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C(3)-AZIDO CEPHEM II

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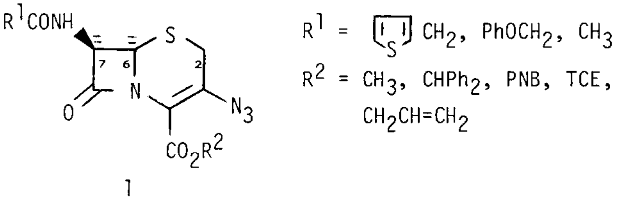
Abstract: The major product from the thermolysis and photolysis of C(3)-azido cephem 2 is the ring expanded 1,4,6-thiadiazepine azetidinone.

Azides are known to undergo thermal and photochemical decomposition to give nitrenes which can then rearrange to give diverse products.

We recently investigated the reaction of the C(3)-azido cephem 1 with nucleophiles and dipolarophiles to give a variety of C(3)-substituted amino cephem products.[1] In this communication we describe the thermolysis and photolysis of 2.

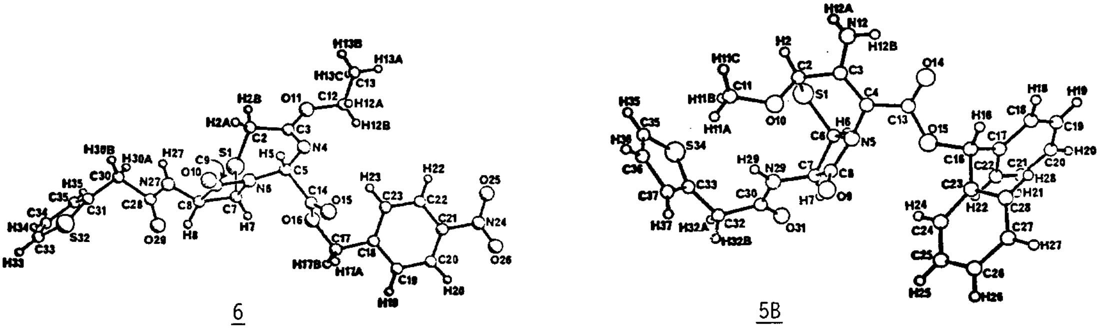


1

It is known that the decomposition temperature of azides decreases in the order of alkyl and aryl azides (150-200°) > azidoformates and sulfonyl azides (100-150°) > acyl azides (25-80°).[2] We considered the C(3)-azido cephem 1 to be a vinylogous acyl azide thereby presumably decreasing the $N-N_2$ double bond character and making this azide thermally less stable than a vinyl or alkyl azide. Indeed, the methanolysis of 2A in 1:1 methanol/acetone occurred at 65° within 1 hr. Although silica tlc showed four products, only three were isolated following silica chromatography and all three contained the β-lactam as judged by ir (1773-1778 cm^{-1}). Isomers I[3], II[4], and III[5], listed in the order of elution, were all isomeric by mass spec, with a molecular weight corresponding to addition of methanol and loss of nitrogen.

The UV spectrum of isomer I showed the absence of the β-amino-α-β-unsaturated ester[6] while the nmr spectrum showed a low field proton (6.1 δ), the AB of the C(2)methylene at 3.10, 3.50 δ (J=14 Hz) and the presence of the methoxyl at 3.65 δ. The β-lactam protons and the PNB protons appeared together as a multiplet. However, MCPBA oxidation of 3A gave a crystalline sulfoxide[7] (191-192°D) whose nmr spectrum showed clean separation of the PNB protons from the β-lactam protons. From this data we concluded that isomer I had structure 3A, i.e., a ring expanded derivative. Indeed, the ethanolysis of 2A gave a crystalline (154-155°)

derivative (33%) which was appropriate for X-ray analysis and its structure was determined to be 6[8], i.e., the C(3)-ethoxy derivative of isomer I.



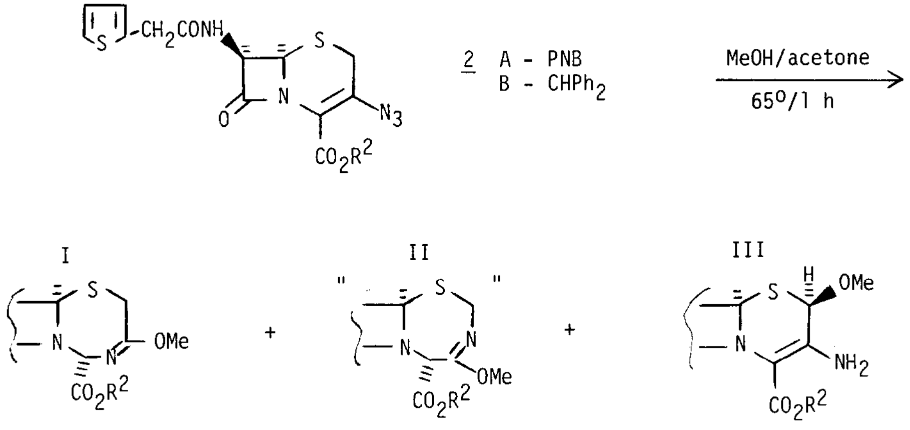
6 5B

Atom numbering scheme and solid-state conformation

Methanolysis of other esters of 2 also gave crystalline derivatives of isomer I, for example, the allyl ester (125-127°) and the benzhydryl ester (186-187°).

Isomer II could not be obtained crystalline and MCPBA oxidation led to degradation. Physical data suggests 4 as a possible structure.

Isomer III was identified from physical data[5] and by X-ray analysis of its benzhydryl ester derivative 5B[9] to be 5.

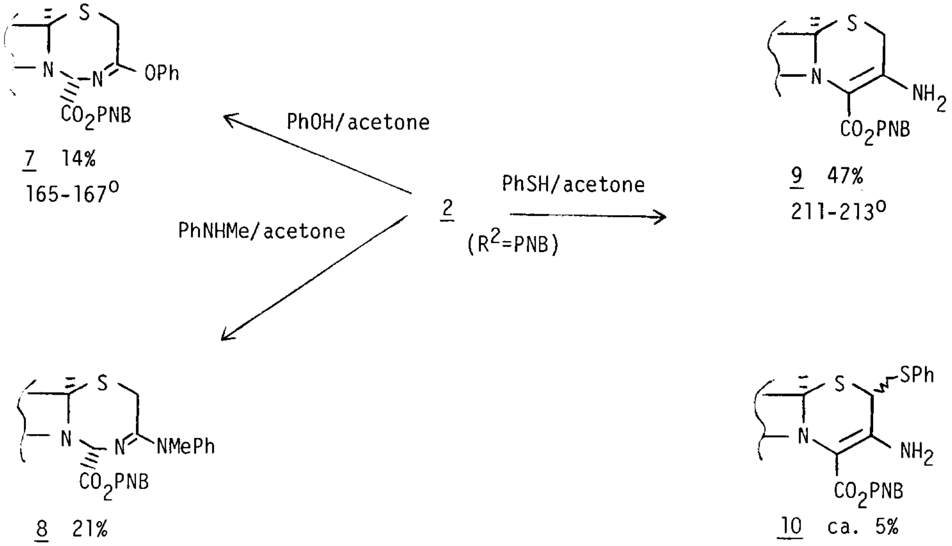


3 A 20% B 25%

4 A 12% B 9%

5 A 8% B 10%

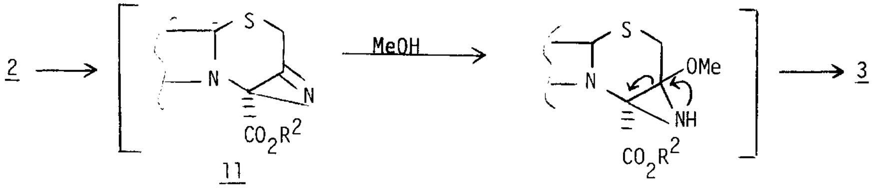
Other nucleophiles have been used with 2 (R^2=PNB) in addition to methanol and ethanol. Phenol gave a crystalline derivative of isomer I, 7[10] (165-167°), while N-methylaniline gave the corresponding ring expanded derivative 8[11] in 21% yield, and thiophenol gave 47% C(3)-amino cephem 9[12] (211-213°) and ca. 5% 10. There is ample precedence in the literature for the reduction of azides by mercaptans.[13]



The sodium salts of isomers I, II and III and compound 8 showed poor microbiological activity relative to cephalothin.

In a preliminary study, photolysis[14] of 2 (R^2=PNB, $CHPh_2$, Me) gave isomer I (27%, 17%, 6%), none of isomer III and only a trace of isomer II (where R^2=Me).

Formation of the two known structures, isomers I and III, from the methanolysis of the C(3)-azido cephem can be explained by the formation of a nitrene. Isomer I, we feel, is derived from the azirine 11, which could be formed by either a synchronous mechanism or by formation of a discrete nitrene. Methanolysis of the azirine followed by rearrangement would then give isomer I. Formation of isomer III can be explained by C(2)-H bond insertion of the singlet nitrene followed by methanolysis. Products resulting from C-H bond insertion are normally taken as evidence for the existence of a discrete nitrene intermediate.[15]



References and Notes

1. C(3)-Azido Cephem. I. D. O. Spry and A. R. Bhala, submitted to J. Org. Chem. (1984).
2. G. L'abbe, Chem. Rev., 69, 345 (1969).
3. Isomer I, 3A: m/e 504; ir ($CHCl_3$) 1773 cm^{-1}; UV (ETOH) 237 nm, ε 12,250, 268 nm, ε 10,200; nmr ($CDCl_3$) δ 3.10, 3.50 (AB, J=14 Hz, 2, C(2) protons), 3.65 (s, 3, OMe), 3.83 (s, 2, thiophene methylene), 5.38 (m, 4, H_7, H_8, PNB), 6.05 (s, 1, H_5).

4. Isomer II, 4A: m/e 504; ir ($CHCl_3$) 1775 cm^{-1}; UV (ETOH) 235 nm, ε 13,500, 277 nm, ε 13,000: nmr ($CDCl_3$) 3.63 (s,3, OMe), 3.83 (s, 2, thiophene methylene), 4.33, 4.55 (AB, J=14 Hz, 2, C(2) protons), 5.1-5.6 (m, H_5, H_7, H_8, PNB).
5. Isomer III, 5A: white crystals from CH_2Cl_2/hexanes, m.p. 236°D; m/e 504; ir ($CHCl_3$) 1778 cm^{-1}; UV (ETOH) 235 nm, ε 14,800, 291-293 nm, 17,000; nmr (DMSOd$_6$) δ 3.33 (s, 3, OMe), 3.92 (s, 2, thiophene methylene), 5.1 (s, 1, C(2)H), 5.14-5.3 (m, 4, H_6, H_7, PNB).
6. UV of 9: (ETOH) 236 nm, ε 14,500- thiophene, 286 nm, ε 19,000, see ref. 12.
7. Sulfoxide of 3A: white needles from CH_2Cl_2/hexanes, m.p. 191-192°D; m/e 520; ir (KBr) 1778 cm^{-1}; UV (ETOH) 235 nm, ε 12,400, 262 nm, ε 9,900; nmr (DMSOd$_6$) δ 3.60 (s, 3, OMe), 3.83 (s, 2, thiophene methylene), 4.27 (s, 2, C(2) protons, 5.40 (s, 2, PNB), 5.42 (d, J=4 Hz, 1, H_7), 5.70 (d, d, J=4, 8 Hz, 1, H_8), 6.27 (s, 1, H_5).
8. 6: white crystals from MeC(O)Et/hexanes, m.p. 154-155°); m/e 518, 338; ir ($CHCl_3$) 1775 cm^{-1}; UV (ETOH) 232 nm, ε 11,510, 266 nm, ε 8,200; nmr ($CDCl_3$/DMSOd$_6$) δ 1.23 (t, J=8 Hz, 3, OEt), 3.33 (s, 2, C(2) protons), 3.80 (s, 2, thiophene methylene), 4.1 (m, OEt), 5.42(m, 4, PNB, H_7, H_8), 6.13 (s, 1, H_5); X-ray data: $P2_1$, 2 molecules/cell, a = 13.123 ± 0.003 A, b = 5.291 ± 0.001 A, c = 17.315 ± 0.006 A, β = 100.95 ± 0.02, V = 1180.5 ± 0.5 A^3, 1938 reflections (CuK$_\alpha$) with no absorption correction, final R = 0.104. Supplementary data has been submitted for deposition at Cambridge Crystallographic Data Center.
9. X-ray data on 5B: $P2_12_12_1$ 4 molecules/cell, a = 10.912 ± 0.002 A, b = 8.691 ± 0.001 A, c = 27.996 ± 0.004 A, V = 2655.1 ± 0.8 A^3, 1627 reflections (CuK$_\alpha$) with no absorption corrections, final R = 0.064. Supplementary data has been submitted for deposition at Cambridge Crystallographic Data Center.
10. 7: white needles from CH_2Cl_2/hexanes, m.p. 165-167°; m/e 566; ir (KBr) 1779 cm^{-1}; UV (ETOH)-not completely sol., 235 nm, ε 7,500; nmr (DMSOd$_6$) δ 3.80 (s, thiophene methylene), 5.37 (m, H_7, H_8, PNB), 6.08 (s, 1, H_5).
11. 8: m/e 579; ir (KBr) 1771 cm^{-1}; nmr (DMSOd$_6$) δ 3.20 (s, 3, Me), 3.34 (s, 2, C(2) protons); 3.75 (s, 2, thiophene methylene), 5.3-5.5 (m, 4, H_7, H_8, PNB), 6.16 (s, 1, H_5), 9.14 (d, J=8 Hz, 1, NH).
12. 9: from CH_2Cl_2/acetone/hexanes, m.p. 211-213°; m/e 474; ir (KBr) 1762 cm^{-1}; UV (ETOH) 236 nm, ε 14,500-thiophene, 286 nm, ε 19,000-PNB + conj. amino; nmr (DMSOd$_6$ δ 3.08, 3.42 (AB, J=11 Hz, 2, C(2) protons), 3.76 (s, 2, thiophene methylene), 5.20 (m, 4, H_6, H_7, PNB), 7.6 (Bs, NH_2).
13. (a) H. Bayley, D. N. Standring, and J. R. Knowles, Tetrahedron Letters, 3633 (1978), (b) T. Adachi, Y. Yamada, I. Inoue, and M. Saneyoshi, Synthesis, 45 (1977), (c) J. A. Edwards, A. Guzman, R. Johnson, P. J. Beeby, and J. H. Fried, Tetrahedron Letters, 2031 (1974).
14. Conditions for the photolysis of 2 (R^2=PNB): 0.501 g (1.0 mm) in 25 ml CH_2Cl_2 plus 1700 ml MeOH photolyzed under Ar 7 min. using a 450 W. Hanovia lamp with a pyrex immersion apparatus.
15. W. Lwowski, Ed., "Nitrenes", Wiley-Interscience, New York, N.Y., (1970), p. 4-5.

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