Azidocubanes. 1. Photolysis: Formation of a Homoprismyl Nitrile

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Direct ultraviolet excitation of saturated azides results in dinitrogen loss, rearrangement, and imine formation.[1] When the azide group is a substituent on certain polycyclic systems, the reaction can lead to exceptionally strained, anti-Bredt, bridgehead imines in seven- or even six-membered rings.[2] Such systems are not stable under ordinary conditions. They have been characterized only by trapping or, more definitively, by low-temperature matrix-isolation spectroscopy.[3] In this paper we report on the behavior of 1-azido-4-methylcubane (**1**). Were **1** to behave like other azides, photolysis would give the azahomocubene **2**, in which the imine double bond would be at a bridgehead within five-membered rings and so twisted that, were there none of the expected rehybridization,[3a,4] the classical p-orbitals of the "double bond" would be essentially orthogonal.

The usual methods for azide synthesis are inapplicable to the synthesis of **1**. Obviously, backside displacement of a cubyl halide by azide ion is impossible. Reaction of a cubyl lithium with an azide transfer reagent is impractical in light of the kinetic difficulties in preparing unstabilized metallocubanes.[5] Cubyl diazonium compounds can be prepared easily enough but are not useful precursors of the desired azide. As aminocubanes suffer rapid degradation in base, reaction of a metal salt of the amine with diazo transfer reagents is not a feasible route to cubyl azides. Fortunately, trifluoromethanesulfonyl azide, developed by Cavender and Shiner,[6] is so exceptionally electrophilic that with it diazo transfer can be accomplished directly to cubyl amines themselves.

1-Amino-4-methylcubane was made from the known[7] carboxylic acid by using the Yamada approach to the Curtius rearrangement, as described already for the synthesis of 1,4-diaminocubane.[8] Treatment of the amine in CH_2Cl_2 solution with 2–3 equiv of triethylamine followed by the same amount of preformed trifluoromethanesulfonyl azide in CH_2Cl_2 gave **1** in 74% yield as a transparent, viscous oil: IR $(CHCl_3)$ ν 2102, 1297, 1278 cm^{-1}; UV (CH_3CN) λ_{max} (approximate ϵ) 288 (40), 235 (900, shoulder), 196 nm (5000).

Figure 1. IR spectra in argon matrix. Bottom: (dashed) **1**, 12 K; (full) **4**, 12 K. Stacked plots: (a) photolysate of **1** (ca. 90% conversion) at 12 K, which was then warmed and held successively for (b) 1.6 h at 25 K, (c) 14.9 h at 25 K, (d) 2.7 h at 28 K, (e) 1.9 h at 32 K, and (f) 3.0 h at 32 K. Top: **4**, 12 K (same at 25 K). Absorbance scale for stacked plots is constant; that of top and bottom spectra, chosen for clarity of illustration.

Unlike adamantyl azide, etc., **1** is frangible and can be dangerous. On the one occasion manual transfer of neat material was attempted, contact of the 5-mg sample with a sharp-edged glass pipet resulted in a detonation of great brisance. Thermal decomposition in CD_3OD, however, occurred smoothly at 100 °C in less than 1 h, giving principally the carbinol amine derivative **3**.[9] This reactivity again sets **1** into a special position; azides of other polycycles require higher temperatures and longer reaction times to effect thermal decomposition.[10] We shall treat the thermolysis of **1** in more detail in a latter paper.

Upon direct UV irradiation[11a] of **1** in CD_3OD at ≤5 °C there was only insignificant production of **3**, quite unlike what would be expected had the azide behaved photochemically like earlier examples. The photolysis took instead an entirely new course; the homoprismane nitrile **4** was formed in 60% (NMR)–80% yield (standardized GC analysis).[12] Irradiation of the azide in degassed CD_2Cl_2 gave the same nitrile in 80% yield consistently.

(1) Wentrup, C. In *Azides and Nitrenes*; Scriven, E. F. V., Ed.; Academic: Orlando, FL, 1984; pp 399–402. Kyba, E. P. *Ibid.* pp 26–28.

(2) For a review of anti-Bredt olefins, see: Szeimies, G. In *Reactive Intermediates*; Abramovitch, R. A., Ed.; Plenum: New York, 1983; pp 329–359.

(3) Recent examples: (a) Radziszewski, J. G.; Downing, J. W.; Jawdosiuk, M.; Kovacic, P.; Michl, J. *J. Am. Chem. Soc.* **1985**, *107*, 594. (b) Radziszewski, J. G.; Downing, J. W.; Wentrup, C.; Kaszynski, P.; Jawdosiuk, M.; Kovacic, P.; Michl, J. *J. Am. Chem. Soc.* **1985**, *107*, 2799. (c) Radziszewski, J. G.; Downing, J. W.; Wentrup, C.; Kaszynski, P.; Jawdosiuk, M.; Kovacic, P.; Michl, J. *J. Am. Chem. Soc.* **1984**, *106*, 7996. (d) Sheridan, R. S.; Ganzer, G. A. *J. Am. Chem. Soc.* **1983**, *105*, 6158. (e) Dunkin, I. A.; Shields, C. J.; Quast, H.; Seiferling, B. *Tetrahedron Lett.* **1983**, *24*, 3887. (f) Sasaki, T.; Eguchi, S.; Okano, T.; Wakata, Y. *J. Org. Chem.* **1983**, *48*, 4067. (g) Jawdosiuk, M.; Kovacic, P. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2583.

(4) Bonačič-Koutecký, V.; Michl, J. *Theor. Chim. Acta* **1985**, *68*, 45.

(5) (a) Eaton, P. E.; Castaldi, G. *J. Am. Chem. Soc.* **1985**, *107*, 724. (b) Della, E. W.; Pigou, P. E. *J. Am. Chem. Soc.* **1984**, *106*, 1085.

(6) Cavender, C. J.; Shiner, V. J., Jr. *J. Org. Chem.* **1972**, *37*, 3567. We thank Prof. Shiner for providing additional information.

(7) (a) Edward, J. T.; Farrell, P. G.; Langford, G. E. *J. Am. Chem. Soc.* **1976**, *98*, 3075. (b) Eaton, P. E.; Cole, T. W. Jr. *J. Am. Chem. Soc.* **1964**, *86*, 962, 3157.

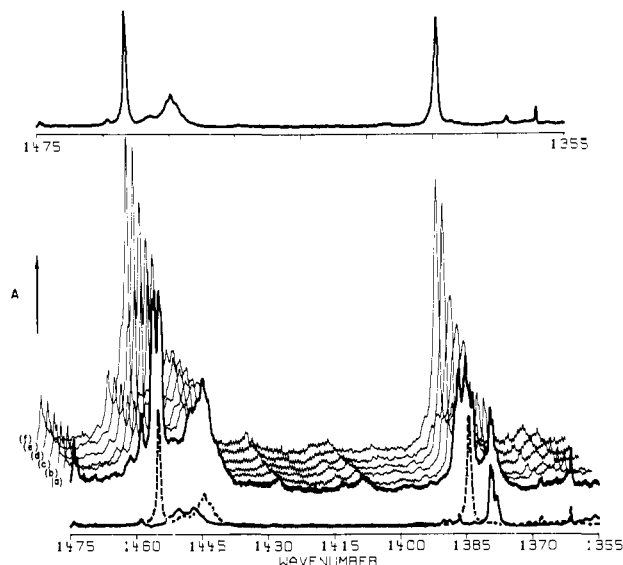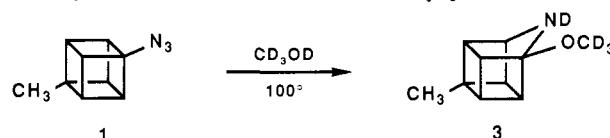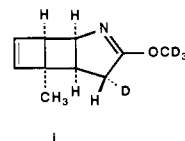(8) Eaton, P. E.; Ravi Shankar, B. K. *J. Org. Chem.* **1984**, *49*, 185.

(9) A small amount of nitrile **4** (<3%) was also formed (cf.: Szeimies, G.; Harnisch, J. *Chem. Ber.* **1979**, *112*, 3914) along with about 15% of the *O*-methyl imidate i.


(10) Cf.: Lwowski, W.; Reed, J. O. *J. Org. Chem.* **1971**, *36*, 2864.

(11) (a) Focused Osram HB0500W source; water and Pyrex filters. (b) Same source; water, Schott #UG5 black glass, and Melles Griot #03F1M022 290-nm interference filters.

(12) A few percent each of i–iii was also formed. On xanthone-sensitized photolysis ii was produced in about 13% yield; **4**, in 50% yield; **3** and i were not found in measurable amounts.
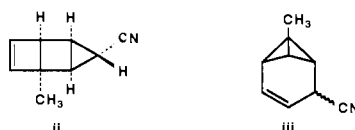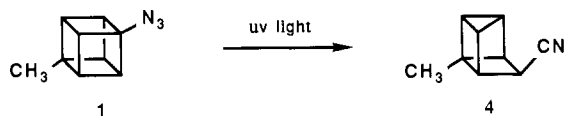
Nitrile **4** is one of the very few examples of the homoprismane (isoquadricyclane) system[13] and the first, to our knowledge, for which the available spectroscopic information permits an unambiguous assignment of structure:[14] ^{1}H NMR (CDCl$_3$, 500 MHz) δ 3.18 (m, 2 H), 2.72 (t, 1 H), 2.67 (t, 1 H), 2.58 (m, 2 H), 0.99 (s, 3 H) ppm; ^{13}C NMR (CDCl$_3$, 50 MHz) δ 120 (s), 55.0 (s), 51.3 (d, J = 161 Hz), 35.2 (d, 188 Hz), 33.5 (d, 145 Hz), 21.1 (d, 184 Hz), 13.9 (q, 125 Hz) ppm; IR (gas) ν 3080, 2236 cm^{-1}.

One obvious possibility for the formation of **4** is that the "expected" azahomocubene **2** forms but is so strained it rearranges before it can be trapped. To examine this possibility, we irradiated azide **1** in a solid argon matrix at ca. 12 K with 290 ($\pm$10)-nm light,[11b] following the reaction by infrared spectroscopy. Even at this low temperature, the nitrile appeared immediately. We estimate, using relative extinction coefficients from a spectrum at 12 K of a measured mixture of pure **1** and **4**, that about 65% of the photolyzed azide went directly to **4**.

Infrared absorptions not attributable to **4** also appeared, most conspicuously at 2991, 1140, 802, and 758 (br) cm^{-1} and, less clearly because of overlap with those of **4**, near 1456, 1387, 1268, 1230 (br), and 942 cm^{-1}. All were stable at 12 K in the dark or to further irradiation at 290 nm but diminished very slowly in the dark at 25 K and disappeared after several hours at 32 K. This was accompanied by concomitant growth in the absorptions of **4**. Insofar as could be estimated by integration of the 2240-cm^{-1} CN stretch, at least 15% more **4** was formed.[15] Thus, there appears to be a minor, exceedingly thermally labile compound produced on photolysis of the azide which is precursor to (but not the only source of) nitrile **4**. This might be azahomocubene **2**.[16]

The C=N stretching frequency for **2** has been estimated to be at about 1420 cm^{-1}.[17] Figure 1 shows the changes recorded in the 1400-cm^{-1} region on photolysis of the azide in the matrix at 12 K followed by warming to and holding at 32 K.[18] Absorptions do appear near the predicted value, but these are very weak. Tempting as it may be to assign one of these or one or another of the more prominent absorptions around 1455 or 1385 cm^{-1} to imine **2**, it is not possible to do this with any certainty. In addition to the caveat that the changes seen may be due partly to matrix effects (e.g., annealing), these regions are overly complicated by the symmetric and asymmetric bending absorptions of the methyl substituent on the compounds present. This substituent, deliberately introduced, had otherwise served its purpose well by simplifying the assignment of structures by NMR. Experiments are now underway on the desmethyl compounds derived from cubyl azide itself.

Although future matrix experiments may reveal otherwise, the major path opened by photolysis of azide **1** seems to lead directly to nitrile **4**.[19] Certainly, the direct conversion of **1** to **4** is

mechanistically viable.[20] To our knowledge, only azide derivatives of three-membered rings have been reported to give nitriles on photolysis.[21] Sometimes the related imines are also formed[21c] but not as progenitors of the nitriles. Like a cubyl azide, the skeleton of a cyclopropyl azide is severely strained, and the C-C bonds are quite out of the ordinary. Perhaps then, photolysis of **1** does not lead primarily to azahomocubene not because of the difficult geometry of the imine but rather because of the idiosyncratic behavior of highly strained azides.

(13) IUPAC nomenclature: tetracyclo[3.2.0.0^{2,7}.0^{3,6}]heptane.

(14) (a) Cf.: Brember, A. R.; Gorman, A. A.; Sheridan, J. B. *Tetrahedron Lett.* **1973**, *7*, 481. (b) Prinzbach, H.; Herr, H.-J.; Regel, W. *Angew Chem., Int. Ed. Engl.* **1972**, *11*, 131.

(15) Additionally, a new, relatively strong absorption appeared at 755 cm^{-1}. GC/IR and ^{1}H NMR analyses of the photo-/thermolysate, pumped and trapped from the slowly warming matrix, revealed, in addition to **4**, a few percent each of ii and iii, neither responsible for the 755-cm^{-1} band, along with 5-10% of unstable olefins.

(16) Azaadamantene, the most strained of the known azaenes, is stable at least up to 100 K in a polyethylene matrix.[3c]

(17) Calculation courtesy of Prof. J. Michl. The calculated frequencies tend to be higher than those actually observed for the more strained azaenes.[3b,c]

(18) We find no evidence for an imine dimer on further warmup. Cf.: (a) Quast, H.; Eckert, P.; Seiferling B.; Peters, E. M.; Peters, K.; Schnering, H. G. *Chem. Ber.* **1985**, *118*, 3058. (b) Quast, H.; Eckert, P. *Liebigs Ann. Chem.* **1974**, 1727.

(19) We cannot yet eliminate entirely the possibility that inefficient coupling to the monoatomic matrix material delays relaxation of a vibrationally excited imine (cf.: Le Blanc, B. F.; Sheridan, R. S. *J. Am. Chem. Soc.* **1985**, *107*, 4554). However, when the photolysis was repeated with **1** in a 3-methylpentane matrix, **4** still appeared immediately.

(20) Cf.: Jackson, J. E.; Mock, G. B.; Tetef, L.; Zheng, G.; Jones, M., Jr. *Tetrahedron* **1985**, *41*, 1453.

(21) (a) Harrison, A. M., Ph.D. Thesis, University of Chicago, 1975. We thank Prof. G. L. Closs for bringing this to our attention. (b) Wulfman, D. S.; Steinheimer, T. R. *Tetrahedron Lett.* **1972**, *37*, 3933. (c) Szeimies, G. private communication. Cf.: Szeimies, G.; Harnisch, J. *Chem. Ber.* **1979**, *112*, 3914. (d) Vogelbacher, V. J.; Regitz, M.; Mynott, R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 842. (e) Hassner, A.; Levy, A. B.; McEntire, E. E.; Galle, J. E. *J. Org. Chem.* **1974**, *39*, 585.

Total Synthesis of (+)-Phyllanthocin

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Phyllanthocin (**3**),[2] the aglycone of the potent antitumor agent phyllanthoside (**1**), has attracted considerable synthetic interest.[3] Isolated by Kupchan in 1977, the structure was secured via single-crystal X-ray analysis;[2] the structure of the biologically active agent, however, remained unknown until 1982. In that year Pettit[4] announced the structure of phyllanthoside (**1**) as well as the closely related phyllanthostatins.[4,5] We also were intrigued with the spiro ketal architecture embodied in phyllanthoside;[6,7] we report here

(1) Camille and Henry Dreyfus Teacher–Scholar, 1978–1983; National Institutes of Health (National Cancer Institute) Career Development Awardee, 1980–1985; J. S. Guggenheim Fellow, 1985–1986.

(2) Kupchan, S. M.; La Voie, E. J.; Branfman, A. R.; Fei, B. Y.; Bright, W. M.; Bryan, R. F. *J. Am. Chem. Soc.* **1977**, *99*, 3199.

(3) For recent syntheses, see: McGuirk, P. R.; Collum, D. B. *J. Am. Chem. Soc.* **1982**, *104*, 4496. Williams, D. R.; and Sit, S.-Y. *J. Am. Chem. Soc.* **1984**, *106*, 2949. McGuirk, P. R.; Collum, D. B. *J. Org. Chem.* **1984**, *49*, 843. Burke, S. D.; Cobb, J. E.; Takeuchi, K. *J. Org. Chem.* **1985**, *50*, 3420. Dappen, M. S.; Dupré, B.; Murphy, C. J.; Martin, S. F. *Abstracts of Papers*, 192nd National Meeting of the American Chemical Society, Anaheim, CA; American Chemical Society: Washington, DC, September 1986; ORGN 291.

(4) (a) Pettit, G. R.; Cragg, G. M.; Gust, D.; Brown, P. *Can. J. Chem.* **1982**, *60*, 544. (b) Pettit, G. R.; Cragg, G. M.; Gust, D.; Brown, P.; Schmidt, J. M. *Can. J. Chem.* **1982**, *60*, 939. Pettit, G. R.; Cragg, G. M.; Suffness, M. I.; Gust, D.; Boettner, F. E.; Williams, M.; Saenz-Renauld, J. A.; Brown, P.; Schmidt, J. M.; Ellis, P. D. *J. Org. Chem.* **1984**, *49*, 4258. Pettit, G. R.; Cragg, G. M.; Niven, M. L.; Nassimbeni, L. R. *Can. J. Chem.* **1983**, *61*, 2630.

(5) Phyllanthoside was selected for human trials in January 1986. Private communication from Dr. Matthew Suffness, Natural Products Branch, NCI Developmental Therapeutics Program.

(6) For leading references on the synthesis and chemistry of spiro ketals, see: Evans, D. A.; Sacks, C. E.; Kleschick, W. A.; Taber, T. R. *J. Am. Chem. Soc.* **1979**, *101*, 6789. Martinez, G. R.; Grieco, P. A.; Williams, E.; Kanai, K.; Srinivasan, C. V. *Ibid.* **1982**, *104*, 1436. Baker, R.; Herbert, R. H.; Parton, A. H. *J. Chem. Soc., Chem. Commun.* **1982**, 601. Williams, D. R.; Barner, B. A. *Tetrahedron Lett.* **1983**, *24*, 427. Ireland, R. E.; Daub, J. P. *J. Org. Chem.* **1983**, *48*, 1303 and references therein. Evans, D. A.; Sacks, C. E.; Whitney, R. A.; Mandel, N. G. *Tetrahedron Lett.* **1978**, 727. Deslongchamps, P.; Rowan, D. D.; Pothier, N.; Sauve, T.; Saunders, J. K. *Can. J. Chem.* **1981**, *59*, 1105.