Tetrahedron Letters No. 16, pp 1487 - 1490, 1974. Pergamon Press. Printed in Great Britain.

THIADIAZEPINONES: SYNTHESIS AND STABILITY

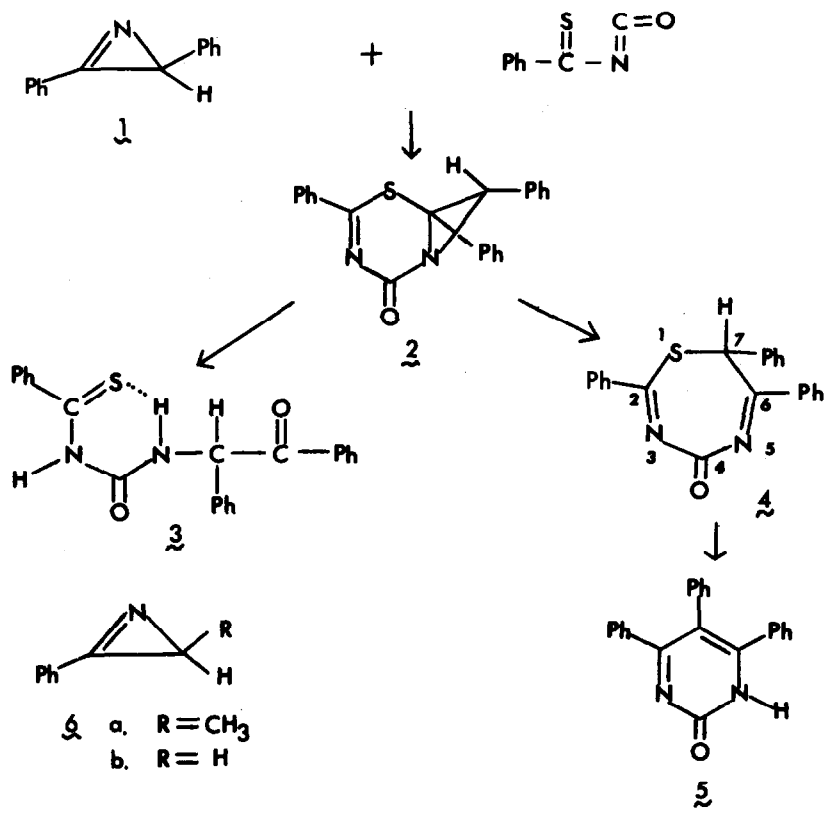
V. Nair* and K. H. Kim
Department of Chemistry, University of Iowa, Iowa City, Iowa 52242

(Received in USA 4 February 1974; received in UK for publication 5 March 1974)

The hypnotic and sedative properties of diazepines and benzodiazepines have resulted in a considerable amount of synthetic, pharmacological, and clinical activity in this area of chemistry.[1-4] Our recent contributions in the area of thermal symmetry-allowed cycloadditions of 1-azirines[5,6] prompted the investigation of the interaction of 1-azirines with isocyanates, and in particular, thiobenzoyl isocyanate.[7-10] We discovered that 1-azirines participated in cycloadditions with thiobenzoyl isocyanate under room temperature conditions to give exclusively [4 + 2] cycloadduction.[11] Thermolytic rearrangement of these cycloadducts gave thiadiazepinones.

Thus, when 2,3-diphenyl-1-azirine (1) was treated with thiobenzoyl isocyanate in p-xylene at room temperature for 12 hr, and the product carefully purified by preparative layer chromatography, the cycloadduct (2) was obtained as white rectangular crystals in 85% yield, mp 154-155. Substantiation of this structure came from analytical and spectroscopic data and chemical transformations. The cycloadduct gave a mass spectral parent ion current at m/e 356 and fragments corresponding to the azirine and the thiobenzoyl isocyanate moieties. Its infrared spectrum (Nujol) showed amide carbonyl absorption at 1720 cm^{-1} and C=N absorption at 1550 cm^{-1}. Its ^{1}H nmr spectrum (in $CDCl_3$) showed considerable deshielding of the aziridine proton (singlet at δ 4.46)[12] and the aromatic protons appeared as a multiplet between δ 7.10 and 8.17. Its ^{13}C nmr spectrum was consistent with the assigned structure.

The regiospecificity of the addition as well as the structure was confirm-



ed by the formation of urea (3) (yellow plates, mp 199-201) on acid hydrolysis of (2). A remarkable observation in the ^{1}H nmr spectrum of (3) was the relatively very slow rate of deuterium exchange of one of the urea hydrogens[13] suggesting the presence of intramolecular hydrogen bonding as shown in structure (3). That this was indeed the case was shown by the diagnostic infrared shift of the hydrogen bonded N-H to 2400 cm^{-1} on deuteration.[14,15]

Controlled thermolysis of the cycloadduct (2) at 80°C gave (4) as yellow prisms, mp 165-167, in 67% yield. The thiadiazepinone structure proposed for (4) was consistent with its mass spectrum (m/e 356, 324, 253, 193, 163, 121, 103), its infrared spectrum in Nujol (1725, 1650 cm^{-1}) and its ^{1}H nmr spectrum in $CDCl_3$

[δ 7.22 to 8.40 (m, 15H), 8.62 (s, 1H)].[16] The ^{13}C nmr spectrum (in $CDCl_3$) provided final spectroscopic confirmation [δ 91.67 (C-7), singlets between 127.44 and 139.42 (phenyl carbons), 162.94 (C-6), 189.27 (C-2), 194.12 (C-4)].

Prolonged thermolysis of (4) resulted in extrusion of elemental sulfur to give a pyrimidine derivative which exists predominantly in the keto form (5).

These studies were extended to two other representative 1-azirines, 3-methyl-2-phenyl-1-azirine (6a) and 2-phenyl-1-azirine (6b).

Acknowledgement - Acknowledgement is made to the donors of the Petroleum Research Fund administered by the American Chemical Society for partial support of this research. We are indebted to the National Science Foundation for providing funds towards the purchase of a Bruker HX-90E PFT NMR Spectrometer.

REFERENCES

1. H. G. Mautner and H. C. Clemson, in "Medicinal Chemistry", A. Burger, Ed., Wiley, New York, N.Y., 1970, p. 1365.

2. L. H. Sternbach, L. O. Randall, R. Banziger, and H. Lehr, in "Drugs Affecting the Central Nervous System", A. Burger, Ed., Dekker, New York, N.Y., 1968, p. 237.

3. G. A. Archer and L.H. Sternbach, Chem. Rev., 68, 747 (1968).

4. J. A. Moore and E. Mitchell, "Heterocyclic Compounds", Vol. 9, Wiley, New York, N.Y., 1967, p. 224.

5. V. Nair, J. Org. Chem., 37, 802, 2508 (1972).

6. V. Nair, Tetrahedron Lett., 4831 (1971).

7. J. Goerdeler and H. Schenk, Chem. Ber., 98, 2954 (1965).

8. O. Tsuge and K. Sakai, Bull. Chem. Soc. Japan, 45, 1534 (1972).

9. O. Tsuge and S. Kanemasa, Bull. Chem. Soc. Japan, 45, 2877, 3591 (1972).

10. O. Tsuge and S. Kanemasa, Tetrahedron, 28, 4737 (1972).

11. cf a) A. Hassner, A. S. Miller, and M. J. Haddadin, Tetrahedron Lett., 1353 (1972)

    b) A. Hassner, M. J. Haddadin and A. B. Levy, Tetrahedron Lett., 1015 (1973).

12. This type of deshielding has been observed on a number of occasions by us and others - see Reference 5.

13. The urea hydrogens exhibit broad resonances (in $CDCl_3$) at δ 9.87 (singlet) and at δ 10.47 (doublet, J = 6.9 Hz).

14. L. J. Bellamy, "The Infrared Spectra of Complex Molecules", Wiley, New York, N.Y., 1960, p. 207.

15. This marked difference in rate of deuterium exchange is also present in the urea from the benzoyl isocyanate adduct. Exchange of the hydrogen bonded N-H in D_2O is rapid as expected when a drop of triethylamine is added.

16. The marked downfield shift of the C-6 hydrogen is unusual but not entirely without precedence as we have observed this type of behavior with phenyl substituted azepines - see Reference 5.

17. All new compounds gave satisfactory elemental analyses.