BROMINATION AND BRIDGEHEAD REACTIVITY OF 1-AZA-ADAMANTANE[1]

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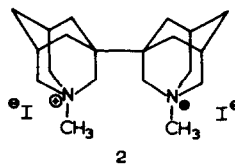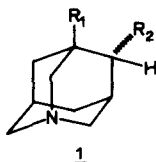
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Much information has been assembled in the last decade on the bromination of adamantane and other cage compounds[2]. Although the major part of this work involves the cationic type of intermediate the formation of 1- and 2-bromo-adamantanes via radical species has also been documented[3].

On the contrary cage heterocyclics have not been investigated in similar reactions. In the course of our work on the reactivity of 1-aza-adamantane[4], we were interested in i) the relative stability of the cage amine versus open-chain tertiary amines in radical bromination[5] ii) the influence of the the nitrogen atom on the reactivity of the secondary and tertiary cage hydrogens of the 1-aza-adamantane skeleton. Therefore we have investigated its bromination and the conversion of the so-formed products. Treatment of <u>la</u> with Br_2(liq.)

			mp	mp HOTs-salt	mp $N^{\oplus}$-$CH_3I^{\ominus}$ salt
<u>a</u>	R_1 = H	R_2 = H	265–269°	–	>350° (dec)
<u>b</u>	R_1 = Br	R_2 = H	65°	153–155°	310–315° (dec)
<u>c</u>	R_1 = H	R_2 = Br	–	154–158°	>300° (dec)
<u>d</u>	R_1 = OH	R_2 = H	>320° dec	170–171.5°	>340° (dec)
<u>e</u>	R_1 = H	R_2 = OH	279–282°	–	–
<u>f</u>	R_1 = H	R_2 = OTs	–	221–227°	209–211°

resulted in the immediate formation of a precipitate[6] which upon refluxing

for prolonged periods with or without addition of Lewis acids either gave

back starting material or afforded stable 1:1 complexes of 1a and the Lewis

acid, e.g. BBr_3 or $AlBr_3$. However, upon heating of the Br_2-1a adduct at

temperatures over $120°C$ varying amounts of bromine substituted 1-aza-adamant-

anes were formed. Some representative results are summarized in the table.

TABLE

ml Br_2	time ^{a}	T(^{o}C)	W ^{b}	1a ^{c}	1b ^{c}	1c ^{c}	1b(%) ^{d}
2	34	120	0.65	2	1	-	26
3	33	135	0.97	10	7.5	1	56
2	77	128	0.93	2	1	-	51
3	25	150	1.23	4	6.5	2	66
2.5	55	160	0.27^e	-	1	1	12

a) in hr
b) weight of solid material obtained after
   work-up and sublimation in g
c) relative amount as determined by PMR-
   analysis of W
d) calculated on converted 1a
e) obtained as oil.

In a typical experiment 1 g. (7.5 mmol) of 1-aza-adamantane and the

amount of bromine indicated were heated in a sealed ampoule. Work-up afforded

a solid residue which was analyzed by PMR after purification by sublimation.

Via crystallization as HOTs-salt, the separation of the brominated compounds

was possible.

The 4-Br derivative 1c independently prepared by PBr_5-treatment of 1e[7]

and isolation as its HOTs-salt was identical in all respects with the product

obtained by bromination of 1a. Reduction of 1b with nBt_3SnH gave back the

starting material 1a, thus proving the absence of skeletal migrations during

the bromination. In all runs minor amounts of dibrominated species were formed

as detected by mass spectral analysis.

From the data it appears well possible to brominate 1-aza-adamantane

without disrupting the skeleton although the fact that C-2 bromo compounds

could not be found might be due to decomposition[8]. The ratio of reactivity

of positions C-3 and C-4 towards bromine corresponds reasonably well with the
one found in the radical bromination of adamantane[3]. The reactivity of the
secondary and tertiary cage hydrogens towards radical abstraction therefore
seems not to be influenced to a great extent by the presence of the nitrogen
atom.

A second point of interest is connected with the reactivity of the bridge-
head bromine atom in nucleophilic substitution. As has been reviewed recent-
ly[9] the nitrogen atom is capable of anchimeric assistence in the hydrolysis
of 3-halosubstituted piperidines via aziridinium intermediate A. Although
not expected to be of major importance a similar type of stabilization would

A   B   C
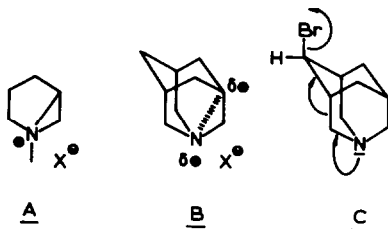
provide information on the existence of the theoretically predicted conjugation
stabilization[10] in 1-aza-adamantane as indicated in B.

Although 1c upon treatment with H_2O-IRA 400 was rapidly converted to 1d
in a quantitative manner kinetic measurements[11] showed its reactivity approx-
imately 2000 times lower compared to 1-bromo-adamantane. Thus instead of
stabilization a considerable destabilization is observed and most probably
this behaviour might be attributed to an unfavorable inductive effect of the
nitrogen. Dimerization of 1b in refluxing toluene-Na[12] proceeded smoothly
to afford the C-3, C-3' dimer 2, isolated as its quarternary N-Me iodide.

On the contrary, the 4-bromo derivative 1c proved to be highly labile in
presence of base, almost certainly involving a heterolytic fragmentation[13]
according to C. Similar behaviour was observed in the reaction of the O-tosyl
derivative 1f with base. Unfortunately as yet no reaction product of definite
structure could be isolated in this fragmentation.

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11. Measured in 50% EtOH buffered with Et_3N at 103,7°C.

$$\frac{K_{1-aza-AdBr}}{K_1-AdBr} = \frac{5.23 \times 10^{-5} \ sec^{-1}}{9.0 \ \times 10^{-2} \ sec^{-1}} = 0.00058$$

    The determination of the solvolysis constants have been carried out
    in the laboratory of Professor P.v.Rague Schleyer, to whom we express
    our sincere gratitude for carrying out the measurements.
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