

Aza-analogues of Cage Compounds: Potential Precursors to Azacubanes and 1-Azahomocubanes

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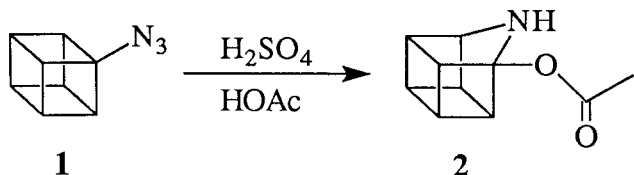
Dedicated to the memory of Dr. Roland K. Robins

Exploration of the reactions of the 9-azahomocubane system led to derivatives of two small-ring systems containing aza-bridging atoms, 5-azatetracyclo[4.2.0.0^{3,8}.0^{4,7}]octane and 9-azatetracyclo[4.3.0.0^{2,5}.0^{4,7}]nonane. The structures were characterized by X-ray diffraction analyses. There are no prior X-ray structural reports on these systems.

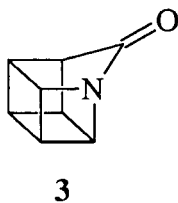
J. Heterocyclic Chem., **30**, 1385 (1993).

As already reported [1], the 9-azahomocubane system (e.g., **2**) can be entered effectively by way of the acid-catalyzed ring expansion of cubyl azide (**1**, Scheme 1).

Scheme 1



Such compounds provide interesting potential precursors for the 1-azahomocubane (**3**) and azacubane (**4**) systems. Respectively, these systems are important aberrations of classical amides and amines. In 1-azahomocubane, the unshared electron pair on the nitrogen is in an orbital essentially orthogonal to the π -bond of the carbonyl group [2]. Resonance delocalization is not possible; 1-azahomocubane must be considered chemically an α -acyl amine rather than a real amide. In azacubane, the "substituents" on nitrogen are orthogonal to one another, unlike those in a typical amine in which the arrangement is pyramidal at 108° [3]. Semiempirical (AM1, MNDO) or *ab initio* quantum-chemical calculations have been carried out on all of the azacubanes up to and including N_8 [4]; the reports indicate that all these structures are at least metastable to rearrangement, and vibrational frequency estimates (greater than 600 cm^{-1}) suggest an absence of low-

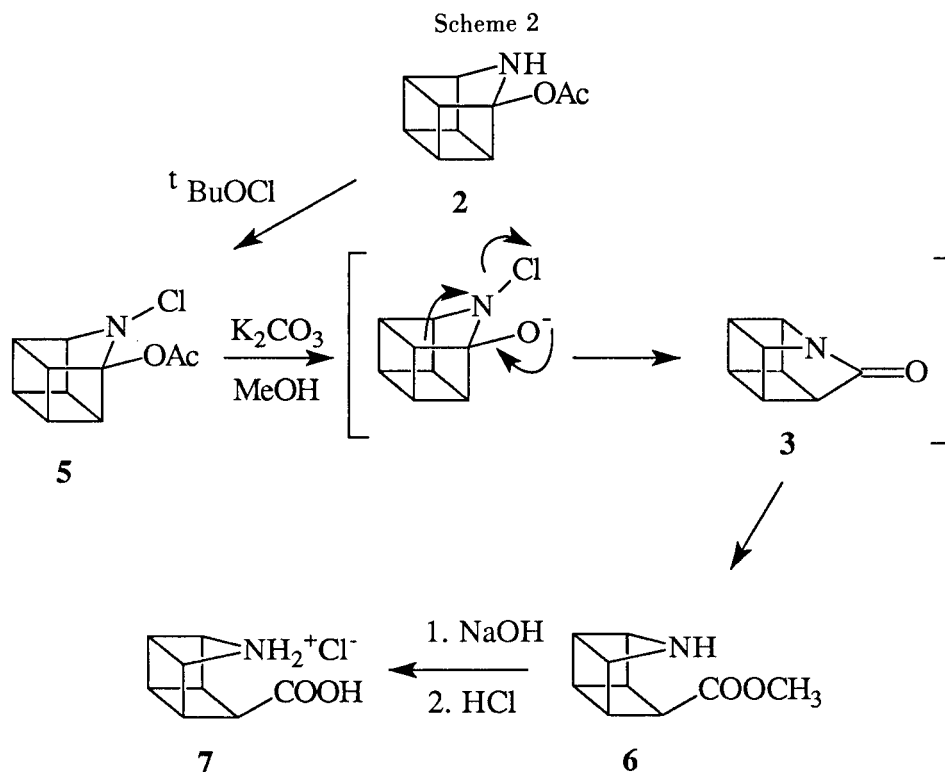


energy, high-amplitude distortions by which the azacubanes could disintegrate. For these reasons 1-azahomocubane and azacubane are major goals in synthesis chemistry.

Numerous explorations into the reactions of 9-azahomocubanes have been carried out to connect this potential precursor to the compounds of real interest. We report here that chlorination of **2** with *tert*-butyl hypochlorite at -78° in dichloromethane gives **5** in 80% yield after chromatography. It was hoped that a pinacol-like rearrangement [5] of **5** could be used to produce azahomocubane as shown in Scheme 2. In practice, the product of reaction of the *N*-chloramine **5** with potassium methoxide in methanol was the carbomethoxy secoazacubane **6**, resulting, it is believed, from successful rearrangement followed by immediate methanolysis of the desired 1-azahomocubane. The structural assignment to **6** was made initially by nmr spectral interpretation; unequivocal proof was obtained from X-ray analysis of the corresponding amino acid hydrochloride **7**.

Treatment of the amino acid hydrochloride with an excess of *p*-bromobenzene sulfonyl chloride in dry DMF gave a new compound, whose structure was not all apparent even after much nmr work. X-ray crystallography on a single crystal grown from benzene by vapor infusion of pentane revealed that the reaction product was the secoazahomocubane **8** (Scheme 3). It might be that this compound is formed as shown, but little is known of the chemistry of the still elusive (putative?) 1-azahomocubane to have real confidence in this speculation.

Though one edge of the azahomocubane **2** is cleaved in the processes leading to their synthesis, **7** and **8** are themselves highly strained tetracyclic aza-cage compounds.



The non-bonded cross-cage distance in **7**, N5...C9 = 2.73(1) Å, is considerably less than the C...N van der Waals contact distance, conservatively estimated to be at least

3.1 Å. The cation of **7** has the potential for mirror symmetry (which may or may not be dynamically attained in solution) but in the crystal, the planar carboxyl group is rotated from a symmetric location to lessen intramolecular crowding. Two carboxyl torsion angles, along C1-C2-C9-O10 and C3-C2-C9-O10, that would be of equal magnitude

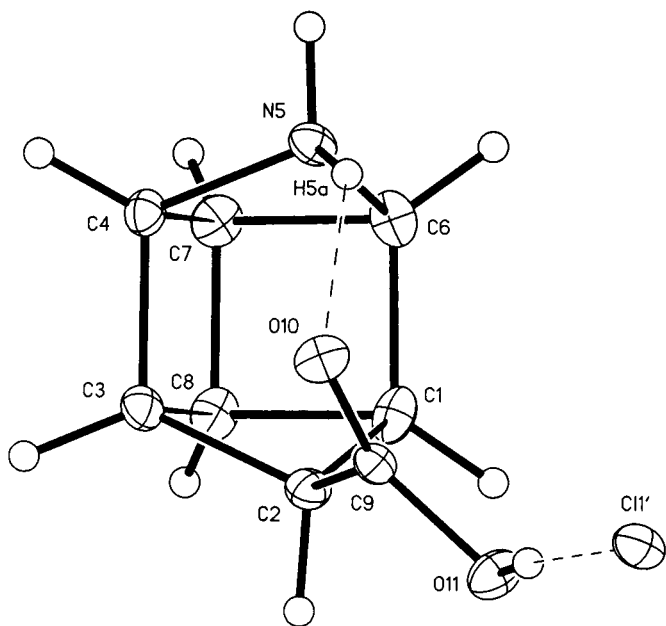


Figure 1. A thermal ellipsoid drawing showing the molecular structure and numbering scheme for 5-Azonia-2-carboxytetracyclo[4.2.0.0^{3,8},0^{4,7}]-octane chloride (**7**).

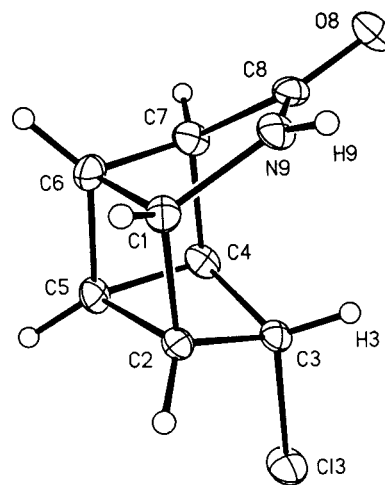
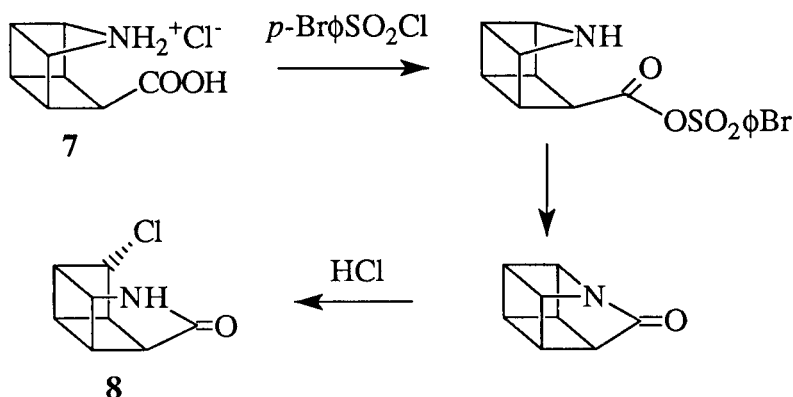


Figure 2. A thermal ellipsoid drawing showing the molecular structure and numbering scheme for 3-Chloro-8-oxo-9-azatetracyclo[4.3.0.0^{2,5},0^{4,7}]-nonane (**8**).



Scheme 3

and opposite sign for a symmetric conformation, are actually $+98.3(4)^\circ$ and $-13.1(4)^\circ$. At this twisted equilibrium position, one amino hydrogen atom, H5a, approaches the carboxyl oxygen atom O10 at a distance of $2.05(1)\text{Å}$, a typical hydrogen bond length. The carboxyl hydrogen, and the other amino hydrogen atom of the cation are linked by intermolecular H-bonds to adjacent chloride ions to form endless chains through the crystal.

The Cambridge Structural Database [6] contains no examples of the ring system of **7** with aza-substitution, and only one carbocyclic example, 4-cyano-4,7-dichloro-4-(*N*-isopropyl-formamide)-tetracyclo[4.2.0.0^{2,5}.0^{3,8}]octane [7]. (The search excluded systems with further cyclization, such as the cubanes, homocubanes, and basketenes, that contain the ring system.)

Molecules of **8** are linked together as dimers in the crys-

tal by a pair of hydrogen bonds from the amino hydrogen and keto oxygen to the keto oxygen and amino hydrogen atoms, respectively, of a centrosymmetrically related molecule. The dimers then stack with no particularly strong inter-dimer associations. There are apparently no examples of this ring system (formed from any combination of C, N or O atoms) in the Cambridge Structural Database [6].

Table 1. Crystal and Refinement Data

	7	8
formula	C ₈ H ₁₀ NO ₂ Cl	C ₈ H ₈ NOCl
crystal system	orthorhombic	monoclinic
space group ^(a)	P2 ₁ cn	P2 ₁ /a
a, Å	8.404(2)	8.894(1)
b, Å	9.455(2)	8.682(1)
c, Å	10.404(3)	9.744(1)
β, deg.		94.84(1)
V, Å ³	826.7(4)	749.8(1)
Z	4	4
formula weight	187.6	169.6
F(000)	392	352
ρ(calc), g cm ⁻³	1.507	1.503
crystal dim., mm	0.11 x 0.22 x 0.54	0.25 x 0.35 x 0.50
μ, absorption coef., mm ⁻¹	0.41	4.04
2θ max., deg.	50	126
ω scan speed, deg./min.	variable, 3.0 to 15.0	variable, 2.3 to 15.0
2θ scan range, deg.	2.0 + Δα1α2	2.0 + Δα1α2
data collected, h k l	0 to 10, 0 to 11, 0 to 12	-24 to 0, -1 to 6, -15 to 16
unique data	785	1216
unique data, F _o > 3σ(F _o)	747	1205
standard refl.	2.4% random	7.5% linear decay
parameters refined	138	133
weighting function, g ^(b)	0.000225	0.000225
R ^(c) , wR ^(d)	0.026, 0.032	0.042, 0.074
Fourier excursions, e Å ⁻³	0.16, -0.23	0.47, -0.30

(a) P2₁cn and P2₁/a are permuted settings of Pna2₁ (space group #33) and P2₁/c (#14), respectively.

(b) $w^{-1} = \sigma^2(F_o) + g F_o^2$; (c) $\Sigma | \Delta I | / \Sigma | F_o |$; (d) $\Sigma [(w \Delta^2) / \Sigma (w F_o^2)]^{1/2}$

Table 2. Bond lengths (Å) and Bond angles (°)

Molecule (7)			
C(1)-C(2)	1.540 (4)	C(1)-C(6)	1.557 (5)
C(1)-C(8)	1.576 (4)	C(2)-C(3)	1.528 (4)
C(2)-C(9)	1.521 (4)	C(3)-C(4)	1.555 (4)
C(3)-C(8)	1.567 (4)	C(4)-N(5)	1.508 (4)
C(4)-C(7)	1.547 (4)	N(5)-C(6)	1.507 (4)
C(6)-C(7)	1.556 (5)	C(7)-C(8)	1.536 (5)
C(9)-O(10)	1.209 (3)	C(9)-O(11)	1.320 (4)
Molecule (8)			
C(1)-C(2)	1.569 (3)	C(1)-C(6)	1.539 (3)
C(1)-N(9)	1.442 (3)	C(2)-C(3)	1.515 (3)
C(2)-C(5)	1.563 (3)	C(3)-C(1(3))	1.796 (2)
C(3)-C(4)	1.525 (3)	C(4)-C(5)	1.567 (3)
C(4)-C(7)	1.583 (3)	C(5)-C(6)	1.546 (3)
C(6)-C(7)	1.529 (3)	C(7)-C(8)	1.513 (3)
C(8)-O(8)	1.232 (3)	C(8)-N(9)	1.336 (3)
Molecule (7)			
C(2)-C(1)-C(6)	114.0(2)	C(2)-C(1)-C(8)	87.6(2)
C(6)-C(1)-C(8)	88.7(2)	C(1)-C(2)-C(3)	87.9(2)
C(1)-C(2)-C(9)	123.6(2)	C(3)-C(2)-C(9)	122.1(2)
C(2)-C(3)-C(4)	114.9(2)	C(2)-C(3)-C(8)	88.4(2)
C(4)-C(3)-C(8)	88.3(2)	C(3)-C(4)-N(5)	110.7(2)
C(3)-C(4)-C(7)	91.0(2)	C(3)-C(4)-C(7)	90.2(2)
C(4)-N(5)-C(6)	87.6(2)	N(5)-C(4)-N(5)	111.4(3)
C(1)-C(6)-C(7)	90.6(2)	C(1)-C(6)-C(7)	89.9(2)
C(1)-C(6)-C(8)	84.5(2)	N(5)-C(6)-C(8)	89.7(2)
C(6)-C(7)-C(8)	90.1(2)	C(4)-C(7)-C(8)	85.3(2)
C(1)-C(8)-C(7)	90.6(2)	C(1)-C(8)-C(3)	85.3(2)
C(2)-C(9)-O(10)	124.3(3)	C(3)-C(8)-C(7)	91.0(2)
O(10)-C(9)-O(11)	123.8(3)	C(2)-C(9)-O(11)	111.9(2)
Molecule (8)			
C(2)-C(1)-C(6)	89.9(2)	C(2)-C(1)-N(9)	117.5(2)
C(6)-C(1)-N(9)	104.9(2)	C(1)-C(2)-C(3)	111.0(2)
C(1)-C(2)-C(5)	89.0(2)	C(3)-C(2)-C(5)	89.5(2)
C(2)-C(3)-C(1(3))	109.4(1)	C(2)-C(3)-C(4)	90.1(2)
C(1(3))-C(3)-C(4)	109.3(2)	C(3)-C(4)-C(5)	88.9(2)
C(3)-C(4)-C(7)	111.7(2)	C(5)-C(4)-C(7)	88.9(2)
C(2)-C(5)-C(4)	86.8(2)	C(2)-C(5)-C(6)	89.9(2)
C(4)-C(5)-C(6)	89.4(2)	C(1)-C(6)-C(5)	90.7(2)
C(1)-C(6)-C(7)	98.5(2)	C(5)-C(6)-C(7)	91.6(2)
C(4)-C(7)-C(6)	89.4(2)	C(4)-C(7)-C(8)	115.0(2)
C(6)-C(7)-C(8)	105.7(2)	C(7)-C(8)-O(8)	127.1(2)
C(7)-C(8)-N(9)	106.7(2)	O(8)-C(8)-N(9)	126.3(2)
C(1)-N(9)-C(8)	112.5(2)		

Table 3. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement coefficients ($\text{\AA}^2 \times 10^3$) for 7 and 8

Molecule 7				
	x	y	z	U(eq)
C1(1)	2255	1183(1)	4954(1)	36(1)
C(1)	1588(5)	26(3)	1472(3)	36(1)
C(2)	2697(4)	-1257(3)	1647(3)	30(1)
C(3)	1280(4)	-2203(3)	1319(3)	31(1)
C(4)	-139(4)	-2109(3)	2275(3)	30(1)
N(5)	256(4)	-1139(2)	3380(2)	30(1)
C(6)	177(4)	72(3)	2441(3)	35(1)
C(7)	-853(4)	-849(3)	1522(3)	36(1)
C(8)	538(4)	-929(3)	566(3)	36(1)
C(9)	3713(4)	-1496(3)	2837(3)	28(1)
O(10)	3349(3)	-2267(2)	3717(2)	35(1)
O(11)	5070(3)	-795(2)	2780(2)	38(1)

Molecule 8				
	x	y	z	U(eq)
C(1)	1300(2)	5976(2)	2099(2)	34(1)
C(2)	2233(2)	4749(2)	1347(2)	31(1)
C(3)	3076(2)	3682(3)	2373(2)	34(1)
C1(3)	4051(1)	2243(1)	1466(1)	59(1)
C(4)	4166(2)	4981(3)	2815(2)	39(1)
C(5)	3610(3)	5874(3)	1470(2)	38(1)
C(6)	2721(3)	6986(3)	2340(3)	42(1)
C(7)	3391(3)	6252(3)	3682(2)	42(1)
C(8)	2057(2)	5697(3)	4413(2)	36(1)
O(8)	2046(2)	5369(2)	5642(2)	49(1)
N(9)	890(2)	5599(2)	3460(2)	34(1)

* Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor

EXPERIMENTAL

Crystallographic Analysis.

Suitable crystals of 5-azonia-2-carboxy-tetracyclo[4.2.0.0^{3,8}.0^{4,7}]-octane chloride (**7**), and 3-chloro-8-oxo-9-azatetracyclo[4.3.0.0^{2,5}.0^{4,7}]nonane (**8**) were selected for data collection on an automated Siemens R3m/V diffractometer. Data were collected in the $\theta/2\theta$ scan mode using an incident beam graphite monochromator [MoK α radiation ($\lambda = 0.71073 \text{ \AA}$) at $T = 233 \text{ K}$ (**7**), and CuK α radiation ($\lambda = 1.54184 \text{ \AA}$) at $T = 295 \text{ K}$ (**8**)]. The data were corrected for Lorentz and polarization effects, and semi-empirical absorption correction factors were derived from the intensity changes of a number of strong reflections during rotation about their diffraction vectors ('psi-scans') and applied to the full dataset for **8**. Transmissions calculated by this scheme varied from 0.56 to 0.88. The space group determinations were based on extinctions present and were confirmed by the structure solution. In each case the structures were determined by direct methods with the aid of the program SHELXTL [8] and refined using a full matrix least-squares program. In each structure the param-

eters refined include the atom coordinates and anisotropic thermal parameters for all but the hydrogens. Hydrogen positions were refined with fixed isotropic thermal parameters for the hydrogen atoms. Table 1 contains additional data collection and refinement parameters, Table 2 contains observed bond distances and angles, and Table 3 lists the fractional atomic coordinates and thermal factors. In the Tables, numbers in parentheses represent the estimated standard deviation in the final digit of the reported parameter.

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