Photochemistry of 4,6-Diazido-3-methylisoxazolo-[4,5-*c*]pyridine: a Convenient Entry to 3-Methylisoxazolo[1,3]diazepine Systems†

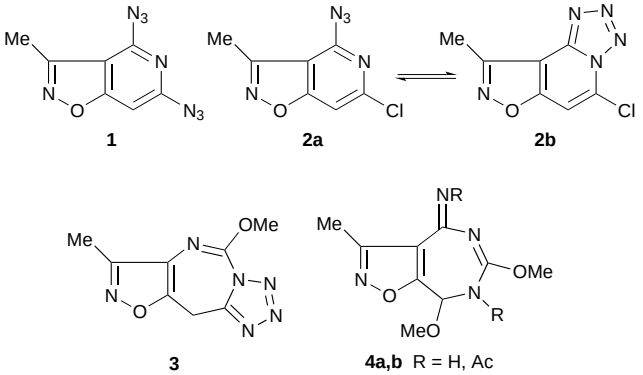
J. Chem. Research (S), 1997, 170–171†

Donato Donati, Stefania Fusi and Fabio Ponticelli*

Istituto di Chimica Organica, Università di Siena, pian dei Mantellini, 44, 53100 Siena, Italy

UV irradiation of 4,6-diazido-3-methylisoxazolo[4,5-*c*]pyridine in methanol gives the 3-methylisoxazolo-1,3-diazepine derivatives **3**,**4** by nitrogen loss and solvent addition.

Following our interest on the photochemistry of heterocycles,[1] we focused our attention on diazido-isoxazolopyridines, in view of the possibility of rearrangement of the isoxazole system[2] and fragmentation of the azide moiety.[3] In addition, cross-over photoreactions involving both processes might be expected. The photochemistry of aromatic azides has been largely investigated as a useful access to seven-membered aza-heterocycles.[3] However, no data have been reported on the photochemical behaviour of α,α'-diazidopyridines (simple or with condensed rings), in spite of the potential synthetic interest in obtaining larger polyazaheterocyclic rings.



Scheme 1

Reaction of 4,6-dichloro-3-methylisoxazolo[4,5-*c*]pyridine[4] with an excess of sodium azide gave the 4,6-diazido derivative **1** in good yield. When an equivalent amount of sodium azide was used, we obtained the diazide **1** and the unreacted dichloroisoxazolopyridine. Only a trace of the 4-azido-6-chloro-3-methylisoxazolo[4,5-*c*]pyridine **2** was formed, as indicated by the NMR spectrum of the reaction mixture. Compound **2** can be easily prepared from the corresponding 4-hydrazino derivative[4] and nitrous acid, the product existing in the solid state as the tetrazole tautomer **2b**, whereas the azide form **2a** is present in solution. In fact, only in the IR spectrum of a chloroform solution of this compound did we find a strong band at 2135 cm^{-1}, attributable to the stretching of the N_3 group. Also, compound **1** exists in solution mainly in the diazide form, since the ^1H and ^{13}C NMR and UV spectra (the last both in $CHCl_3$ and in methanol) are very similar to those of **2a**.

UV irradiation of **1** in methanol gave two main products, arising from **1** through the loss of one or two molecules of nitrogen followed by the addition of one or two molecules of the solvent. NMR and mass spectral analysis of both compounds did not allow any definitive conclusion about their structures. The complete configurational assignment of the isoxazolotetrazolodiazepine **3** was performed *via* X-ray crystallographic analysis (Fig. 1), using a crystal obtained by slow evaporation of an ethereal solution of this compound.

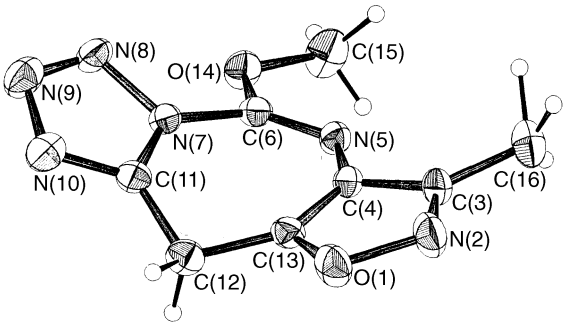


Fig. 1 X-Ray structure of compound **3**, with 30% probability thermal ellipsoids

In spite of several attempts using different solvents, we were unable to obtain well formed crystals of compound **4a**. However, acetylation of **4a** with acetyl chloride–triethylamine gave the diacetyl derivative **4b**, which from cyclohexane–diethyl ether afforded crystals suitable for X-ray crystallographic analysis (Fig. 2).

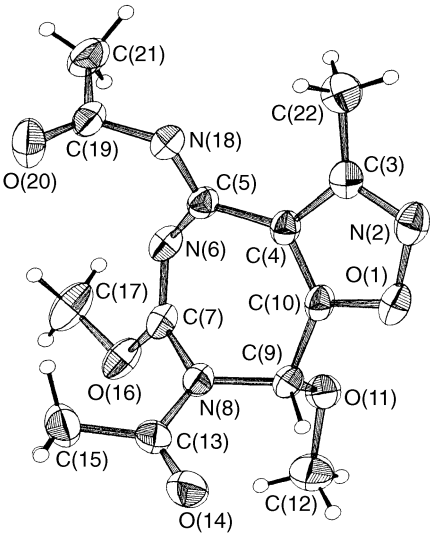


Fig. 2 X-Ray structure of compound **4b**, with 30% probability thermal ellipsoids

The formation of the diazepines **3** involves elimination of N_2 from the azido group in position 4, ring enlargement to a cyclic carbodiimide[3] and methanol addition. Similarly, in order to explain the formation of **4a**, we may suppose N_2 elimination from the azido group in position 6, ring enlargement and methanol addition, but in this case, the intermediate 4-azido diazepine decomposes and the resulting nitrene adds methanol without a second ring insertion.

*To receive any correspondence (*E-mail:* donati@unisi.it).

†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1997, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

‡Atomic coordinates, thermal parameters, and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Research (S)*, 1997, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 423/4.

It is to be noted that, unexpectedly, the isoxazole ring is not involved in these photochemical rearrangements.

These results show that this reaction is a good entry to the previously unknown isoxazolo[4,5-*d*]- and -[4,5-*e*]-[1,3]diazepine systems. Taking into account the easy opening of the isoazole moiety and the versatile addition on the intermediate carbodiimides, it is possible to prepare also several diazepine derivatives, a class of heterocycles with potential biological interest.[5]

Experimental

IR spectra were obtained, unless otherwise stated, for KBr discs with a Perkin-Elmer 782 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded for solutions in $CDCl_3$ on a Bruker AC 200 instrument operating at 200 MHz for ^{1}H and at 50 MHz for ^{13}C. Chemical shifts are given in ppm relative to internal $SiMe_4$. Electron-impact mass spectra (70 eV) were recorded on a VG 70 250S instrument. Photochemical reactions were carried out with a medium-pressure mercury immersion lamp (125 W) filtered and cooled with copper(II) sulfate solution (30 g dm^{-3}; cut off 300 nm); nitrogen was constantly bubbled through the irradiated solution. Diffractometer data were collected on a Siemens P4 diffractometer, at room temperature (293 ± 2 °K), using graphite monochromated MoKα radiation ($\lambda = 0.7107$) with the ω-scan technique and corrected for Lorentz and polarization effect, no absorption corrections. The structures were solved by direct methods and refined by full-matrix least-squares on F^2 using the program packages SHELXTL-PC[6] and SHELXL93.[7]‡

4,5-*Diazido*-3-*methylisoxazolo*[4,5-c]*pyridine* **1**.—Reaction of 4,6-dichloro-3-methylisoxazolo[4,5-*c*]pyridine[4] with an excess of sodium azide in propan-1-ol–water, 5:1 at 60 °C for 24 h gave compound **1** as a colourless *solid*, yield 88%, mp 71–72 °C (from ethanol–water); ν_{max}/cm^{-1} 3095 (CH), 2230, 2200, 2135 (N_3), 1610, 1590 and 1450; ν_{max}/cm^{-1} ($CHCl_3$), 2180, 2090; δ_H 2.56 (3 H, s, Me), 6.59 (1 H, s, 7-H); δ_C 11.0 (Me), 90.7 (C-7), 108.1 (C-3a), 149.0 (C-4), 153.6 (C-6), 153.8 (C-3), 171.1 (C-7a); *m*/*z* 216 (M^+, 34%), 160 (6), 107 (87), 79 (34), 67 (100) (Found: C, 39.0; H, 1.9; N, 51.6. $C_7H_4N_8O$ requires C, 38.9; H, 1.9; N, 51.8%).

5-*Chloro*-9-*methylisoxazolo*[4,5-c][1,2,3,4]*tetrazolo*[1,5-a]*pyridine* **2b**.—6-Chloro-4-hydrazino-3-methylisoxazolo[4,5-*c*]pyridine[4] (10 mmol) dissolved in 3 M hydrochloric acid (30 cm^3) was treated with sodium nitrite (10 mmol) and the mixture was repeatedly extracted with diethyl ether. Solvent evaporation and sublimation *in vacuo* gave compound **2b** as a colourless *solid*, yield 62%, mp 95–96 °C; ν_{max}/cm^{-1} 3060 (CH), 1650 (C=N), 1580, 1515; ν_{max}/cm^{-1} ($CHCl_3$) 2230, 2135; δ_H 2.59 (3 H, s, Me), 7.20 (1 H, s, 6-H); δ_C 11.2 (Me), 102.2 (C-6), 109.8 (C-9a), 149.7 (C-10), 149.8 (C-5), 153.9 (C-9), 170.4 (C-6a); *m*/*z* 209/211 (M^+, 42/14%), 181/183 (12/4), 146 (29), 114 (22), 88 (43), 67 (100) (Found: C, 39.9; H, 1.9; N, 33.6. $C_7H_4ClN_5O$ requires C, 40.1; H, 1.9; N, 33.4%).

Irradiation of Compound **1**.—Compound **1** (2 mmol) in methanol (100 ml) was irradiated until about half of the starting material had disappeared (TLC). Solvent evaporation and column chromatography on silica gel [chloroform–methanol 95:5 (v/v)] gave, after the unreacted compound **1** (0.8 mmol), 5-*methoxy*-7-*methyl*-10H-*isoxazolo*[5,4-f][1,2,3,4]*tetrazolo*[1,5-c][1,3]*diazepine* **3** as a white solid, yield 15%, mp 155–156 °C (from diethyl ether); ν_{max}/cm^{-1} 1700 (C=N), 1625, 1590, 1440; δ_H 2.34 (3 H, s, Me), 4.20 (3 H, s, OMe), 4.65 (2 H, s, CH_2); δ_C 8.9 (Me), 22.7 (C-10), 56.9 (OMe), 121.2 (C-6a), 141.3 (C-5), 150.5 (C-10a), 150.9 (C-9a), 158.4 (C-7); *m*/*z* 220 (M^+, 10%), 191 (3), 151 (14), 136 (9), 123 (46), 108 (100), 83 (18), 66 (69) (Found: C, 43.8; H, 3.7; N, 38.4. $C_8H_8N_6O_2$ requires C, 43.6; H, 3.7; N, 38.2%).

Crystal Data for **3**: $C_8H_8N_6O_2$, $M_r = 220.20$, orthorhombic, space group *Fdd*2, $a = 17.244(3)$, $b = 34.136(7)$, $c = 6.802(1)$ Å, $V = 4003.9(12)$ Å^3, $Z = 16$, $D_c = 1.461$ Mg m^{-3}, $F(000) = 1824$, $\mu = 0.112$ mm^{-1}, crystal dimensions $0.15 \times 0.20 \times 0.65$ mm. 1565 unique reflections were collected. Non-hydrogen atoms were refined as anisotropic, hydrogen atoms were located in the difference-Fourier map and refined as isotropic. Final $R_1 = 0.042$, $wR_2 = 0.091$ for 176 parameters. Largest difference peak in the Fourier map was 0.207 e.Å^{-3}, maximum shift/esd = 0.425 for *U*11 of H16A.

Further elution afforded 6,8-*dimethoxy*-3-*methyl*-5,6-*dihydro*-4H-*isoxazolo*[4,5-e][1,3]*diazepin*-4-*imine* **4a** as a yellowish solid, yield 25%, mp > 330 °C (from benzene–hexane); ν_{max}/cm^{-1} 3400 (NH), 3150br (NH), 1680 (C=N), 1635, 1610, 1550, 1520; δ_H 2.48 (3 H, s, Me), 3.57, 3.69 (each 3 H, 2 s, 2 × OMe), 5.63 (1 H, s, CH); δ_C 11.2 (Me), 54.8 (6-OMe), 55.5 (8-OMe), 82.5 (C-8), 106.2 (C-3a), 155.0 (C-4), 155.7 (C-6), 158.9 (C-3), 172.4 (C-8a); *m*/*z* 224 (M^+, 47%), 223 (16), 209 (59), 194 (70), 193 (100), 181 (79), 168 (28), 136 (40), 122 (18), 107 (26), 81 (32) (Found: C, 47.9; H, 5.2; N, 25.2. $C_9H_{12}N_4O_3$ requires C, 48.2; H, 5.4; N, 25.0%).

N-(7-*Acetyl*-6,8-*dimethoxy*-3-*methyl*-7,8-*dihydro*-4H-*isoxazolo*[4,5-e][1,3]*diazepin*-4-*ylidene*)*acetamide* **4b**.—To a solution of compound **4a** (1 mmol) in anydrous dichloromethane (16 cm^3) and triethylamine (0.3 cm^3) acetyl chloride (0.28 cm^3) was added. After 30 min, water was added and the organic layer was washed with water and evaporated to give, after column chromatography on silica gel with diethyl ether–hexane 3:1 (v/v), compound **4b** as colourless *crystals*, yield 78%, mp 141–142 °C (from cyclohexane–diethyl ether); ν_{max}/cm^{-1} 1717 (CO), 1709 (CO), 1660, 1640, 1605, 1435; δ_H 2.21, 2.32 (each 3 H, s, 2 × MeCO), 2.48 (3 H, s, Me), 3.54, 3.93 (each 3 H, 2 s, 2 × OMe), 6.74 (1 H, s, CH); δ_C 11.6 (Me), 22.9, 25.0 (2 × *Me*CO), 76.8 (C-8), 112.6 (C-3a), 144.0 (C-4), 149.5 (C-6), 159.5 (C-3), 167.5 (C-8a), 169.2, 185.8 (2 CO); *m*/*z* 308 (M^+, 10%), 293 (38), 251 (100), 225 (36), 219 (34), 191 (18), 43 (79) (Found: C, 50.4; H, 5.1; N, 18.2. $C_{13}H_{16}N_4O_5$ requires C, 50.6; H, 5.2; N, 18.2%).

Crystal data for **4b**. $C_{13}H_{16}N_4O_5$, $M_r = 308.30$, monoclinic, space group *C*2/*c*, $a = 16.580(1)$, $b = 11.750(1)$, $c = 16.664(1)$ Å, $\beta = 101.05(1)°$, $V = 3109.1(4)$ Å^3, $Z = 8$, $D_c = 1.317$ Mg m^{-3}, $F(000) = 1296$, $\mu = 0.103$ mm^{-1}, crystal dimensions $0.20 \times 0.45 \times 0.60$ mm. 5314 reflection were collected with 4464 unique reflections ($R_{int} = 0.0160$). Non-hydrogen atoms were refined as anisotropic. Hydrogen atoms were located in the difference Fourier map and refined as isotropic with a common displacement parameter free to refine for the methyl groups. Final $R_1 = 0.051$, $wR_2 = 0.138$ for 249 parameters. Largest difference peak in the Fourier map was 0.232 e Å^{-3}, maximum shift/esd = 0.103 for y/b of H17C.

The availability of the mass spectrometer and of the X-ray diffractometer in the 'Centro di Analisi e Determinazioni Strutturali' of the University of Siena is gratefully acknowledged. This work was supported by the 'Ministero dell'Università e della Ricerca Scientifica e Tecnologica' (MURST).

Received, 16th December 1996; Accepted, 3rd February 1997
Paper E/6/08413C

References

1 D. Donati, S. Fusi and F. Ponticelli, *Tetrahedron Lett*., 1996, **37**, 5783 and references cited therein.
2 D. Donati, F. Ponticelli, P. Bicchi and M. Meucci, *J. Phys. Chem*., 1990, **94**, 5271.
3 A. Reisinger and C. Wentrup, *Chem. Commun*., 1996, 813 and references cited therein; J. C. Hayes and R. S. Sheridan, *J. Am. Chem. Soc*., 1990, **112**, 3879; C. J. Shields, D. R. Chrisope, G. B. Schuster, A. J. Dixon, M. Poliakoff and J. J. Turner, *J. Am. Chem. Soc*., 1987, **109**, 4723; C. Wentrup and H. W. Winter, *J. Am. Chem. Soc*., 1980, **102**, 6161; Y. Z. Li, J. P. Kirby, M. W. George, M. Poliakoff and G. B. Schuster, *J. Am. Chem. Soc*., 1988, **110**, 8092.
4 G. Adembri, A. Camparini, F. Ponticelli and P. Tedeschi, *J. Chem. Soc*., *Perkin Trans. 1*, 1975, 2190.
5 R. I. Fryer and A. Walser, in *Bicyclic Diazepines*, ed. R. I. Fryer, John Wiley, New York, 1991, pp. 130–131.
6 G. M. Sheldrick, SHELXTL-PC, Siemens Analytical X-Ray Instruments, Madison, Wisconsin, USA, 1990.
7 G. M. Sheldrick, SHELXL93, Program for Crystal Structure Solution, University of Gottingen, Germany, 1993.