3-AZANORADAMANTANES

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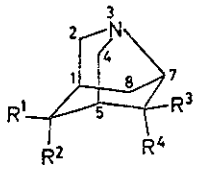
Abstract – 3-Azanoradamantanes 1-3 are obtained by ring closure in acid medium of C_7-substituted N-tosyl-3-azabicyclo[3.3.1]-nonanes. The basicity of 1-3 and the behaviour in the near UV region of 2 and 3 are discussed.

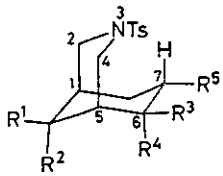
As suitable rigid models for studies on heterolytic fragmentation, intramolecular charge transfer phenomena and gas-phase basicity 1-azaadamantanes have served useful purposes.[1] Its versatile preparation by ring closure of C_7-substituted 3-azabicyclo[3.3.1]nonanes[2] has been invited to the synthesis of 3-azanoradamantane 1 and derivatives.[3]

Compounds of special interest were 3-azanoradamantan-9-one (2), possessing the 4-piperidone ring system, and 3-azanoradamantan-6-one (3), in which a 3-pyrrolidone moiety constitutes the functionalized part of the heterocage molecule. Both compounds were expected to provide information on the effects of ring contraction in this type of strained molecule, especially with regard to its physico-chemical behaviour.

Refluxing of the C_7-exo bicyclic alcohol 4[4] in conc. HCl/HOAc (1/1) for 5 hr yielded 3-azanoradamantane (1) in 70% yield as a highly volatile compound, m.p. (sealed capillary) 258-260°. ^{1}H-NMR δ(C_6D_6): 3.55 (t, J=6 Hz, H_7); 2.78 (s, $H_{2,4}$); 1.83 (s, $H_{1,5}$); 1.50 (A_2B_2, J=15 Hz, $H_{6,8}$); 1.50 (s, H_9). Like 1-azaadamantane amine 1 is also a strong base (Table I) and possesses a high nucleophilic character. Within the latter context it is of interest to note the reaction of 1 with $CHCl_3$, producing the dichloromethylene complex 5. The ^{1}H-NMR spectrum ($CDCl_3$) shows an absorption at δ=9.18 due to $\underline{H}CCl_2$,[5] while the other absorptions are shifted to lower field.

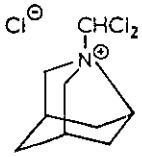
Upon refluxing either the C_7-exo chloride 6[4] or the C_7-exo alcohol 7[4] in conc. HCl/HOAc (1/1) for 5 hr 3-azanoradamantan-9-one (2) was obtained in 75% yield; m.p. (sealed capillary) 146-148°. ^{1}H-NMR δ($CDCl_3$): 3.90 (t, J=5.5 Hz, H_7); 3.09 (s,





1	R^1,R^2,R^3,R^4 = H				
2	R^1,R^2 = O	R^3,R^4 = H			
3	R^1,R^2 = H	R^3,R^4 = O			
11a	R^1 = OH	R^2 = H	R^3,R^4 = H		
11b	R^1 = H	R^2 = OH	R^3,R^4 = H		
12	R^1,R^2 = H		R^3 = H	R^4 = OH	

4	R^1,R^2 = H	R^3,R^4 = H		R^5 = OH	
6	R^1,R^2 = O	R^3,R^4 = H		R^5 = Cl	
7	R^1,R^2 = O	R^3,R^4 = H		R^5 = OH	
8a	R^1,R^2 = O	R^3 = OH	R^4 = H	R^5 = H	
8b	R^1,R^2 = O	R^3 = H	R^4 = OH	R^5 = H	
9	R^1,R^2 = H	R^3,R^4 = O		R^5 = H	
10	R^1,R^2 = H	R^3,R^4 = O		R^5 = Br	



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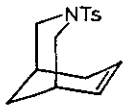

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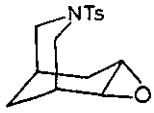

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$H_{2,4}$); 2.75 (s, $H_{1,5}$); 2.06 (A_2B_2, J = 14 Hz, $H_{6,8}$). The compound proved to be extremely hygroscopic, a behaviour which also was noted for the corresponding HCl salt. When 2 ·HCl was isolated from the acidic fraction, it was shown to exist completely in its hydrate form, m.p. >300° (dec), as was manifested by its analytical data, e.q. lack of C = O absorption and appearance of OH absorption at 3500 cm^{-1} in IR (KBr). 1-Azaadamantan-4-one and 3-azanoradamantan-6-one (m.p. HCl salt 282-285°) show similar behaviour.

Precursors for the C_6-substituted heterocyclic compounds were the C_6-OH isomeric bicyclic compounds 8a and 8b, obtained via α,α'-annelation of N-tosyl-4-piperidone enamine with acrolein.[6] 8a and 8b are converted via thioketalization and desulfurization of the C_9-oxo group and oxidation of the C_6-OH with pyridinium chlorochromate into 9 (total yield 60%). Treatment of 9 with Br_2 in CH_2Cl_2 afforded quantitatively N-tosyl-3-aza-7β-bromobicyclo[3.3.1]-nonan-6-one (10); ^{1}H-NMR δ($CDCl_3$) H_7: 5.45 (J = 8 and 11 Hz), indicative of an axial proton.

Refluxing of 10 in conc. HCl/HOAc (1/1) yielded 3-azanoradamantan-6-one (3) in 94% yield, m.p. (sealed capillary) 167-170°. ^{1}H-NMR δ($CDCl_3$): 3.50 (d, J = 7 Hz, H_7); 3.12 (A_2B_2, $H_{2,4}$); 2.50-1.75 (6H).

The influence of the ring-contraction upon the basicity of these compounds is

measured both in water (Table I) and in the gas-phase (ICR).

TABLE I

compound	pK_b measured in H_2O at 22°		
	pK_b	compound[1a]	pK_b
1	2.61	1-azaadamantane	2.96
2	4.31	1-azaadamantan-4-one	5.43
3	5.17		

In solution the 3-azanoradamantanes are slightly more basic, but in the gas-phase the basicity equals the basicity of the corresponding 1-azaadamantanes.

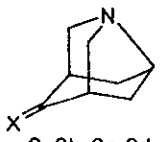
The change of hybridization of the N-electrons in the 3-azanoradamantanes as result of the ring-contraction and the effect on the basicity of the loss of one C-atom, as compared with the 1-azaadamantanes, probably equal the effect on the basicity resulting from increased strain energy effects.[7] The difference in basicity in solution is probably a result of solvation effects.[8]

Reduction of 2 with LAH yielded the two isomeric alcohols 11a and 11b as a mixture in a ratio 40 : 60 (76% yield). Reduction of 3 with LAH yielded exclusively the C_6-anti alcohol 12 in 94% yield. ^{1}H-NMR $\delta(D_2O)$: 4.28 (dd, J = 3 and 7 Hz, H_6); 3.45 (t, J = 7, H_7); 2.95 (A_2B_2, $H_{2,4}$); 2.43 and 1.50 (AB, H_8); 2.20 (s, H_5); 1.95 (s, H_1); 1.95 (H_9). The coupling of 7 Hz between H_6 and H_7 is indicative of an equatorial H_6.[9] The reduction selectivity can be explained by a diminution of the steric hindrance for the reagent at the syn-side of the molecule, resulting in an anti-substituted alcohol.

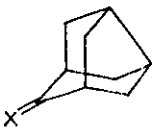
The C_6-anti configuration of 12 is supported by an independent synthesis via N-tosyl-3-azabicyclo[3.3.1]non-6-ene (13).[4] Epoxidation with m-chloroperbenzoic acid gave 14 with the epoxy ring exo substituted[10] in 96% yield. Refluxing of 14 in conc. HCl/HOAc (1/1) for 5 hr afforded 12 in 85% yield; no other isomers were isolated. 1-Azaadamantan-4-one and derivatives possess the ideal rigid cage for intramolecular charge transfer between the free electron pair of the N-atom and the carbonyl- or C = C electrons.[1] To investigate the latter phenomenon in the nor series the UV absorption data for the 3-azanoradamantanes and the C_9-substituted carbocyclic analogs are compiled in TABLE II. The $n-\pi^*$ transition of the carbocyclic compound 15a is at 290 nm and the $n-\pi^*$ transitions of 15b, 15c and 15d at 239 nm, 224 nm and 240 nm respectively.

The UV spectra of the 3-azanoradamantanes show two absorptions: the absorption for the normal transition of the C = X chromophore and an extra absorption for the

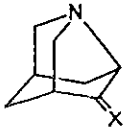
sigma-coupled transition. As compared to the C_9-substituted 3-azanoradamantanes the C_6-substituted compounds show a markedly diminished absorption for the sigma-coupled transition, indicating a smaller charge transfer interaction. Presumably the deviation from the ideal geometry in the C_6-substituted 3-azanoradamantanes causes a decrease of the magnitude of the sigma-coupling between the lone pair of the N-atom and the π-system of the C = X in the transition state. Therefore a gradual diminishing of the intramolecular charge transfer effect in dependence of the orbital geometries involved seems indicated. In reverse these results show nicely the ability of 3-azanoradamantanes to serve as models for a further study of intramolecular charge transfer phenomena in heterocage-like compounds.



2, 2b, 2c, 2d



15, a, b, c, d



3, 3b, 3c

TABLE II

UV absorption data as measured in n-hexane at 20°

Nr	X	$\lambda^{(1)}_{max}$ (nm)	$\lambda^{(2)}_{max}$ (nm)	$\varepsilon^{(1)}_{max}$	$\varepsilon^{(2)}_{max}$
1	-	<200	-	-	-
15a	O	-	290	-	17
2	O	229	290 sh	1400	30
3	O	230	300	137	23
15b	$C(CN)_2$	239	-	16500	-
2b	$C(CN)_2$	227	285	10200	6300
3b	$C(CN)_2$	237	290	10200	240
15c	CHCOOEt	224	-	20200	-
2c	CHCOOEt	208	260	10900	5100
3c	CHCOOEt	216	sh[a)]	13700	-
15d	C(CN)COOEt	240	-	17500	-
2d	C(CN)COOEt	224	298	8900	6000

a) The sigma-coupled transition is present as a shoulder.

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