

THERMOLYSIS OF 4-PYRIDYLAZIDES LEADING TO THE SYNTHESIS OF
6H-1,4-DIAZEPINES

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Abstract- Thermolysis of a methanolic solution of 4-pyridylazides (1) at 200 °C for 8-12 min was found to give unstable but isolable 5-methoxy-6H-1,4-diazepines (4) and (5), along with 32-45% yield of 5,6-dihydro-6-methoxy-7H-tetrazolo[1,5-d][1,4]diazepines (6).

Little is known about the chemistry of 1,4-diazepines¹ except for their hydrogenated derivatives, and, in particular, nothing is known about less substituted and fully conjugated 6H-1,4-diazepines. A photochemical preparation of 5-methoxy-6H-1,4-diazepines from pyridylazides announced very recently by Sawanishi, *et al.*² prompted us to report our own results on the thermolysis of 4-pyridylazides (1) to provide less substituted and fully conjugated 6H-1,4-diazepines (4) and (5) in moderate yield.

Heating a methanolic solution (42 mmol/20 ml) of (1a) at 200 °C for 8 min³ as described earlier by us for azidoacetophenone⁴ and medium pressure liquid chromatography of the reaction mixture on alumina (pre-treated with ethyl acetate) with n-hexane-ethyl acetate (4:1) gave unstable and oily 5-methoxy-6H-1,4-diazepine (4a)^{5,6} and 4-methoxypyridine (10%). The structure of (4a) was consistent with its ¹H n.m.r.⁶ and other spectral data. Further elution with ethyl acetate afforded 5,6-dihydro-6-methoxy-7H-tetrazolo[1,5-d][1,4]diazepine (6a) (mp 144-145 °C)^{5,6} whose structure was established by an X-ray crystallographic analysis (Fig. 1).⁷

Thermolysis of a methanolic solution (45 mmol/20 ml) of the azide (1b) at 200 °C

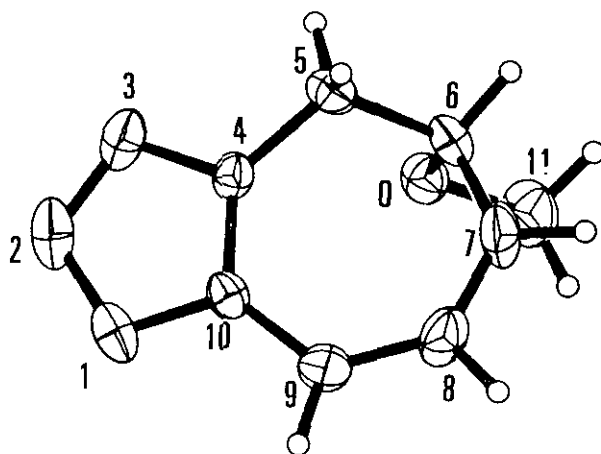
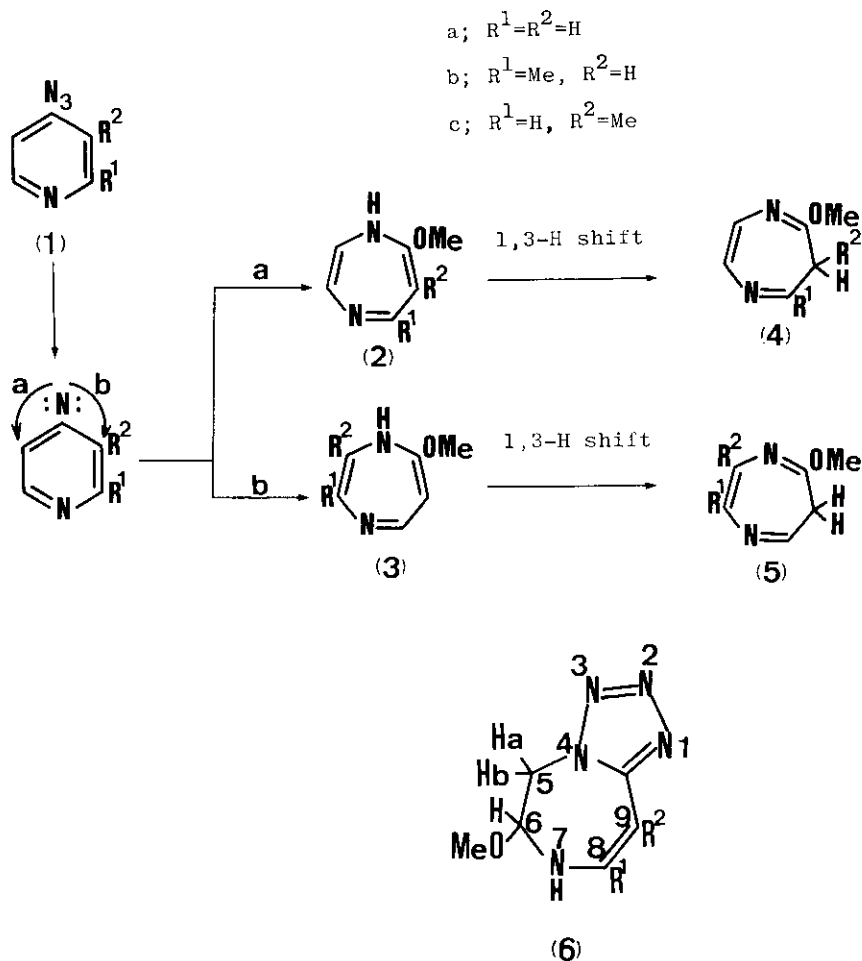


Fig. 1. Molecular structure of (6a).

for 9 min³ gave a 2:1 chromatographically inseparable mixture of the diazepines (4b) and (5b) in 74% yield⁸, whereas that of a solution (40 mmol/20 ml) of (1c) at 200 °C for 12 min³ yielded a 2:1 chromatographically separable mixture of the diazepines (4c)⁵ and (5c)⁵ in 40% yield^{8,9}, together with the tetrazolodiazepine (6c)⁵ (mp 127-128 °C) (32%⁸; 14%¹⁰) and 4-methoxy-3-methylpyridine (15%). The ¹H n.m.r. spectra (60 MHz, CDCl₃) of the diazepines (4c) and (5c) were distinguishable from each other; the Me signal was seen as a doublet (*J* 6 Hz) at δ 1.66 for (4c) and as a singlet at δ 2.06 for (5c), whereas the 6-H signal was observed as a one-proton multiplet at δ 1.75-2.11 for (4c) and as a two-proton doublet (*J* 5 Hz) at δ 2.91 for (5c).

However, from the thermolysate of a more concentrated solution of the azide [(1b) (280 mmol/40 ml) or (1c) (194 mmol/40 ml)] were obtained only the diazepine (4) [(4b)⁵ (20%⁸; 16%¹⁰) or (4c)⁵ (23%⁸; 15%¹⁰)] and the tetrazolodiazepine (6) [(6b)⁵ (mp 160-162 °C) (38%⁸; 33%¹⁰) or (6c) (45%⁸; 18%¹⁰)]. The structures of (6b) and (6c) were deduced from their ¹H n.m.r. spectra (60 MHz, CDCl₃) which had amongst others 5-H_a and 5-H_b at δ 4.04 (1H, d, *J* 13 Hz) and 5.05 (1H, dd, *J* 13 and 4 Hz) for (6b) and at δ 4.14 (1H, d, *J* 14 Hz) and 5.30 (1H, dd, *J* 14 and 5 Hz) for (6c), and also a single olefinic proton at δ 5.30 (1H, d, *J* 1 Hz) for (6b) and at δ 6.20-6.60 (1H, m) for (6c).

The diazepines are unstable even at room temperature, as shown by their short half-life times [(4a), 7 h; (4b), 49 h; (4c), 15 h; (5c), 12 h] determined by means of their ¹H n.m.r. spectrometry.



Ring expansion of the nitrene generated from the azide (1) could proceed in two directions to give 1H-1,4-diazepines (2) and (3), which lead to (4) and (5) after non-thermal 1,3-hydrogen shift.

Presence of a tetrazole ring fused to a diazepine ring in the molecule of (6) and detection of 4-methoxypyridine among the reaction mixture suggest that the 1,3-dipolar cycloaddition of the azide to an C=N bond of either (4) or (5) and loss of 4-methoxypyridine have occurred at some stage of a sequence of the reactions. We are now studying the mechanistic aspect of the formation of (6) in detail.

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1. F. D. Popp, *J. Heterocycl. Chem.*, 1974, 11, 79; H. Kolbinger, G. Reissenweber, and J. Sauer, *Tetrahedron Lett.*, 1976, 4321; H. D. Fuhlhuber and J. Sauer, *Tetrahedron Lett.*, 1977, 4389.
2. H. Sawanishi, K. Tajima, M. Osada, and T. Tsuchiya, 'Abstracts of Papers, 16th Congress of Heterocyclic Chemistry,' Osaka, 1984, p. 93.
3. The heating conditions are fairly critical.
4. Y. Ohba, S. Kubo, T. Nishiwaki, and N. Aratani, *Heterocycles*, 1984, 22, 457.
5. Satisfactory high resolution mass spectral determinations of M^+ (for the diazepines) and elemental analyses (for the tetrazolodiazepines) have been obtained.
6. Yields of (4a) and (6a), determined by integration of the MeO signals in the 1H n.m.r. spectrum of the crude reaction mixture, were 50% [based on 1 mol of (1a)] and 45% [based on 2 mol of (1a)], respectively. Yield of (4a) decreased substantially after chromatography. The tetrazolodiazepine (6a) had to be further purified by medium pressure liquid chromatography on Woelm silica gel with ethyl acetate followed by recrystallisation from chloroform. During the course of these works-up, it decomposed appreciably. Selected spectral data: (4a), $\delta_H(CDCl_3)$ (60 MHz) 2.96 (2H, d, J 5 Hz, 6-H), 3.75 (3H, s, MeO), 6.65 (1H, dd, J 5.5 and 1 Hz, 2-H), 6.72 (1H, dt, J 5 and 1 Hz, 7-H), and 6.96 (1H, d, J 5.5 Hz, 3-H); (6a), $\delta_H(CDCl_3)$ (200 MHz) 3.29 (3H, s, MeO), 4.23 (1H, dd, J 13.8 and 0.8 Hz, 5-H_a), 4.98 (1H, dddd, J 4.8, 4.8, 0.8, and 0.8 Hz, 6-H), 5.29 (1H, ddd, J 13.8, 4.8, and 0.8 Hz, 5-H_b), 5.66 (1H, dd, J 9.8 and 1.4 Hz, 9-H), 5.62-5.80 (1H, br s, 7-H), and 6.57 (1H, ddd, J 9.8, 7.0, and 0.8 Hz, 8-H).
7. Crystal data: $C_6H_9N_5O$, $M=167.17$; monoclinic, $a=19.625(3)$, $b=6.255(1)$, $c=14.053(2)$ Å, $\beta=105.77(1)^\circ$, $U=1660.3$ Å³, space group C 2/c, $Z=8$, $R=0.0450$ for 1501 independent reflections (measured on a Syntex R-3 diffractometer using $Mo-K_\alpha$ radiation). The structure was solved using Hitachi M200 with all computations except for MULTAN 78 being carried out using UNICS III.
8. Yield determined from the 1H n.m.r. spectrum of the crude reaction mixture.
9. Isolation yields of (4c) and (5c) were 15% and 3%, respectively, because of their decomposition during the course of chromatography.
10. Isolation yield.

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