allowed to dry in air.

#### Separation of the 1-Methyl-*s*-triazolo[4,3-*a*]pyridinium Iodide from the Isomeric 2-Methyl-*s*-triazolo[4,3-*a*]pyridinium Iodide.

The mixture (0.58 g.) of the two isomers was dissolved in hot absolute ethanol (15 ml.) and this hot solution was then poured onto a chromatographic column of grade No. 3 alumina (1 in. thick and 1.5 in. in diameter). After the ethanol on the alumina had cooled to room temperature, the material was eluted with absolute ethanol. The initial fractions were enriched in the 1-methyl derivative (as determined by the decrease in the N-2 methyl proton signal in the NMR). This process was repeated, whereupon pure 1-methyl-*s*-triazolo[4,3-*a*]pyridinium iodide was obtained in the first fractions. This pure isomer was recrystallized from absolute ethanol (m.p. 235-236°).

*Anal.* Calcd. for C<sub>7</sub>H<sub>8</sub>N<sub>3</sub>I: C, 32.20; H, 3.09; N, 16.10. Found: C, 32.31; H, 3.11; N, 16.13.

A portion of the same mixture of isomers as above was repeatedly recrystallized from absolute ethanol. After six recrystallizations a pure isomer identified as 2-methyl-*s*-triazolo[4,3-*a*]pyridinium iodide crystallized as needles, which melted at 230-231.5°.

*Anal.* Calcd. for C<sub>7</sub>H<sub>8</sub>N<sub>3</sub>I: C, 32.20; H, 3.09; N, 16.10. Found: C, 32.03; H, 3.01; N, 16.20.

#### Thermal Rearrangements of the Various Isomeric Methiodide Mixtures.

A portion (300 mg.) of each of the mixtures of the 1 and 2-methyl derivatives of the various *s*-triazolo[4,3-*a*]pyridinium iodides (Table I) was placed into pyrex tubes. The tubes were then evacuated and sealed, and were heated at the temperature and for

the time indicated in Table III. The contents of the pyrex tubes were dissolved in deuterium oxide and their NMR spectra were recorded and the pertinent features (N-CH<sub>3</sub> proton signals) are recorded in Table II.

#### Thermal Rearrangement of the Mixture of the 1- and 2-Methyl-*s*-triazolo[4,3-*a*]pyridinium Iodides in an Open Vessel.

A mixture (300 mg.) of the two isomeric parent methiodides was placed into a pyrex tube and the tube was evacuated ( $\cong 0.5$  mm Hg) while it was heated at 235° for 2.5 hours. A yellow oil which distilled and found by NMR (deuteriochloroform solution) to be *s*-triazolo[4,3-*a*]pyridine. The non-sublimable residue was found, by NMR (deuterium oxide solution) to be pure 1-methyl-*s*-triazolo[4,3-*a*]pyridinium iodide.

#### Thermal Rearrangement of the Mixture of 1,8-dimethyl-*s*-triazolo[4,3-*a*]pyridinium Iodide and 2,8-Dimethyl-*s*-triazolo[4,3-*a*]pyridinium Iodide in an Open Vessel.

A mixture (300 mg.) of the two isomeric methiodides was placed into a pyrex tube. This tube was then kept under vacuum ( $\cong 0.5$  mm Hg) and heated at 220° for 2.5 hours. Some chloroform soluble material sublimed. This solid was shown to be 8-methyl-*s*-triazolo[4,3-*a*]pyridine by its NMR spectrum. The nonsublimed residue was found to be (by NMR) a mixture of the 1,8-dimethyl methiodide and the 2,8-dimethyl methiodide in a ratio of 44:56 percent.

#### Cross-over Product Obtained From a Mixture of 8-Methyl-*s*-triazolo[4,3-*a*]pyridine and Pure 1-methyl-*s*-triazolo[4,3-*a*]pyridinium Iodide.

The pure isomeric 1-methyl derivative (0.355 g., 1.36 mmoles) of the parent compound was thoroughly mixed with 0.1 g. (0.75 mmole) of 8-methyl-*s*-triazolo[4,3-*a*]pyridine. The resulting mixture was then placed into a pyrex tube which was evacuated and sealed. The tube was then heated at 225° for 30 minutes. The reaction mixture was separated into ether soluble and ether insoluble material. The NMR spectrum of the ether insoluble material showed the presence of the N-1 methiodide of the *s*-triazolo[4,3-*a*]pyridine and a mixture of the N-1 and N-2 methiodides of the 8-methyl-*s*-triazolo[4,3-*a*]pyridine. The N-1 and N-2 methiodides of 8-methyl-*s*-triazolo[4,3-*a*]pyridine were formed to the extent of 0.38 mmole (determined by NMR) and in a ratio of 60:40 percent of the N-1 to the N-2 methiodide. The remaining methiodide (shown by NMR) corresponds to 0.98 mmole of the N-1 parent methiodide.

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- (4) This, of course, assumes the absence of any compensating effects due to charge changes on C-3. We consider this a reasonable assumption.
- (5) M. Hesse, *Fortschritte Der Chemischen Forschung*, **8**, 608 (1967).
- (6) NMR spectra were obtained with a Varian A-60 spectrometer (0.5 M solutions). The microanalyses were performed by Mrs. Wm. Decker of this department. Melting points are corrected.

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