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STRUCTURAL STUDIES ON SOME 1,3,5,7-TETRAAZABICYCLO-[3.3.1]-NONANE DERIVATIVES

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Abstract—From a study of the ^1H NMR spectra of a number of 3,7-disubstituted derivatives of 1,3,5,7-tetraazabicyclo-[3.3.1]-nonane it is concluded that these molecules exist in either chair-chair or flattened chair-chair conformations. The derivatives containing $-COCH_3$ and $-NO$ substitutents have room temperature spectra consistent with restricted rotation about their N–C and N–N bonds respectively. High temperature spectra reveal an activation energy, for the rotational barrier of the N–C bond in the diacetyl derivative, of 23 ± 2 K.Cal/mol.

INTRODUCTION

There is considerable interest in the structures of compounds which have hexamethylenetetramine (hexamine) as one of their degradation products.[1-3] In the present work we report the preparation and structures of some 1,3,5,7-tetraazabicyclo-[3.3.1]-nonane derivatives as obtained from ^1H NMR data.

The NMR spectrum of hexamine has a single resonance at $\delta = 4{\cdot}72$ in acetone showing that the protons in the six methylene groups are all equivalent. This equivalence is removed in all of the 1,3,5,7-tetraazabicyclo-[3.3.1]-nonanes considered in the present work (Fig 1), as indicated by the presence of AB quartets for the ring methylene protons (Table 1).

A study of these quartets at room and other temperatures permits estimates of the conformations of the cyclohexane rings in these compounds to be made.

RESULTS AND DISCUSSION

The NMR data for the 1,3,5,7-tetraazabicyclo-[3.3.1]-nonane derivatives **1–8**, (Table 1), consist of a singlet for the methylene bridge protons and AB quartets, arising from the inequivalence of the axial and equatorial protons, for the ring methylene groups. The spectrum of the 3,7 dichoro derivative, **1**, is given as a typical example in Fig 2.

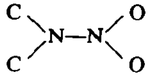
The singlet attributed to the bridge protons is usually broadened due to long range coupling with the equatorial protons of the ring methylene groups. These protons are connected by favourable 'W' bonding arrangements.

The low field portions of the AB quartets are attributed to the equatorial protons, these being broadened due to long range coupling. This is consistent with the analysis of the NMR data of some 1,3-diazabicyclo-[3.3.1] nonanes.[4]

In the case of derivatives **6** and **7** the signals of the ring methylene protons are considerably broadened. This presumably arises from quadrupolar relaxation induced by the nitrogen nuclei in the 3,7 substituents. The coupling is still resolvable in the spectrum of **6**, whereas in the case of **7** the AB quartet is reduced to two very broad singlets with half-height widths of about 40 Hz.

The dichloro derivative, **1**, has the lowest value (9·5 Hz) for the coupling constant J_{ae}. This is consistent with the molecule being in a chair-chair conformation such that the ring methylene protons have one adjacent N atom with its lone-pair axial and the other, the bridgehead nitrogen, with its lone-pair equatorial. For closely related molecules the value of J_{ae} is usually lower for methylene groups between one axial and one equatorial nitrogen lone pair than for methylenes between two equatorial nitrogen lone pairs.[13,14]

The coupling constant data for the derivatives **2–6** suggest that some flattening of the rings occurs. A consideration of the electronic nature of the substituents in these compounds indicates that electron delocalization could be concomitant with ring flattening thus leading to higher values of J_{ae}. Electron delocalization is expected to be appreciable for the nearly planar grouping



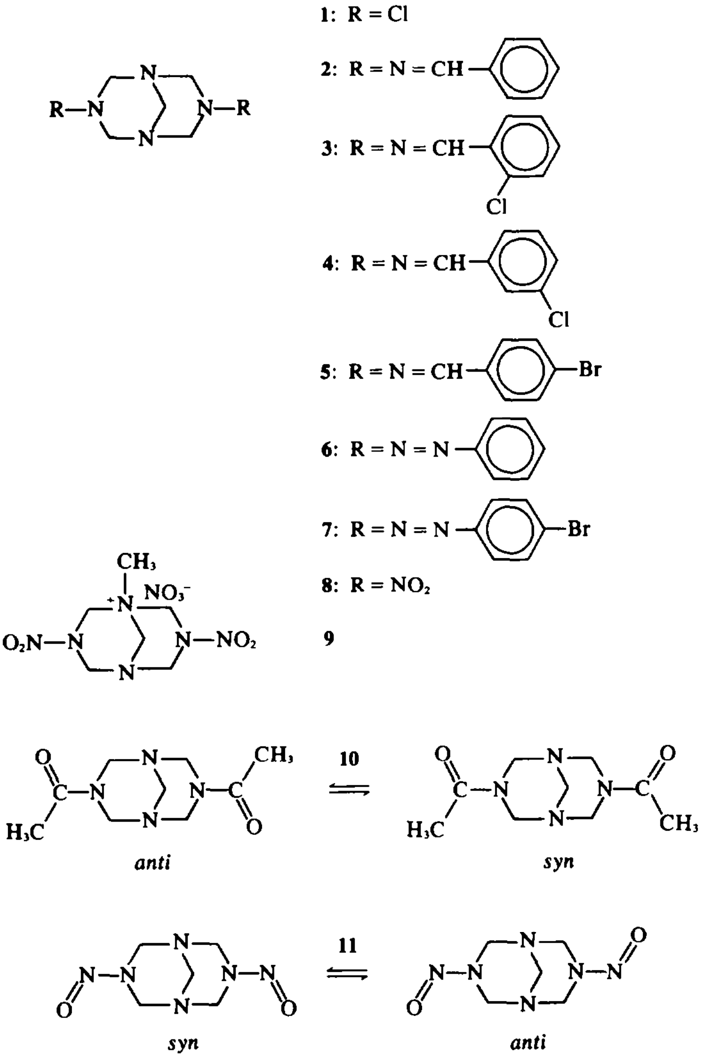


Fig 1.

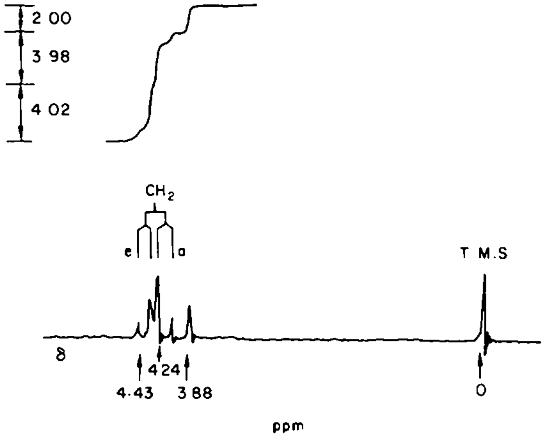


Fig. 2.

in secondary nitramines.[5] When two groupings of this type are incorporated into a molecular model of **8** flattening of the cyclohexane rings occurs thus supporting the interpretation of the coupling constant data.

Variable temperature NMR spectra were obtained for **1**, from 253 to 328 K, and for **8** from 203 to 323 K. The spectra do not show any significant variation with temperature for these compounds with symmetrical substituents, Cl and NO_2 respectively.

In the case of the unsymmetrically substituted derivative, **9**, the NMR spectrum consists of a singlet for the bridge methylene protons and two sets of AB quartets due to the pairs of ring methylene protons adjacent to the substituted and unsubstituted bridgehead N atoms.

The pairs of lines at $\delta = 6{\cdot}42$ and $5{\cdot}26$ are shown

Table 1. ^{1}H NMR data for some 1,3,5,7 - Tetraazabicyclo - [3.3.1] - nonane derivatives

Compound	Temp(K)	Solvent	Bridge $-CH_2-$	Max AB Quartets	H_{eq}	Δ_{ae} ppm	J_{ae} Hz	Others
1	299	$CDCl_3$	3·88(s)	4·24(p)	4·43(p)	0·19	9·5	
2	299	CCl_4	4·02(s)	4·30(p)	4·88(p)	0·58	12·0	
3	299	CCl_4	3·97(s)	4·30(p)	4·85(p)	0·55	12·0	
4	299	CCl_4	3·97(s)	4·27(p)	4·76(p)	0·49	12·0	
5	299	CCl_4	4·07(s)	4·35(p)	4·88(p)	0·53	12·0	
6	304	$CDCl_3$	4·38(s)	4·73(p)	5·58(p)	0·85	13·0	(c ~ 7·09$^{(a)}$(bs))
7	304	$CDCl_3$	4·38(s)	4·7(bs)	5·5(bs)	~0·8	—	(c ~ 7·08$^{(a)}$)
8	299	$(CD_3)_2CO$	4·32(s)	5·01(p)	5·71(p)	0·70	13·0	AB Quartet
	304	$(CD_3)_2SO$	4·14(s)	4·96(p)	5·52(p)	0·56	13·0	
9	304	$(CD_3)_2SO$	4·96(s)	4·91(p)	5·79(p)	0·88	14·0	3·12(s)
				5·26(p)	6·42(p)	1·16	12·0	$^+N-CH_3$
10	485	$CDCl_3$	4·23(s)	4·50(p)	5·34(p)	0·84	13·0	2·10(s)
								$COCH_3$
	299	$CDCl_3$	4·23(s)	4·23(p)	5·81(p)	1·58	13·0	2·10(s)
				4·74(p)	4·94(p)	0·20	13·0	$-COCH_3$
11	302	$(CD_3)_2CO$	4·59(s)	4·25(p)	5·81(p)	1·56	13·0	
Syn				5·30(p)	5·49(p)	0·19	13·0	
Anti			4·59(s)	4·33(p)	5·81(p)	1·48	13·0	
				5·30(p)	5·53(p)	0·23	13·0	

Chemical Shifts on the δ scale in ppm relative to TMS, (bs) very broad singlet; (p) pair of lines; (s) singlet; (a) aromatic protons; c centre of multiplet.

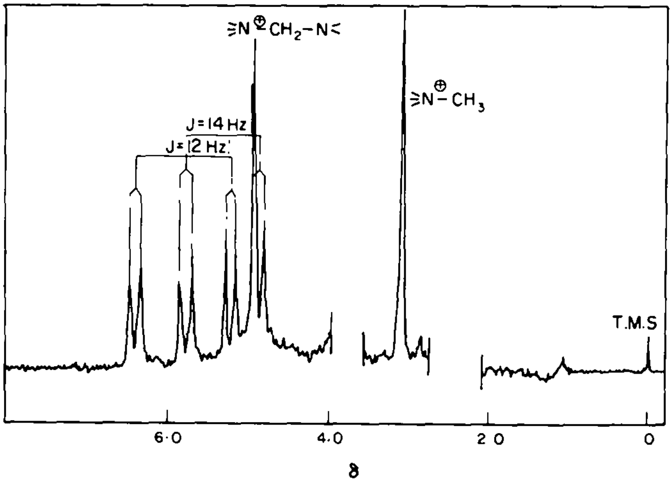


Fig. 3.

to be coupled by decoupling experiments, and attributed to the methylene group adjacent to the substituted bridgehead nitrogen atom. The pairs of lines at δ = 5·79 and 4·91 are also coupled, these are assigned to the methylene protons adjacent to the unsubstituted bridgehead nitrogen. The environment and spectra of these protons are comparable to those of the ring methylene groups in the disubstituted derivative **8**.

The NMR spectra of **10** and **11** are interpreted on the basis of restricted rotation about the N–C and N–N bonds, respectively, linking the acetyl and nitroso groups to the nonane ring system. At 299 K the spectrum of **10** in $CDCl_3$ shows that AB quartet for the ring methylene groups. The spectrum remains essentially unchanged at all temperatures down to 213 K. However, upon increasing the temperature the AB quartet signals broaden and coalesce at about 415 K. At higher temperatures a single broad AB quartet appears which continues to sharpen until about 483 K (Fig 4). The high temperature spectra are consistent with a flattened chair-chair conformation for **10**, whilst the room temperature data indicate the presence of the *syn* and *anti* forms, shown in Fig 1, due to restricted rotation around the N–C bond. It is expected that the anisotropic shielding produced by the C=O grouping will shield the axial proton *cis* to it to a

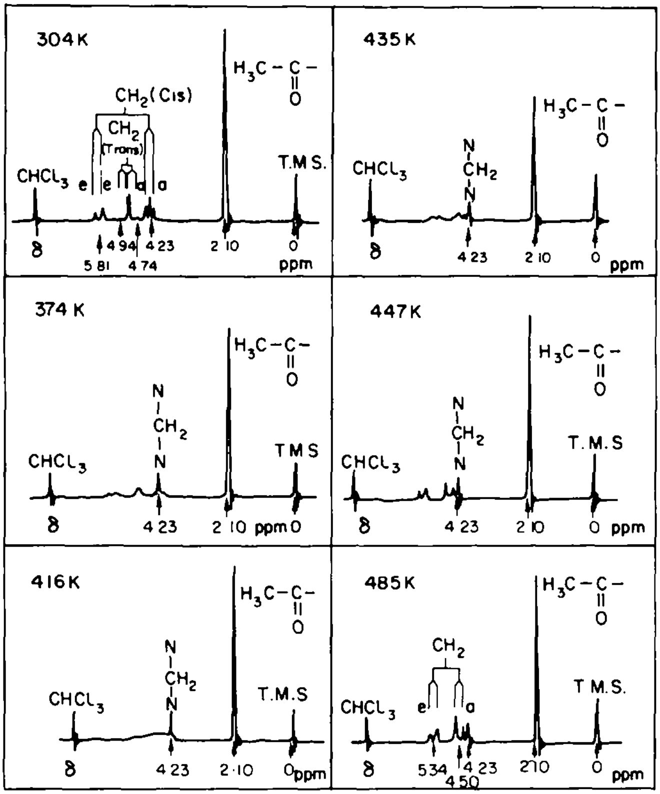


Fig. 4.

greater extent than the one *trans* to this grouping, whereas the *cis* and *trans* equatorial protons will be influenced to a smaller extent. Off-resonance decoupling experiments show that the lines centred at $\delta = 5{\cdot}81$ and $4{\cdot}23$ are coupled and are assigned to the protons *cis* to the $\rangle$C=O grouping, whilst the inner quartet which is also coupled is attributed to the protons *trans* to this grouping.

Analysis of the variable temperature line half-widths of the AB lines, Table 2, permits an activation energy of 23 ± 2 K cal/mol to be obtained for the barrier to rotation around the N—C bond which is in reasonable agreement with values reported for amides and other comparable compounds.[6]

Table 2. Temperature dependence of the AB signals from the ring methylene protons of **10**

$1/T{\cdot}10^{-3}$ (K^{-1})	Half-Width (Hz)		K	Log K
3·289	3·4		—	—
2·674	7·9		14·1	1·15
2·299	14·9	7·9	31·3	1·49
2·237	5·8	3·4	32·3	2·51
2·062	4·9	2·9	—	—

The anisotropic shielding produced by the $\rangle$C=O grouping in **10** is insufficient to permit the signals from either the *cis* or the *trans* axial protons of the *syn* and the *anti* isomers to be distinguished at room temperature. However, the nitroso group produces a greater shielding anisotropy such that the room temperature spectrum of **11** may be interpreted in terms of individual spectra for the two isomers, both of which have flattened chair-chair conformations, together with some accidental degeneracy. (Fig 5).

The *cis* axial ring methylene protons of the two isomers are both shielded, but to different degrees, and produce two high field pairs of lines at $\delta = 4{\cdot}25$ and 4·33. The *trans* axial protons are shielded to a smaller extent and the signals for the two isomers coincide at $\delta = 5{\cdot}30$. The remaining two pairs of lines at $\delta \approx 5{\cdot}5$ (5·49 and 5·53) and $\delta = 5{\cdot}81$, are assigned to coincidental signals arising from the *trans* and *cis* equatorial protons of the ring methylene groups. This assignment is supported by decoupling experiments, and from a consideration of the integrals.

The above discussion of the spectra of **10** and **11** in terms of geometrical isomerism and restricted rotation rather than conformational differences between the rings in the bicyclic system is

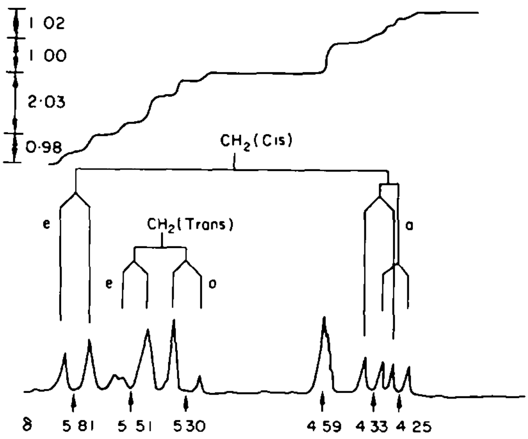


Fig. 5.

supported by the variable temperature data on **1** and **8**.

EXPERIMENTAL

Compounds **1**,[7] **2**,[8] **6**,[8] **7**,[8] **8**,[9] **9**,[10] **10**,[11] and **11**[12] were prepared by published procedures. The derivatives **3**, **4**, and **5** were prepared by dissolving 18·6 gm (0·1 mole) 3,7 - dinitroso - 1,3,5,7 - tetraazabicyclo - [3.3.1] - nonane in water and reducing with Na/Hg. The resulting 3,7 diamine was not isolated. A stoichiometric amount (0·2 mole) of the appropriately substituted benzaldehyde was added. After 24 hr the crystalline products were filtered off and recrystallised from EtOH. Compound **3**, mp 149–150°; (Found: C, 56·75; H, 5·06; N, 20·71. Calc. for C, 56·58, H, 5·00, N, 20·84%) Compound **4**, mp 143–145°; (Found: C, 56·73; H, 5·02; N, 20·73. Calc. for C, 56·58; H, 5·00; N, 20·84%). Compound **5** m.p. 205–206°; (Found: C, 46·56; H, 3·96; N, 17·03. Calc. for C, 46·36; H, 4·10; N, 17·07%).

The NMR spectra were obtained at 60 and 100 MHZ using TMS as internal reference.

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