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ETHANOLYSIS AND BASE PROMOTED ELIMINATION REACTION OF BRIDGEHEAD α-AMINO SULFIDES

3-THIOETHOXY-4-AZAHOMOADAMANTANES[1]

PIOTR M. STAREWICZ[2], GERDA E. BREITWIESER, E. ALEXANDER HILL* and PETER KOVACIC*
Department of Chemistry, University of Wisconsin-Milwaukee, Milwaukee, WI 53201, U.S.A.

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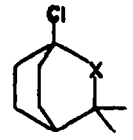
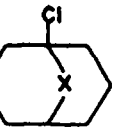
Abstract—Solvolysis of N-methyl-3-thioethoxy-4-azahomoadamantane (4c) in ethanolic sodium ethoxide followed first order kinetics. Reaction presumably proceeds via an S_N1 mechanism with resonance stabilization of the bridgehead carbonium ion by the electrons on adjacent nitrogen. Addition of ethoxide to the bridgehead carbonium ion yields N-methyl-3-ethoxy-4-azahomoadamantane (4a). Solvolysis of N-protio compound (4b) under similar conditions was much more rapid, and followed first order kinetics for both substrate and base. The mechanism apparently involves an elimination-addition pathway in which ethoxide promoted elimination of ethyl mercaptan is followed by net addition of ethanol across the bridgehead imine to form ether 4d.

A number of recent publications[3-5] deal with the effect of heteroatoms (N, O and S) on the stability of an adjacent bridgehead carbonium ion in bi- and tricyclic compounds. The involvement of resonance is most pronounced when the carbon adjacent to the bridgehead is replaced by nitrogen.[3,4] For instance, it appears that solvolyses of 1 - chloro - 3,3 - dimethyl - 2 - azabicyclo[2,2,2]octane (1a)[4] and its carbon analog (1b) proceed by an S_N1 mechanism. The aza compound 1a was estimated to be more reactive in solvolysis in 70% aqueous dioxane at 52° by a factor of 2×10^5. A sizeable rate acceleration was observed upon addition of base to the reaction medium, which was attributed to the base promoted elimination of HCl.[4] Net addition of ethanol to either the carbonium ion from neutral solvolysis or to the bridgehead imine from base promoted reaction afforded the ether product. A solvolysis study by Wiseman *et al.*[3] on 1 - chloro - 9 - methyl - 9 - azabicyclo[3,3,1] - nonane (2a) and its carbocyclic analog (2b) in 96% ethanol at 29° revealed a relative rate of 8×10^6 : 1.

In the present paper, we report a study of the ethanolysis of N-methyl-3-thioethoxy-4-aza-homoadamantane (4c) and base promoted elimination of the N-protio compound (4b).



1	X
a	NH
b	CH_2



2	X
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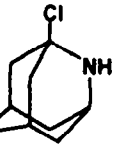
b	CH_2



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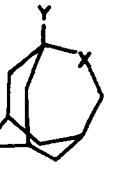
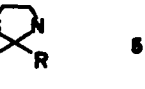


4	X	Y
a	NH	Cl
b	NH	SC_2H_5
c	NCH_3	SC_2H_5
d	NH	OC_2H_5
e	NCH_3	OC_2H_5
f	NH	OH
g	CH_2	Cl
k	NH	OCH_3



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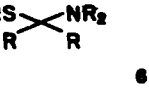

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$(p\text{-}CH_3OC_6H_4)_3C\text{—}X$

7	X
a	SC_2H_5
b	Cl
d	OC_2H_5

RESULTS AND DISCUSSION

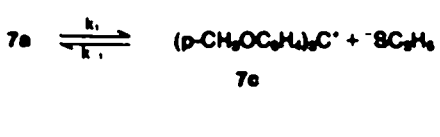
1-Chloro-2-azaadamantane (3) has been synthesized.[5] However, we were unable to prepare 3 - chloro - 4 - azahomoadamantane (4a), in which bridgehead strain should be decreased by an increase in ring size. It becomes apparent that our lack of success was due to the extremely high susceptibility of 4a to solvolysis (*vide infra*). In search of a less reactive system, we prepared 4b and its N-Me derivative 4c. Relatively few compounds containing an α-amino sulfide moiety have been previously reported. For example, cyclic types, such as 5[6] and open chain 6[7] can be found in the literature, although only one report[7f] dealt with alicyclic α-amino sulfides containing a quaternary α-carbon. There are apparently no quantitative studies of sulfide solvolysis reported in the prior literature.

Substrate 4b for solvolysis investigations was synthesized by acid catalyzed reaction of ethyl mercaptan with 3-hydroxy-4-azahomoadamantane (4f); subsequent N-methylation with methyl fluorosulfonate produced 4c.

Ethanolysis of 4c was carried out in a strongly basic solution of sodium ethoxide in ethanol (up to 1 M). Satisfactory plots for first order kinetics were obtained for reactions at 70, 100 and 110°. Ten to fifteen points were used for each run, taken during the first 2–3 half-lives. Results are listed in Table 1.

Solvolyses were carried out in basic medium to avoid potential acid catalysis;[8] preliminary work without base gave erratic results. Relatively high base concentrations were used to assure that the carbonium ion would react with ethoxide, rather than be trapped by thioethoxide and returned to starting material (Scheme 1). The rate was insensitive to changes in base concentration above 0.1 M. This insensitivity contrasts with our earlier observations in the solvolysis of 4,4',4'' - trimethoxytriphenylmethyl ethyl sulfide (7a) (Scheme 2).[9] In that case, thioethoxide appears to compete more effectively with ethoxide for the carbonium ion, since a large excess of base (25–30 fold, 0.8–1.0 M) was necessary to obtain a limiting reaction rate in which carbonium ion formation was rate-determining. The greater efficiency of thioethoxide in trapping the 4,4',4'' - trimethoxytriphenylmethyl cation may be rationalized on the basis of hard and soft acid-base theory (HSAB).[10] The more extensively delocalized (and therefore softer) triarylmethyl cation apparently exhibits a greater kinetic preference for coordination with the softer thioalkoxide ion.

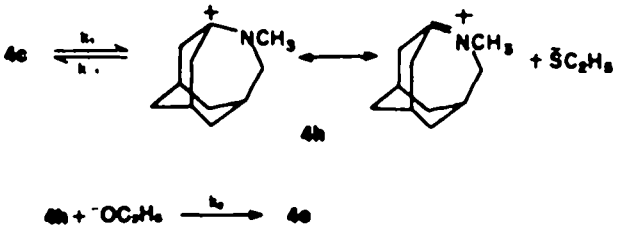
The thioalkoxide solvolyses in the azahomoadamantyl (4c) and tri-*p*-anisylmethyl (7a) systems occur at comparable rates, and exhibit similar activation parameters (Table 1). In the latter system, it was estimated[9] (by extrapolation from literature values for related compounds) that the sulfide 7a solvolyses more slowly than the corresponding chloride by a factor of about 10.[14] If this factor is taken as representative of the chloride: sulfide solvolysis rate ratio for kinetically similar systems, such as the present one, we would estimate the ethanolysis rate constant for chloride 4a as about 4×10^6 sec^{-1}.



Scheme 2.

Stetter and Goebel[11] have studied the solvolysis of 3-chlorohomoadamantane (4g). Extrapolation of their rate constant of 3.45×10^{-6} sec^{-1} in 80% ethanol by use of the Grunwald–Winstein[12] relationship (m = 1) leads to a value of 3.7×10^{-9} sec^{-1} in 100% ethanol at 25°. Comparison of this value with the estimated rate for ethanolysis of 4a affords the remarkable rate enhancement of about 10^{14} due to the introduction of nitrogen in the 4-position of the homoadamantyl skeleton. This is markedly greater than effects reported previously for 1 and 2.

An important feature facilitating stabilization of the bridgehead cation (4b) by nitrogen is increased flexibility of the C_3–C_6 bridge. Examination of a model suggests that a very favorable geometry may be achieved for overlap of the empty *p*-orbital with the nitrogen lone pair, i.e. formal C–N bridgehead double bonding. Formation and trapping of such strained double bonds in azahomoadamantene[13a] and homoadamantene[13b] have been described previously. This favorable arrangement



Scheme 1.

Table 1. Comparison of ethanolyses[a,b] of 4c and 7a

Compound	$k_1 \times 10^6$ [sec^{-1}]					$\Delta H^{\ddagger}$ [kcal mol^{-1}]	$\Delta S^{\ddagger}$ [eu]
	120°C	110°C	100°C	70°C	25°C[c]		
4c	---	69.8 ± 2.1	40.4 ± 1.8	3.06 ± 0.14	0.038[d]	20.3 ± 1.2	-26.1 ± 4.2
7a[f]	11.6 ± 0.6	5.46 ± 0.36	2.84 ± 0.26	---	0.0026[e]	19.9 ± 1.2	-30.8 ± 4.2

[a] 0.8 - 1.0 M ethanolic sodium ethoxide

[b] Error limits are standard deviations

[c] Extrapolated from higher temperatures

[d] Error limits 2.6 - 4.4 × 10^{-8} sec^{-1}

[e] Error limits 1.0 - 8.2 × 10^{-9} sec^{-1}

[f] Data from Ref. 9

may be inhibited to some extent by the N-Me group, which should experience increased interaction with ring hydrogens as the interacting orbitals become more coplanar. Another factor which should affect the ability of adjacent nitrogen to interact with the bridgehead cationic center is the increased flexibility of the entire homoadamantyl framework. This factor allows a more nearly planar 3 - homoadamantyl cation position than in the other bridgehead carbonium ions under discussion.[14] The nearly *p*-hybridized orbital in the cation 4a overlaps better with the nitrogen lone pair than in strained systems in which the bridgehead carbonium ion center has more *s*-character.

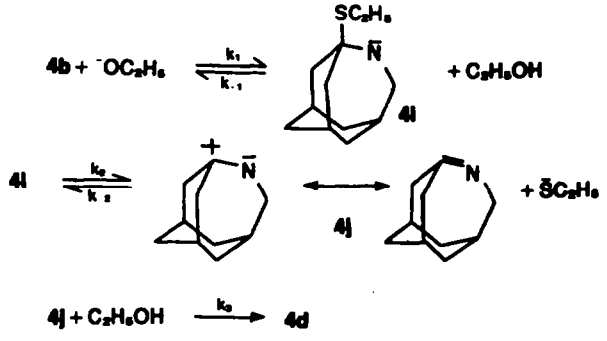
With acyclic α-haloamines, in which there is no geometric restriction to overlap of a vacant *p*-orbital on the solvolytic center with the nitrogen lone pair, carbonium ion stabilization becomes pronounced to the extent that an ionic immonium chloride structure is favored[15] over the covalent alternative. Most cyclic analogs appear to fall in this category also. An exception to this generalization has been reported for some chloroaziridines, in which the well-documented difficulty of forming a carbonium ion in a 3-membered ring[17] is responsible for destabilization of ionic structure. The covalent bi- and tricyclic chlorides 1a, 2a and 3, which were noted above, owe their stability to orbital misalignment between carbon and nitrogen, forced by the rigidity of the molecular framework. Chloride 4a, which we were unable to prepare, must be approaching the borderline in stability between ionic and covalent structures.

Compound 4b, which lacks the N-Me group, reacts more rapidly than 4c in basic ethanolic solution at a rate proportional to the concentration of sodium ethoxide. The kinetic form appears to require an addition-elimination sequence, as shown, for example, in Scheme 3, with the strained imine 4j as an intermediate. Reasonable variants involving this mechanistic approach would include: (1) reversible deprotonation of 4b, followed by rate-determining loss of thioethoxide ($k_{-1} > k_2$); (2) rate-determining deprotonation of 4b, followed by rapid loss of thioethoxide ($k_{-1} < k_2$); and (3) concerted elimination of thioethanol. Addition of ethanol, most likely via nucleophilic attack of ethoxide ion on 4j, forms the bridgehead ether 4d as the sole product. Addition of ethanol is irreversible under the conditions employed, since treatment of the methyl ether 4k for a period equivalent to several solvolytic half-lives led to no incorporation of ethoxide.

This work comprises one of the first studies of sulfide solvolysis.[9] Only a semiquantitative investigation of sulfide elimination has been previously reported with other substrates.[18]

EXPERIMENTAL

Commercial materials were used without purification except for ethanol (see kinetic procedures). IR spectra were obtained on a Beckman IR8 spectrophotometer, and NMR spectra on Varian



Scheme 3.

Table 2. Ethanolysis of 4b in ethanolic sodium ethoxide[a,b]

52°C		70°C	
$NaOC_2H_5$ [M]	$k_1 \times 10^6$ [sec^{-1}]	$NaOC_2H_5$ [M]	$k_1 \times 10^6$ [sec^{-1}]
0.87	3.48 ± 0.18	0.75	18.4 ± 1.1
0.87	4.28 ± 0.52	0.85	19.9 ± 0.9
1.28	6.46 ± 0.77	0.88	21.0 ± 1.7
1.36	5.76 ± 0.09	1.05	30.6 ± 1.0
1.74	9.13 ± 0.72	1.15	29.6 ± 2.4
1.75	9.19 ± 0.25	1.85	46.5 ± 4.1
$k_2 \times 10^6$	5.96 ± 0.66 [sec^{-1} $l mol^{-1}$]		25.9 ± 2.5 [sec^{-1} $l mol^{-1}$]

[a] Error limits are standard deviations

[b] Extrapolated rate constant $k_2^{25°C} = 4.8 \times 10^{-7}$ $sec^{-1} l mol^{-1}$ (Error limits $6.7\text{-}3.4 \times 10^{-7}$)

$\Delta H^{\ddagger} = 17.5 \pm 1.2$ kcal mol^{-1}, $\Delta S^{\ddagger} = -27.3 \pm 4.2$ eu.

T-60, A-60 and CFT-20 instruments. Elemental analyses were performed by Microtech Laboratories, Skokie, Illinois, and Galbraith Laboratories Inc. Knoxville, Tenn. Mps are uncorrected.

3 - *Hydroxy* - 4 - *azahomoadamantane* (4f). A prior procedure[19] was followed without modification. Yields (about 50% based on 1-aminoadamantane) of sublimed (140°, 0.2 mm Hg) product, m.p. 164–167°, were erratic, presumably due to differences in the grade of $AlCl_3$.

3 - *Thioethoxy* - 4 - *azahomoadamantane* (4h). Trifluoroacetic acid (5.8 g, 0.05 mol) was added dropwise at room temp. over 1/2 hr to a mixture of 4f (8.7 g, 0.05 mol) and ethyl mercaptan (120 ml). The mixture was stirred under N_2 for 8 days during which time most of the mercaptan evaporated. The solid residue was suspended in 1 N NaOH (100 ml) and extracted thoroughly with CH_2Cl_2. Drying with Na_2SO_4 and evaporation afforded a greenish oil which was distilled under reduced pressure (0.15 mm Hg). The major fraction, b.p. 97–99°, solidified in the receiver; yield 8.9 g (94%); m.p. 39.5–41.5°: IR (KBr) 3350, 1440, 1155, 1065 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.01 (d, J = 4.0 Hz, NCH_2), 2.67 (q, J = 7.5 Hz, SCH_2), 2.4–1.0 (m, ring protons), 1.23 (t, J = 7.5 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ (position) 68.22 (3), 53.56 (5), 46.27 (2, 11), 36.69 (7, 10), 35.49 (9), 33.82 (6), 28.07 (1, 8), 22.43 (SCH_2), 15.13 (CH_3). (Found: C, 68.52; H, 10.17; N, 6.73; S, 14.99. Calc. for $C_{12}H_{21}SN$: C, 68.19; H, 10.01; N, 6.63; S, 15.17%).

N - *Methyl* - 3 - *thioethoxy* - 4 - *azahomoadamantane* (4e). Compound 4h (2.10 g, 0.01 mol) was dissolved in 50 ml dry CH_2Cl_2, and methyl fluorosulfonate (Magic Methyl) (1.20 g, 0.0105 mol) in 30 ml dry CH_2Cl_2 was added dropwise at room temp. with stirring over 1 hr. After stirring was maintained overnight, 1 N NaOH (50 ml) was then added, and the layers were separated, followed by repeated extraction of the aqueous portion with CH_2Cl_2. Drying and evaporation of solvent afforded yellow oil (2.4 g) which was chromatographed on basic alumina with CH_2Cl_2. Evaporation of solvent from fractions containing product (tlc) afforded 1.6 g (71%) of oil; n_D^{25} 1.5464; IR (NaCl) 2740, 1440, 1125, 1110, 1030, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.13 (d, J = 4.0 Hz NCH_2), 2.73 (s, NCH_3), 2.53 (q, J = 7.5 Hz, SCH_2), 2.4–1.0 (m, ring protons), 1.20 (t, J = 7.5 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ (position) 73.48 (3), 60.18 (5), 51.09 (2, 11, NCH_3), 36.81 (9), 36.25 (7, 10), 34.64 (6), 28.56 (1, 9), 21.61 (SCH_2), 15.08 (SCH_2CH_3). (Found: C, 69.35; H, 10.32; N, 6.22; S, 14.14. Calc. for $C_{13}H_{23}SN$: C, 69.27; H, 10.28; N, 6.22; S, 14.23%).

3 - *Ethoxy* - 4 - *azahomoadamantane* (4d). The procedure described[19] for synthesis of 4k was followed without modification. Product was recrystallized from hexane; yield 37%; m.p. 53–54.5°; IR (KBr) 3250, 1450, 1150, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.58 (q, J = 7.0 Hz, OCH_2), 2.95 (d, J = 4.0 Hz, NCH_2) 2.3–1.0 (m, ring protons), 1.10 (t, J = 7.0 Hz CH_3); ^{13}C NMR ($CDCl_3$) δ (position) 88.24 (3), 54.44 (OCH_2), 50.84 (5), 44.42 (2, 11), 36.67 (7, 10), 35.85 (9), 33.89 (6), 27.14 (1, 8), 16.31 (OCH_2CH_3). (Found: C, 74.06; H, 11.09; N, 6.88. Calc. for $C_{12}H_{21}NO$: C, 73.79; H, 10.84; N, 7.17%).

N - *Methyl* - 3 - *ethoxy* - 4 - *azahomoadamantane* (4e). The procedure described for 4e was used without modification. Compound 4d (0.75 g; 0.0038 mol) afforded 0.50 g (63%) of yellow oil; IR (NaCl) 2800, 1460, 1155, 1120, 1075, 735 cm^{-1}; ^1H NMR ($CDCl_3$) 3.43 (q, J = 7.0 Hz, OCH_2), 3.00 (d, J = 4.0 Hz, NCH_2), 2.43 (s, NCH_3), 2.4–1.0 (m, ring protons), 1.12 (t, J = 7.0 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ (position) 90.07 (3), 58.60 (5), 53.99 (OCH_2), 39.14 (2, 11), 38.61 (NCH_3), 36.53 (7,10), 34.36 (9), 33.51 (6), 27.40 (1, 8), 15.95 (OCH_2CH_3); mass spectrum *m/e* (relative intensity) 163 (100), 164 (80), 165 (80), 180 (55), 181 (23), 194 (4), $M^{\cdot+}$ 209 (14).

Kinetic procedures. EtOH was purified according to Perrin[20] by refluxing with Mg for several days and then distilling. Kinetic samples were prepared by placing a weighed amount of compound (110 mg, 4.89×10^{-4} mol of 4c; 100 mg, 4.73×10^{-4} mol of 4h) in a pyrolysis tube, adding a titrated soln of fresh NaOEt in EtOH (10 ml, 0.8–1.0 M) under N_2, freezing the sample in liquid N_2 and sealing under vacuum. Kinetic runs under 100° were done in a glycerol bath and above 100° in a GC oven. Work-up involved adding the contents of the pyrolysis tube to 30 ml water and extracting with CH_2Cl_2 (2 × 15 ml) and ether (2 × 15 ml). The combined organic layer was washed with sat NaCl$_{aq}$ (15 ml) and dried with Na_2SO_4 (4 g) and $MgSO_4$ (4 g). After evaporation of solvent and storage of samples under vacuum (0.1 mm Hg), the NMR spectra were obtained in $CDCl_3$. Integration of the methylene groups adjacent to S, O, and N was used for calculations.

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