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PROTON MAGNETIC RESONANCE STUDIES OF COMPOUNDS WITH BRIDGEHEAD NITROGEN ATOMS—VII*

CONFIGURATIONAL AND CONFORMATIONAL STUDIES WITH SUBSTITUTED 1,8-DIAZABICYCLO[4.3.0]NONANES

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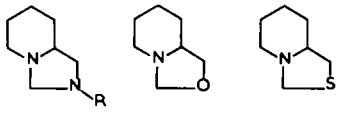
Abstract—The configurations and preferred conformations of some 8-alkyl 1,8-diazabicyclo[4.3.0]nonanes and the corresponding 2-Me substituted compounds have been deduced on the basis of their NMR spectra.

THE synthesis of 1,8-diazabicyclo[4.3.0]nonane (I, R = H) was first reported[1] in 1960 and assigned a *cis*-fused ring conformation on the basis of the IR spectrum of its phenylurea derivative which showed no bands in the 2800–2700 cm^{-1} region. In previous papers in this series we have shown that 8-oxa,[2] and 8-thia-1-azabicyclo-[4.3.0]nonane[3] (II and III) exist at room temperature as conformational mixtures consisting of ca. 50% *cis*- and 50% *trans*-fused ring conformations. The presence of the latter conformation was clearly indicated in both cases by strong absorption in the 2800–2700 cm^{-1} region of the IR spectra.



I II III

One of the most important factors influencing conformational equilibria in II and III is the dipole-dipole interaction arising from the presence of the heteroatoms. The unfavourable dipole interaction present, for example, in the *trans*-fused ring conformation (V) is relieved in the *cis*-fused ring conformation (VI) but not in the alternative *cis*-fused ring conformation (VII). The significance of dipole-dipole interactions in affecting the position of conformational equilibria in 1,3-hetero-systems was clearly demonstrated[4] in the case of *trans*-10,6-H-10-methyl-3-oxa-1-azabicyclo[4.4.0]decane (VIII) which adopts a predominantly *cis*-fused ring conformation at room temperature. In the light of this one might expect 1,8-diazabicyclo-[4.3.0]nonane to exist either, like II and III, as an equilibrium mixture of *cis*- and *trans*-fused ring conformations (IX, X, XI) or predominantly in the *trans*-fused ring conformation (IX), since the destablizing influence of the dipolar interaction has

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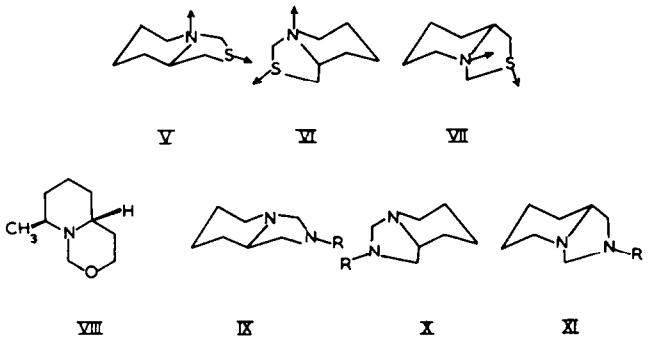
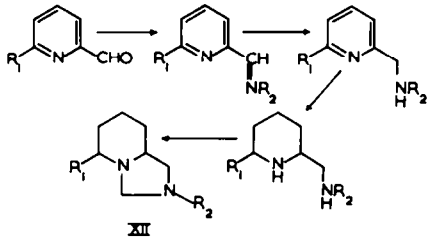
been relieved in these conformations by inversion at the 8N atom. Indolizidine, in which there is no dipole interaction involving heteroatoms, has been shown[5] to exist in a predominantly *trans*-fused ring conformation at room temperature and so one might expect IX to be the preferred conformation for 1,8-diazabicyclo-[4.3.0]nonane.



V VI VII

VIII IX X XI

To investigate the claim[1] that I (R = H) exists in a *cis*-fused ring conformation, a series of N-alkyl substituted 1,8-diazabicyclo[4.3.0]nonanes along with the corresponding 2-Me derivatives have been synthesized by the route shown in Fig. 1. The pyridine 2-aldehyde was condensed with various alkylamines to give the corresponding



XII

FIG. 1 Preparation of 8-alkyl-1,8-diazabicyclo[4.3.0]nonane.

Schiff's bases. Reduction of these with sodium borohydride gave pyridine 2-alkylamines which were further reduced with sodium and ethanol to piperidine-2-alkylamines. Cyclization with formaldehyde gave the substituted 1,8-diazabicyclo-[4.3.0]nonanes and the two racemic epimers possible when R_1 = Me were separated by preparative GLC. The configurations of the 2-Me substituted compounds can be deduced from chemical evidence. Thus Na–EtOH reduction of 6-methylpyridine-2-alkylamines is expected to yield epimeric mixtures richer in the diequatorially substituted product; the epimer obtained in highest yield was therefore assumed* to be the *cis*-2,6-H-2-methyl compound in each case.

* That this assumption is justified is shown by the absence of a signal arising from a C2-equatorial proton in the NMR spectra of the diazabicyclo[4.3.0]nonanes derived from these alkylamines. For a discussion of the stereochemical outcome of Na-EtOH reductions see "Elucidation of structures by physical and chemical methods" Vol. XI, Part II Interscience (1963).

There are six possible conformations for each of the N-substituted compounds, interconvertible by ring inversion or N inversion and in Fig. 2 these conformations for 8-alkyl-*cis*-2,6-H-2-methyl-1,8-diazabicyclo[4.3.0]nonane are shown. To decide, *a priori*, on the preferred conformation of this compound, conformations c, e, and f can be excluded because of the presence of unfavourable non-bonded interactions,

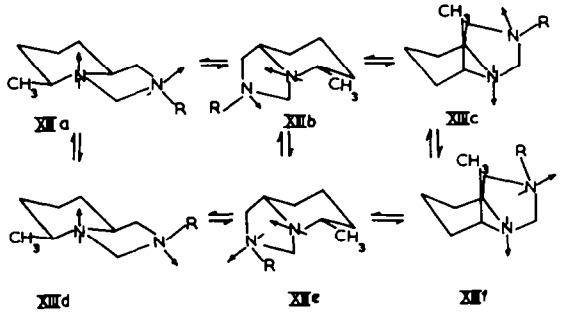


FIG. 2 Conformations of 8-alkyl *cis*-2,6-H-2-methyl-1,8-diazabicyclo[4.3.0]nonanes.

clearly evident in Dreiding models, and conformations a and e suffer from the destabilising influence of dipole-dipole interactions involving the N atoms. The two remaining conformations are d which has a *trans*-ring fusion and b with a *cis*-ring fusion. Since Aaron[6] has shown that for the *trans*-indolizidine $\rightleftharpoons$ *cis*-indolizidine equilibrium ΔG° must be greater than $-1{\cdot}9$ kcal mole^{-1} at 25°, the preferred conformation of 8-alkyl *cis*-2,6-H-2-methyl-1,8-diazabicyclo[4.3.0]nonane is therefore expected to be XIIId.* The qualitative nature of this argument does not, however, preclude the presence of, for example, conformation XIIIa from the equilibrium mixture. The preferred conformation of the 8-alkyl *trans*-2,6-H-2-methyl compound (Fig. 3) can be deduced using similar arguments. Conformations c, e and f are destabilized by non-bonded interactions and conformations a and f by unfavourable

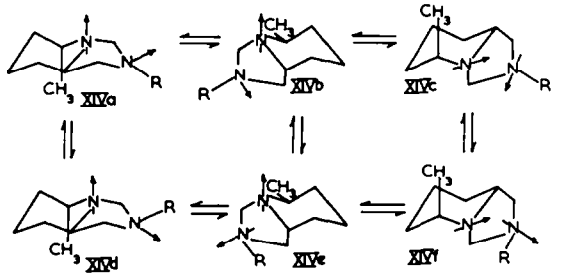


FIG. 3 Conformations of 8-alkyl *trans*-2,6-H-2-methyl-1,8-diazabicyclo[4.3.0]nonanes.

dipole-dipole interactions. The two energetically most stable conformations are therefore expected to be b and d. The *trans*-fused ring conformation d has an axial Me group introducing three gauche-butane interactions (ca. 2·55 kcal.mole^{-1}) into the

* A comparison of the stereochemistry of indolizidine and the type of system described in this paper has been discussed more fully in Part III.[2]

molecule, while the *cis*-conformation b has the Me group in an equatorial position introducing only one gauche-butane interaction (ca. 0·85 kcal.mole^{-1}). Thus, if the free energy difference between the *cis*- and *trans*-conformations of 1,8-diazabicyclo-[4.3.0]nonane is assumed to be similar to that of indolizidine, then the *cis*- and *trans*-conformations of 8-alkyl-*trans*-2,6-H-2-methyl-1,8-diazabicyclo[4.3.0]nonane will have roughly the same free energy and on these grounds this compound might then be expected to exist as an equilibrium mixture containing appreciable amounts of both conformations XIVb and XIVd at room temperature. In order to test the validity of these conclusions the IR and PMR spectra of the compounds were determined.

IR Spectra of 1,8-*diazabicyclo*[4.3.0]*nonanes*

The utility of the Bohlmann IR criterion (originally applied to quinolizidines[7]) in conformational studies with derivatives of II and III has been demonstrated.[2,3] A study of the 2700–2800 cm^{-1} region of the IR spectra of derivatives of I (R = alkyl) should therefore provide evidence regarding their preferred conformations but since it is well known[8] that many secondary and tertiary amines with α-hydrogen atoms

TABLE 1. IR SPECTRA OF 1,8-DIAZABICYCLO[4.3.0] NONANES

Compound	cm^{-1}	ε_a*
8-Methyl-1,8-diazabicyclo[4.3.0]nonane	2810	160
	2790	180
	2740	55
	2670	28
8-Isopropyl-1,8-diazabicyclo[4.3.0]nonane	2800	104
	2773	78
	2732	46
8-t-Butyl-1,8-diazabicyclo[4.3.0]nonane	2797	82
	2770	60
	2735	51
	2670	23
8-Cyclohexyl-1,8-diazabicyclo[4.3.0]nonane	2797	82
	2670	24
cis-2,6-H-2,8-Dimethyl-1,8-diazabicyclo[4.3.0]nonane	2796	64
	2728	43
	2600	13
cis-2,6-H-2-Methyl,8-isopropyl-1,8-diazabicyclo[4.3.0]nonane	2801	82
	2740	40
	2600	23
cis-2,6-H-2-Methyl,8-t-butyl-1,8-diazabicyclo[4.3.0]nonane	2796	64
	2728	43
	2600	13
trans-2,6-H-2,8-Dimethyl-1,8-diazabicyclo[4.3.0]nonane	2787	88
trans-2,6-H-2-Methyl,8-isopropyl-1,8-diazabicyclo[4.3.0]nonane	2818	83
trans-2,6-H-2-Methyl,8-t-butyl-1,8-diazabicyclo[4.3.0]nonane	2825	60

* Apparent extinction coefficient.

give rise to bands in this region of the IR, the interpretation of the spectra of I(R = Me, iPr, cyclohexyl) will be rendered more difficult. The spectrum of I(R = tBu) will be free of this complicating factor.

All the 8-alkyl-1,8-diazabicyclo[4.3.0]nonanes (I, R = alkyl) show a strong band in the IR (Table 1, Fig. 4) between 2785–2800 cm^{-1} with one or more shoulders on the low wave number side gradually decreasing in intensity until the band tails off at ca. 2500 cm^{-1}. In the case of I(R = tBu) these bands must have their origin in the presence

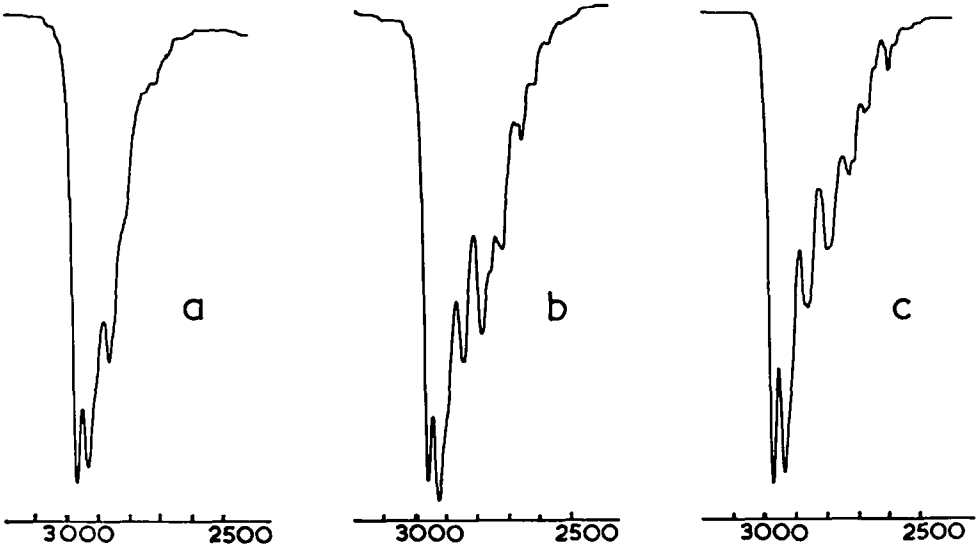
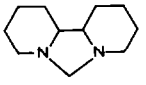


FIG. 4 C—H stretching region of IR spectra of:
a. *trans*-2,6-H-2-methyl,8-t-butyl-1,8-diazabicyclo[4.3.0]nonane
b. 8-t-butyl 1,8-diazabicyclo[4.3.0]nonane
c. *cis*-2,6-H-2-methyl,8-t-butyl-1,8-diazabicyclo[4.3.0]nonane.

of two C—H bonds *trans* and axial with respect to the lone pair of electrons on the bridgehead N, indicating the presence of an appreciable amount of the *trans*-fused ring conformation in the equilibrium mixture at room temperature. It seems highly probable therefore that this is also the preferred conformation for I(R = Me, iPr, cyclohexyl) but the IR spectra cannot provide clear evidence for this or information regarding the stereochemistry at the conformationally unstable 8N atom. The IR spectra of the 8-alkyl *cis*-2,6-H-2-methyl-1,8-diazabicyclo[4.3.0]nonanes (XII, R_1 = Me, R_2 = alkyl) also show a prominent peak at 2800 cm^{-1} with shoulders extending down to 2500 cm^{-1}. The intensity of the 2800 cm^{-1} peak decreases in the sequence R_2 = Me, iPr, tBu, indicating contributions to this peak from both the C_2—H and C_6—H bonds in the *trans*-fused ring conformation (XIIIa or d) and from the presence of the 8N-alkyl group.

The 8-alkyl-*trans*-2,6-H-2-methyl compounds have rather variable IR spectra. The 8-tBu compound has no bands between 2800–2700 cm^{-1}, the only evidence of any bands near this region being a small shoulder at 2820 cm^{-1}, whereas the 8-Me and 8-iPr compounds both exhibit a band at ca. 2780 cm^{-1} (much weaker in the case of the 8-iPr compound) which must therefore owe its origin to the presence of the 8-alkyl substituent. Unfortunately the IR evidence does not permit conformational preferences to be assigned to these compounds since both the *cis*-fused ring conformer (XIVb) and the *trans*-fused ring conformer (XIVd) lack the two axially situated C—H bonds

adjacent to the bridgehead N required to give rise to Bohlmann's bands. Thus, although the IR spectra of the 1,8-diazabicyclo[4.3.0]nonanes show interesting variations in the appearance of the bands in the 2700–2800 cm^{-1} region, the presence of the 2-Me and of the 8-alkyl substituents in these compounds renders Bohlmann's criterion of much less importance in determining the conformational preferences in this series of compounds than in our studies on derivatives of II and III. The ambiguity of some of the IR data could of course have been avoided by studying the 3,4 or 5-Me substituted derivatives, but the commercial availability of 6-methylpyridine-2-aldehyde prompted us to begin our investigations on the 2-Me compounds readily prepared from this (Fig. 1). In addition, initial attempts to separate the racemic epimers of certain of these other 8-alkyl-Me-substituted compounds proved to be



XV

much more difficult than the rather facile separation achieved with the 2-Me compounds.

NMR spectra of 1,8-*diazabicyclo*[4.3.0]*nonanes*

(a) 8-*Alkyl*-1,8-*diazabicyclo*[4.3.0]*nonanes* (I) *and* 8-*alkyl* cis-2,6-H-2-*methyl*-1,8-*diazabicyclo*[4.3.0]*nonanes* (XIII). The preceeding conformational arguments suggest that the 8-alkyl-*cis*-2,6-H-2-methyl and 8-alkyl-1,8-diazabicyclo[4.3.0]nonanes exist predominantly in the *trans*-fused ring conformations XIIId and IX respectively, and the IR spectra (Table 1) of these compounds indicate the presence of *trans*-fused ring conformations. The NMR spectra (Table 2, Fig. 5) provide evidence in support of these conclusions but do not permit firm decisions regarding the stereochemistry about the 8N atom to be made. During our studies on II[2] and III[3] two NMR criteria were developed and discussed for the determination of preferred conformations in these systems; the geminal coupling constant (J_{gem}*) for the methylene group between the heteroatoms in the *trans*-fused ring conformers was always more positive than for the *cis*-fused ring conformers and the chemical shift between these two protons was always greater in the predominantly *trans*-fused ring conformers. As can be seen from Table 2 all the compounds have a J_{gem} for the C_9 methylene group of between $-4{\cdot}1$ and $-4{\cdot}8$ c/s and $\Delta H_{9\alpha}H_{9\beta}$ from 0·54 to 0·87 ppm. This range of J_{gem} is similar to the values observed for the *trans syn trans* and *trans anti trans* compounds of type XV[9] and indicates a *trans*-fused ring conformation for I and XIII. The $H_{9\beta}$ protons in the 8-alkyl-1,8-diazabicyclo[4.3.0] nonanes all appear at slightly higher field than in the corresponding *cis*-2,6-H-2-methyl compounds which, as discussed[2] in connection with II, is evidence for an equatorial 2-Me group and thus a *trans*-fused ring conformation XIIIa or XIIId. This, together with the large $\Delta H_{9\alpha}H_{9\beta}$ for the compounds under discussion all seems to indicate either conformation XIIIa or XIIId. One further point in support of this conclusion is the lack of a signal at about 7 τ due to an

* J_{gem} is assumed negative.

TABLE 2. NMR SPECTRA OF *trans*-FUSED 1,8-DIAZABICYCLO[4.3.0]NONANES

Compound	Coupling Constants (c/s)[a]				Chemical Shifts (τ)[b]						Others
	$J_{H_{9\beta}H_{9\alpha}}$	$J_{H_{7\beta}H_{7\alpha}}$	$J_{H_{7\beta}H_6}$	$J_{H_{7\alpha}H_6}$	$H_{9\beta}$	$H_{9\alpha}$	$\Delta H_{9\alpha}H_{9\beta}$	$H_{7\alpha}$	$H_{7\beta}$	H_{2e}	
8-Methyl-1,8-diazabicyclo[4.3.0]nonane	−4·7	—	—	—	6·32	6·86	0·54	—	—	7·0 (m)	—
8-Isopropyl-1,8-diazabicyclo[4.3.0]nonane	−4·3	−7·8	5·6	9·2	6·14	6·85	0·71	7·07	7·43	7·0 (m)	7·85 H_{6a}
8-t-Butyl-1,8-diazabicyclo[4.3.0]nonane	−4·1	−7·8	5·25	9·5	6·15	6·87	0·72	7·10	7·44	7·0 (m)	7·85 H_{6a}
8-Cyclohexyl-1,8-diazabicyclo[4.3.0]nonane	−4·2	−7·8	5·5	9·75	6·14	6·87	0·73	7·10	7·42	7·0 (m)	7·80 H_{6a}
cis-2,6-H-2,8-Dimethyl-1,8-diazabicyclo[4.3.0]nonane	−4·8	—	—	—	6·21	6·82	0·61	—	—	—	—
cis-2,6-H-2-Methyl,8-isopropyl-1,8-diazabicyclo[4.3.0]-nonane	−4·5	−7·8	6·1	9·6	6·05	6·86	0·81	7·11	7·43	—	7·80 H_{6a}
cis-2,6-H-2-Methyl,8-t-butyl-1,8-diazabicyclo[4.3.0]nonane	−4·3	−7·5	5·9	8·9	6·00	6·87	0·87	7·06	7·38	—	7·80 H_{6a}

[a] ±0·3 c/s, [b] ±0·05 ppm, m = multiplet measured from centre.

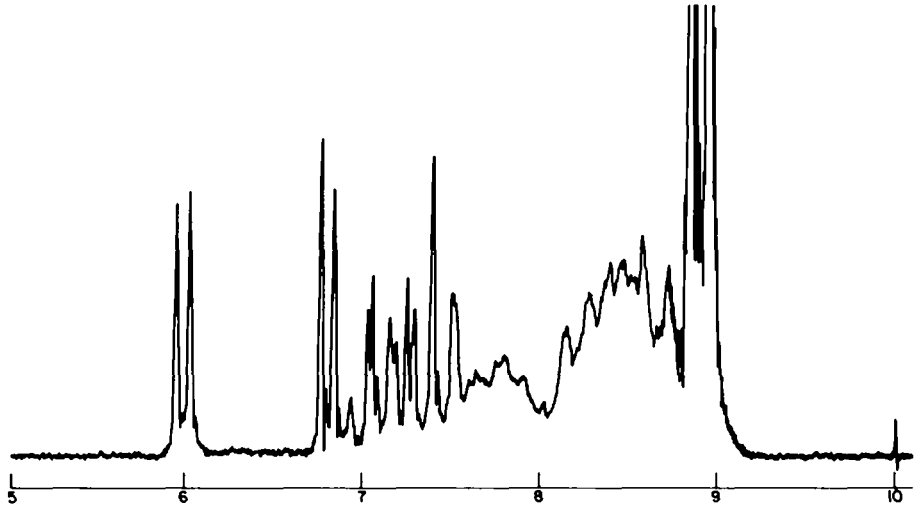


FIG. 5 NMR spectrum of *cis*-2,6-H-2-methyl-8-isopropyl 1,8-diazabicyclo[4.3.0]nonane.

equatorial proton adjacent to the N atom. The values of J_{gem} and the chemical shifts of the C_9 methylene protons show several interesting regularities. Thus, whereas the chemical shift of H_{9_α} is ca. 6·86 τ for all the compounds the chemical shift of $H_{9\beta}$ for the two 8-Me compounds is ca. 0·2 ppm to higher field than $H_{9\beta}$ in the remaining compounds. A similar effect has been observed by Booth[10] who suggests that variation in the shielding of the axial proton at position 2 in various N-alkyl piperidines is due in part to an electron release mechanism similar to hyperconjugation. The same

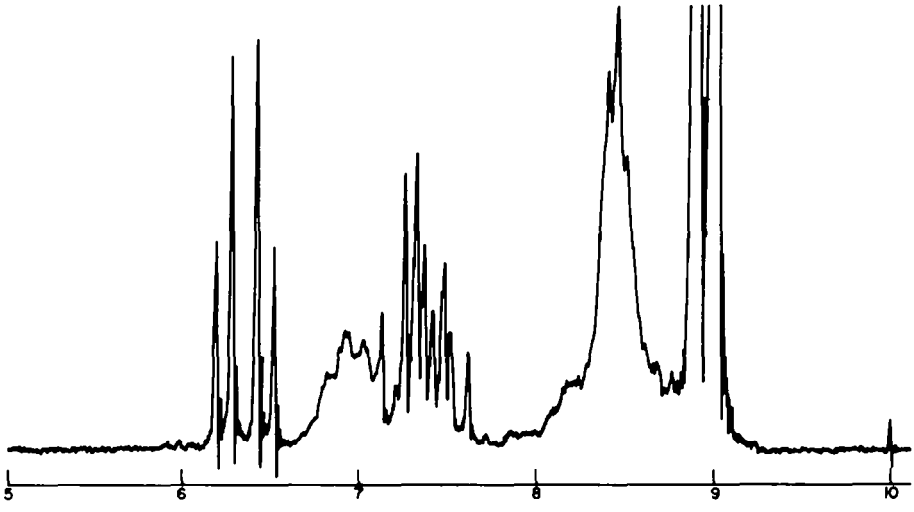


FIG. 6 NMR spectrum of *trans*-2,6-H-2-methyl-8-isopropyl 1,8-diazabicyclo[4.3.0]nonane.

mechanism could be operative in these compounds. The values of J_{gem} for the C_9 methylene protons become increasingly positive in the series I, R = Me, i-Pr, t-Bu and in XII (R_1 = Me) R_2 = Me, i-Pr, t-Bu. This could be due to the above mentioned electron release mechanism but could also arise from the increasing planarity of the N atom as the N-alkyl substituent increases in bulk. Riddell[11] has advanced this idea to explain changes in the free energy of activation of inversion in *syn*-hexahydrotriazines. However one cannot rule out the possibility that these variations in NMR parameters of the C_9 methylene protons are due in part to conformational mobility

TABLE 3. NMR OF *cis*-FUSED 1,8-DIAZABICYCLO[4.3.0]NONANES

Compound	Coupling Constants (c/s)[a]	Chemical Shifts (τ)[b]				
	$J_{H_9H_{9'}}$	H_9	$H_{9'}$	$\Delta H_9H_{9'}$	$H_{7a}H_{7\beta}$	$H_{2a}H_{6e}$
trans-2,6-H-2,8-Dimethyl-1,8-diazabicyclo[4.3.0]nonane	−6·5	6·28	6·60	0·32	7·45 (m)	7·0 (m)
trans-2,6-H-2-Methyl,8-isopropyl-1,8-diazabicyclo[4.3.0]nonane	−5·9	6·24	6·47	0·23	7·40 (m)	6·9 (m)
trans-2,6-H-2-Methyl,8-t-butyl-1,8-diazabicyclo[4.3.0]nonane	−5·7	6·23	6·41	0·18	7·35 (m)	7·0 (m)

[a] ±0·3 c/s. [b] ±0·05 ppm. (m) = multiplet measured from centre.

at the 8N atom. The J_{gem} for the C_7 methylene protons remain constant at −7·8 c/s and the vicinal couplings of the C_7 protons with the C_6 proton show only small variations.

(b) trans-2,6-H-2-*Methyl*-1,8-*diazabicyclo*[4.3.0]*nonanes* (XIV). The NMR spectra of these compounds (Table 3, Fig. 6) are very different from the spectra of the compounds listed in Table 2 (Fig. 5), the values of $J_{H_9H_{9'}}$ being more negative and ΔH_9H_9, varying over the range 0·18–0·32 ppm. These two facts, by analogy with our previous work[2,3] suggest the presence of appreciable amounts of *cis*-fused ring conformations in the equilibrium mixture of XIV. In addition the NMR spectra of the *trans*-2,6-H-2-methyl compounds all show a broad two proton multiplet centred at ca. 7·0 τ. Part of this signal will be due to the equatorial proton on the bridgehead C atom (gauche to the bridgehead N atom in XIVb) and part to the axial proton on C_2 which will suffer two 1–3 deshieldings from the *cis*-fused 5-membered ring in XIVb. A similar deshielding was observed in the NMR of VIII[4] which exists in a predominantly *cis*-fused ring conformation.

CONCLUSION

Although not entirely free from ambiguity, the weight of the IR and NMR evidence particularly when compared with our work on systems II[2] and III[3], together with the preceding conformational argument, suggests a predominantly *trans*-fused ring conformation for the 8-alkyl-1,8-diazabicyclo[4.3.0]nonanes and for the *cis*-2,6-H-2-methyl-1,8-diazabicyclo[4.3.0]nonanes. The *trans*-2,6-H-2-methyl compounds appear to exist at room temperature with a considerable proportion of *cis*-fused ring conformations in the equilibrium mixture. These conclusions lead us to question the claim[1] that 1,8-diazabicyclo[4.3.0]nonane exists in a *cis*-fused ring conformation and so the

described synthesis of this compound was repeated. An examination of the compound (Experimental section) showed it to be 2-methylaminomethyl piperidine and not 1,8-diazabicyclo[4.3.0]nonane as claimed. An attempt to prepare 1,8-diazabicyclo-[4.3.0]nonane by the reaction of 2-aminomethyl piperidine with formaldehyde gave only polymeric material.

EXPERIMENTAL

M.ps are uncorrected, IR spectra were run on a Perkin Elmer 557 grating instrument as 0·2M solns in $CDCl_3$ using 0·1 mm matched cells and on a Unicam S.P.100 as 0·1M solns in $CDCl_3$ using 0·5 mm matched cells.

The NMR spectra were determined on a Perkin Elmer R-10 and on a Varian HA-60 spectrometer as 10% solns in $CDCl_3$.

Preparation of 2-alkylaminomethylpyridines via 2-alkyliminomethylpyridines

General procedure. The pyridine-2-aldehyde (0·19M) was added to a soln of the alkylamine (0·25M) in benzene (200 ml) and the reaction mixture was refluxed until the theoretical amount of water had been removed by a Dean and Stark apparatus. Excess benzene was removed under reduced press and the crude product was distilled. To the 2-alkyliminomethylpyridine (0·1M) in dry MeOH (200 ml) was added $NaBH_4$ (0·2M) with stirring. When the reaction had ceased the mixture was acidified with dil HCl, basified with NaOHaq and ether extracted. The ether extract was dried (Na_2SO_4) and concentrated and the crude 2-alkylaminomethylpyridine was distilled.

2-Isopropyliminomethylpyridine (25·5 g, 92%) was obtained from pyridine-2-aldehyde (20 g) as a colourless mobile oil b.p., 92–93°/15 mm $n_D^{22\cdot0}$ 1·5163. (Found: C, 73·41; H, 7·96; N, 18·60. $C_9H_{12}N_2$ requires: C, 72·94; H, 8·16; N, 18·90%). *2-isopropylaminomethylpyridine* (23 g, 90%) was obtained from 2-isopropyliminomethylpyridine (25 g) as a colourless mobile oil b.p., 97–99°/10 mm $n_D^{22\cdot0}$ 1·5012. (Found: C, 72·08; H, 8·97; N, 19·03. $C_9H_{14}N_2$ requires: C, 71·95; H, 9·39; N, 18·65%).

2-t-Butyliminomethylpyridine (27·0 g, 89%) was obtained from pyridine-2-aldehyde (20 g) as a colourless mobile oil b.p., 65–66°/0·5 mm $n_D^{21\cdot0}$ 1·5131. (Found: C, 74·82; H, 8·90; N, 18·00. $C_{10}H_{14}N_2$ requires: C, 74·03; H, 8·70; N, 17·27%). *2-t-Butylaminomethylpyridine* (22·4 g, 82%) was obtained from 2-t-butyliminomethylpyridine (27 g) as a colourless mobile oil b.p., 79–80°/0·6 mm $n_D^{21\cdot0}$ 1·4977. (Found: C, 73·21; H, 9·85; N, 17·21. $C_{10}H_{16}N_2$ requires: C, 73·12; H, 9·82; N, 17·06%).

2-Cyclohexyliminomethylpyridine (27 g, 77%) was obtained from pyridine-2-aldehyde (20 g) as a colourless mobile oil b.p., 105–106°/0·5 mm $n_D^{21\cdot0}$ 1·5433. (Found: C, 76·70; H, 8·66; N, 15·10. $C_{12}H_{16}N_2$ requires: C, 76·55; H, 8·57; N, 14·88%). *2-Cyclohexylaminomethylpyridine* (17·5 g, 71%) was obtained from 2-cyclohexyliminomethylpyridine (24 g) as a deep yellow oil b.p., 131–133°/1·3 mm. This compound rapidly decomposed on exposure to air and analysis was inaccurate.

2-Isopropyliminomethyl-6-methylpyridine (19 g, 95%) was obtained from 6-methylpyridine-2-aldehyde (15 g) as a pale yellow mobile oil b.p., 104–106°/16 mm $n_D^{21\cdot0}$ 1·5132. (Found: C, 73·62; H, 8·54; N, 17·30. $C_{10}H_{14}N_2$ requires: C, 74·03; H, 8·70; N, 17·27%). *2-Isopropylaminomethyl-6-methylpyridine* (15 g, 95%) was obtained from 2-isopropyliminomethyl-6-methylpyridine (15 g) as a yellow oil b.p., 115–117°/20 mm. This compound decomposed on distillation and analyses were inaccurate.

2-t-Butyliminomethyl-6-methylpyridine (19·2 g, 89%) was obtained from 6-methylpyridine-2-aldehyde (15 g) as a colourless mobile oil b.p., 105–106°/10 mm $n_D^{13\cdot5}$ 1·5143. (Found: C, 74·34; H, 9·14; N, 16·14. $C_{11}H_{16}N_2$ requires: C, 74·95; H, 9·15; N, 15·90%). *2-t-Butylaminomethyl-6-methylpyridine* (14.1 g, 93%) was obtained from 2-t-butyliminomethyl-5-methylpyridine (15 g) as a colourless mobile oil b.p., 81–83°/0·3 mm $n_D^{13\cdot5}$ 1·5080. (FSund: C, 7*a*·95; H, 10·26; N, 15·76. $C_{11}G_{18}N_2$ requires: C, 74·11; H, 10·18; N, 15·71%).

Sodium-ethanol reduction of 2-alkylaminomethylpyridines

General procedure. The 2-alkylaminomethylpyridine (0·1M) was refluxed in abs EtOH (500 ml) and Na (40 g) was added. When all the Na had dissolved the soln was acidified with dil HCl and excess EtOH removed. The soln was basified with NaOHaq and ether extracted. The ether soln was dried (Na_2SO_4) and concentrated and the crude 2-alkylaminomethylpiperidine was distilled.

2-*Methylaminomethylpiperidine* (12 g, 58%) was obtained from 2-methylaminomethylpyridine (20 g) as a colourless oil b.p., 76–78°/15 mm $n_D^{14.0}$ 1·4761. (Found: C, 65·28; H, 12·92; N, 21·67 $C_7H_{16}N_2$ requires: C, 65·57; H, 12·58; N, 21·85%).

2-*Isopropylaminomethylpiperidine* (11·3 g, 60%) was obtained from 2-isopropylaminomethylpyridine (18 g) as a colourless mobile oil b.p., 96–98°/15 mm $n_D^{14.0}$ 1·4677. (Found: C, 68·93; H, 13·35; N, 17·70. $C_9H_{20}N_2$ requires: C, 69·17; H, 12·90; N, 17·93%).

2-*t-Butylaminomethylpiperidine* (13·8 g, 89%) was obtained from 2-t-butylaminomethylpyridine (15 g) as a colourless mobile oil b.p., 73–74°/1·3 mm $n_D^{17.5}$ 1·4661. (Found: C, 70·34; H, 13·41; N, 16·34. $C_{10}H_{22}N_2$ requires: C, 70·53; H, 13·02; N, 16·45%).

2-*Cyclohexylaminomethylpiperidine* (12 g, 78%) was obtained from 2-cyclohexylaminomethylpyridine (15 g) as a colourless mobile oil b.p., 104–106°/0·55 mm $n_D^{21.0}$ 1·4943. (Found: C, 73·21; H, 12·61; N, 14·66. $C_{12}H_{24}N_2$ requires: C, 73·41; H, 12·32; N, 14·27%).

An epimeric mixture of the 2-methylaminomethyl-6-methylpiperidines (17 g, 65%) was obtained from 2-methylaminomethyl-6-methylpyridine (25 g) as a colourless oil b.p., 94–95°/26 mm. (Found: C, 67·05; H, 13·12; N, 19·59. $C_8H_{18}N_2$ requires: C, 67·55; H, 12·76; N, 19·70%).

An epimeric mixture of the 2-isopropylaminomethyl-6-methylpiperidines (12 g, 68%) was obtained from 2-isopropylaminomethyl-6-methylpyridine (17 g) as a colourless mobile oil b.p., 88–90°/10 mm. (Found: C, 70·50; H, 13·13; N, 16·40. $C_{10}H_{22}N_2$ requires: C, 70·53; H, 13·02; N, 16·45%).

An epimeric mixture of the 2-t-butylaminomethyl-6-methylpiperidines (8·3 g, 67%) was obtained from 2-t-butylaminomethyl-6-methylpyridine (12 g) as a colourless mobile oil b.p., 68–70°/0·3 mm. (Found: C, 72·01; H, 13·27; N, 15·26. $C_{11}H_{24}N_2$ requires: C, 71·68; H, 13·13; N, 15·20%).

Preparation of 1,8-*diazabicyclo*[4.3.0]*nonanes*

General procedure. The alkylaminomethylpiperidine was shaken with an excess of 40% formaldehyde soln for ½ hr. The reaction mixture was basified with NaOH aq and ether extracted 3 times. The ether extract was dried (Na_2SO_4) and concentrated and the crude product was distilled under vacuum.

8-*Methyl*-1,8-*diazabicyclo*[4.3.0]*nonane* (8·1 g, 74%) was obtained from 2-methylaminomethylpiperidine (10 g) as a colourless mobile oil b.p., 86–87°/27 mm $n_D^{14.0}$ 1·4780. (Found: C, 68·16; H, 11·91; N, 19·72. $C_8H_{16}N_2$ requires: C, 68·52; H, 11·50; N, 19·98%).

8-*Isopropyl*-1,8-*diazabicyclo*[4.3.0]*nonane* (5·0 g, 93%) was obtained from 2-isopropylaminomethylpiperidine (5·0 g) as a colourless mobile oil b.p., 94–95°/11 mm $n_D^{14.0}$ 1·4789. (Found: C, 71·22; H, 12·27; N, 16·41. $C_{10}H_{20}N_2$ requires: C, 71·37; H, 11·98; N, 16·65%).

8-*t-Butyl*-1,8-*diazabicyclo*[4.3.0]*nonane* (4·3 g, 80%) was obtained from 2-t-butylaminomethylpiperidine (5·0 g) as a colourless mobile oil b.p., 107–108°/13 mm $n_D^{22.5}$ 1·4761. (Found: C, 71·96; H, 12·38; N, 15·33. $C_{11}H_{22}N_2$ requires: C, 72·47; H, 12·16; N, 15·37%).

8-*Cyclohexyl*-1,8-*diazabicyclo*[4.3.0]*nonane* (4·3 g, 86%) was obtained from 2-cyclohexylaminomethylpiperidine (5·0 g) as a colourless oil b.p., 120–121°/1·3 mm $n_D^{18.0}$ 1·5040. (Found: C, 74·76; H, 11·88; N, 13·29. $C_{13}H_{24}N_2$ requires: C, 74·94; H, 11·61; N, 13·45%).

An epimeric mixture of *cis*- and *trans*-2,6-H-2,8-dimethyl-1,8-diazabicyclo[4.3.0]nonane (9·7 g, 89%) was obtained from an epimeric mixture of 2-methylaminomethyl-6-methylpiperidine (10 g) as a colourless mobile oil b.p., 95–96°/26 mm. (Found: C, 69·68; H, 12·10; N, 18·09. $C_9H_{18}N_2$ requires: C, 70·07; H, 11·76; N, 18·16%). Separation was achieved using an Aerograph Autoprep gas chromatogram with a 20% carbowax column and H_2 carrier gas. cis-2,6-H-2,8-*Dimethyl*-1,8-*diazabicyclo*[4.3.0]*nonane* had the shorter retention time and was obtained as a colourless mobile oil b.p., 88–89°/22 mm $n_D^{13.5}$ 1·4755. trans-2,6-H-2,8-*Dimethyl*-1,8-*diazabicyclo*[4.3.0]*nonane* was obtained as a colourless mobile oil b.p., 97–98°/24 mm $n_D^{13.5}$ 1·4813.

An epimeric mixture of *cis*- and *trans*-2,6-H-2-methyl,8-isopropyl-1,8-diazabicyclo[4.3.0]nonane (3·7 g, 69%) was obtained from an epimeric mixture of 2-isopropylaminomethyl-6-methylpiperidine (5·0 g) as a colourless mobile oil b.p., 120–121°/26 mm. (Found: C, 72·44; H, 12·46; N, 15·12. $C_{11}H_{22}N_2$ requires: C, 72·47; H, 12·16; N, 15·37%). Separation was achieved using GLC as above. cis-2,6-*H*-2-*Methyl*-8-*isopropyl*-1,8-*diazabicyclo*[4.3.0]*nonane* had the shorter retention time and was obtained as a colourless mobile oil b.p., 119–120°/24 mm $n_D^{13.7}$ 1·4764. trans-2,6-*H*-2-*Methyl*-8-*isopropyl*-1,8-*diazabicyclo*[4.3.0]-*nonane* was obtained as a colourless mobile oil b.p., 124–125°/25 mm $n_D^{13.7}$ 1·4813.

An epimeric mixture of *cis*- and *trans*-2,6-H-2-methyl,8-t-butyl-1,8-diazabicyclo[4.3.0]nonane (5·6 g, 75%) was obtained from an epimeric mixture of 2-t-butylaminomethyl-6-methylpiperidine (7·0 g) as a colourless mobile oil blp., 67–70°/0·6 mm. (Found: C, 73·37; H, 12·32; N, 14·18. $C_{12}H_{24}N_2$ requires:

C, 73·41; H, 12·32; N, 14·27%). The mixture was separated by GLC as above, cis-2,6-*H*-2-*methyl*,-8-*t*-*butyl*-1,8-*diazabicyclo*[4.3.0]*nonane* had the shorter retention time and was obtained as a colourless oil b.p., 86–88°/5 mm $n_D^{13·5}$ 1·4754. trans-2,6-*H*-2-*Methyl*-8-*t*-*butyl*-1,8-*diazabicyclo*[4.3.0]*nonane* was obtained as a colourless oil b.p., 98–99°/8 mm $n_D^{13·5}$ 1·4831.

1,8-*Diazabicyclo*[4.3.0]*nonane*[1]

The reported synthesis of this compound was repeated as in the literature. 7,9-diketo-1,8-diazabicyclo-[4.3.0]nonane was obtained as a white crystalline solid from ether m.p., 121–122° (Lit. 123–123·5°). (Found: C, 54·42; H, 6·71; N, 18·16. Calc. for $C_7H_{10}N_2O_2$: C, 54·53; H, 6·54; N, 18·17%). The diketone was reduced with LAH to give the compound previously reported to be 1,8-diazabicyclo[4.3.0]nonane. It was obtained as a colourless mobile oil b.p., 140–142°/205 mm $n_D^{15·0}$ 1·4748 (Lit. $n_D^{23·0}$ 1·4740). (Found: C, 65·69; H, 12·90; N, 22·12. Calc. for $C_7H_{16}N_2$: C, 65·57; H, 12·58; N, 21·85%). The phenylurea derivative was recrystallized from EtOH m.p., 206–208° (Lit. 210–210·5°). The NMR spectra of the unknown compound had an N–Me resonance at 7·59 τ. Comparison of the NMR and IR spectra of the unknown compound with the NMR and IR spectra of an authentic sample of 2-methylaminomethylpiperidine showed them to be identical. A phenylurea derivative of authentic 2-methylaminomethylpiperidine was prepared m.p., 207–208° from EtOH. A mixed m.p., of this and the phenylurea derivative of the unknown compound showed no depression of m.p.

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