

## A Study on the Ring Contraction of 5-Diazo-1-methyluracil-6-methanolate and a Convenient Method for Establishing the Site of Heterocyclic *N*-Substitution (1)

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Sir:

We recently reported (2) that *O*5'-6(S)-cyclo-5-diazouridine undergoes a novel ring contraction. We have now found that ring contraction of 5-diazo-1-methyluracil-6-methanolate (I) (3) gave a product with properties quite different from those reported (4) for 1-methyl-1,2,3-triazole-4-carboxamide (IV). In view of these differences, it appeared that I had undergone a reaction quite different from the ring contraction previously observed for *O*5'-6(S)-cyclo-5-diazouridine. This required us to initiate a study designed to unequivocally assign a structure to our product.

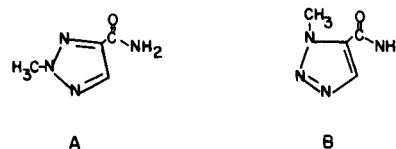
A solution of I (0.5 g.) in 5% aqueous acetonitrile (5) (15 ml.) was heated in a stainless steel reaction vessel at 100° for 3.5 hours and the solution was then allowed to stand at ambient temperature for 18 hours to afford a white solid. This solid was initially assumed to be IV. However, the physicochemical properties of our product were subsequently found to be different from those described for IV in the literature (4), e.g., m.p. 261-263°; uv  $\lambda$  max (water): 207 nm,  $\epsilon$ , 11,800 were obtained for our product while the reported (4) values for IV were: m.p. sublimes at 150-220°; uv  $\lambda$  max (water): 212 nm,  $\epsilon$ , 10,400.



Elemental analyses (CHN) were obtained for our product and found to be consistent with the empirical formula  $C_4H_6N_4O$  (6). This empirical formula was confirmed by a molecular ion at  $m/e$  126 in the mass spectrum. The pmr spectra (DMSO- $d_6$  and DMSO- $d_6$ -deuterium oxide) revealed the presence of a methyl group ( $\delta$  4.15), an aromatic proton ( $\delta$  8.50), and two broad exchangeable singlets ( $\delta$  7.53, 7.79) which were suggestive of an amide group. The presence of an amide group was corroborated by ir spectroscopy ( $3195\text{ cm}^{-1}$ ,  $3095\text{ cm}^{-1}$ ,  $\text{NH}_2$ ;  $1629\text{ cm}^{-1}$ ,  $\text{C=O}$ ), a positive hydroxylamine-ferric chloride test (7) and a loss

of  $-\text{CONH}_2$  ( $m/e$  82, M-44) in the mass spectrum.

These data were all consistent with a methyl-substituted, five-membered heterocyclic ring containing three nitrogens (triazole) and bearing a carboxamide substituent. However, since it was assumed (*vide supra*) that our product was not IV, there were only two possible structures (A and B) consistent with the observed properties.



Structure A was eliminated since the base peak in the mass spectrum of our compound occurred at  $m/e$  98 which corresponded to a loss of diatomic nitrogen without the concomitant loss of a methyl group. Therefore, the only remaining possibility was the isomeric structure B.

A perusal of the literature revealed that previous assignments for the position of alkylation of isomeric *N*-substituted triazoles have been made on the basis of solvent induced chemical shifts (8) of the aromatic ring proton and arguments based on combined proton/ $^{13}\text{C}$  magnetic resonance (9). We could not ascertain the actual site of alkylation for our compound by solvent induced chemical shifts since we did not have both of the *N*-methyl isomers.

Previous reports (10a-c, 11) have demonstrated that protonation of anionic nitrogen heterocycles effects an upfield chemical shift at adjacent ( $\alpha$ ) carbons and a downfield shift at  $\beta$ -carbons in 5- and 6-member ring systems as well as the bicyclic purine ring (12). Alkylation of the neutral specie produces similar shift changes in a wide range of heterocyclic systems (10d-f). While replacement of a labile proton by a methyl or  $\beta$ -D-ribofuranosyl group does not reproduce  $\alpha$ - and  $\beta$ -protonation parameters identical to those given in Ref. 10b, a study in our laboratories (10e-f) involving a large number of heterocyclic systems has shown that these effects are qualitatively preserved. Although the existence of tautomeric structures can complicate the

analysis (10a-c, 11) a comparison of the cmr shift data of the free base and the *N*-alkylated specie can still be used to establish the position of alkylation by a qualitative analysis of the  $\alpha$ ,  $\beta$ -substituent effects without resorting to a comparison with the appropriate anionic specie. This suggested that the structure of our product could be established by a comparison of the cmr spectrum of this compound with that of III. That the  $\alpha$  and  $\beta$  carbon chemical shift changes (*vide supra*) actually apply to *N*-substituted-1,2,3-triazole-4-carboxamides was first demonstrated by a study of compounds which were prepared by reported (2a, 13) procedures. The chemical shift assignments for C-5 in III - VI are straightforward by means of off-resonance decoupling (14). Differentiation between C-4 and the carboxamide group is possible by a comparison of II with III and noting

TABLE

Carbon-13 Chemical Shifts for Certain 1,2,3-Triazoles<sup>a,b</sup>

	CONH <sub>2</sub>	C-4	C-5	$\Delta^c$ C-4	$\Delta$ C-5
II <sup>d</sup>		130.4	130.4		
III	161.65	141.78	129.93		
IV	161.64	142.96	127.28	-1.18	+2.65
V <sup>e</sup>	161.53	143.34	125.01	-1.56	+4.92
VI <sup>f</sup>	158.97	131.64	134.63	+10.14	-4.70

(a) Chemical shifts are in ppm from TMS. *p*-Dioxane was used as internal reference and converted to the TMS scale using the relationship  $\delta_{\text{TMS/Dioxane}} = 17.5 \times 10^{-4} T (^{\circ}\text{C}) - 66.315$  (M. -T. Chenon and D. M. Grant, private communication). (b) All samples were dissolved in 1.75 ml. of DMSO-*d*<sub>6</sub> except IV which was dissolved in 2.5 ml. of DMSO-*d*<sub>6</sub>. The cmr spectra for III-V used 110 mg. samples while the spectrum of VI used a 153 mg. sample. (c)  $\Delta$  Represents the difference in chemical shift of III. (d) Ref. 14b; Chemical shift values were converted from the CS<sub>2</sub> scale using the relationship  $\delta_{\text{TMS}} = \delta_{\text{CS}_2} + 192.8$ . (3) R =  $\beta$ -D-ribofuranosyl. (f) For comparative purposes the carbon to which the amide group is attached has been numbered as C-4 rather than C-5.

the range of chemical shifts observed for -CONH<sub>2</sub> carbons reported in Ref. 15. In the Table it is noted that ribosylation of III at N-1 (V) produced an upfield shift at C-5 ( $\alpha$  carbon) and a downfield shift at C-4 ( $\beta$  carbon) while

ribosylation of III at N-3 (VI) produced a downfield shift at C-5 and an upfield shift at C-4. While the magnitude of the shift changes for our product were not identical to those obtained for V (due to small variations in the *N* substituent parameters for CH<sub>3</sub> and ribose; see Ref. 10e-f), the data demonstrated that the methyl group was located at N-1 since a 2.65 ppm upfield shift was observed at C-5 while C-4 shifted 1.18 ppm to lowerfield. Therefore, the structure of our product was established as 1-methyl-1,2,3-triazole-4-carboxamide (IV). The difference in physical properties between IV as reported (4) in the literature and IV obtained by ring contraction of I may be due to the presence of an isomeric impurity in the reported (4) compound.

The use of cmr in assigning the position of *N*-substitution as described in this paper represents a convenient method by which such assignments may be made in a wide variety of heterocyclic systems. This is the first report of the exclusive use of cmr for assigning the position of *N*-substitution based on a simple comparison with the neutral non-alkylated specie. This method may be more convenient and practical than the procedures currently described in the literature (8,9).

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