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

CONFIGURATIONAL AND CONFORMATIONAL STUDIES WITH DERIVATIVES OF 8-OXA-1-AZABICYCLO [4.3.0] NONANE

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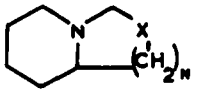
Abstract—Some Me substituted 8-oxa-1-azabicyclo[4.3.0] nonanes have been prepared and their configurations and preferred conformations assigned. The importance of geminal coupling constants in studying the conformations of these compounds is demonstrated.

IN a recent review[1] of geminal coupling constants (J) in methylene groups, the variation of J with the molecular environment of the CH_2 group was discussed. It was found that in heterocyclic systems the overlap of the C—H bonds of the methylene group with electron pairs on adjacent hetero-atoms produced significant changes in the value of J. This has been discussed[2] in a paper describing a MO treatment of nuclear spin coupling between geminal hydrogen atoms. A study of the value of J for CH_2 groups adjacent to hetero-atoms in heterocyclic systems would therefore be expected to give information regarding conformation. In view of the current interest in the stereochemistry of systems possessing N at a ring fusion. and in the problem of the spatial requirements of nonbonding electrons. it seemed of interest to assess the utility of geminal coupling constants in studying the conformations of compounds of the type I (X = hetero-atom).



I

As part of this study some Me substituted 8-oxa-1-azabicyclo[4.3.0]nonanes have been prepared. Two racemic epimers (II and III) are possible for each Me derivative

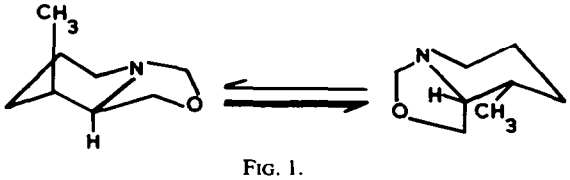


FIG. 1.

* Part I. T. A. Crabb and R. F. Newton, *J. Heterocyclic Chem.* 3, 418 (1966); Part II. T. A. Crabb and R. O. Williams, *Ibid.*, 4, 169 (1967).

depending on the configuration of the C_6-H relative to that on the substituted C atom. In addition each epimer is expected to exist as an equilibrium mixture of the *cis*- and *trans*-fused ring conformers (Fig. 1), with a predominance of that conformer in which the Me substituent occupies an equatorial position.

Synthesis of the methyl 8-oxa-1-azabicyclo[4.3.0.]*nonanes*

Lutidine N-oxides were converted to Me substituted 2-pyridyl acetates by reaction with acetic anhydride. Hydrolysis of the acetates followed by reduction of the pyridine ring gave a mixture of epimeric racemic piperidyl carbinols (IV and V), the composition of which depended on the method of reduction.

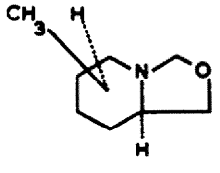
Since the work of Linstead[3] catalytic hydrogenation of pyridine rings has been assumed to proceed by the *cis*-addition of hydrogen to the ring, and in the light of this, catalytic reduction of the Me substituted pyridine 2-methanols is expected to yield IV as the major product. On the other hand, mixtures of the piperidyl carbinols obtained from sodium-ethanol reduction are expected to be richer in the di-equatorially substituted epimer. The results of these reductions are summarized in Table 1.

TABLE 1. PREPARATION OF EPIMERIC METHYL SUBSTITUTED 2-PIPERIDYL CARBINOLS

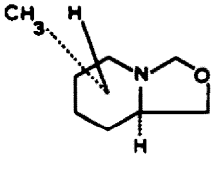
2-Pyridyl carbinols	Method of reduction	Approximate % epimer IV–V
3-Methyl 2-pyridyl carbinol	H_2-PtO_2/AcOH	90–10
	Na-EtOH/EtOH	10–90
4-Methyl 2-pyridyl carbinol	H_2-PtO_2/AcOH	90–10
	Na-EtOH/EtOH	70–30
5-Methyl 2-pyridyl carbinol	H_2-PtO_2/AcOH	55–45
	Na-EtOH/EtOH	30–70
6-Methyl 2-pyridyl carbinol	H_2-PtO_2/AcOH	100– 0
	Na-EtOH/EtOH	100– 0

Thus both catalytic and sodium ethanol reduction of 6-methyl-2-pyridyl carbinol yields only one racemic epimer which is therefore deduced to be *cis*-2.6-H 2-methyl piperidyl carbinol (IV). Catalytic hydrogenation of 5-methyl 2-pyridyl carbinol yields 55% of one epimer and 45% of the other leaving an assignment of configuration unsure. However, sodium-ethanol reduction gave 30% of the first epimer and 70% of the second which is therefore *trans*-5,6-H 5-methyl piperidyl carbinol. Similar reasoning enables the configurations of the remaining racemic alcohols to be deduced.

The mixture of piperidyl carbinols was not separated but converted to a mixture

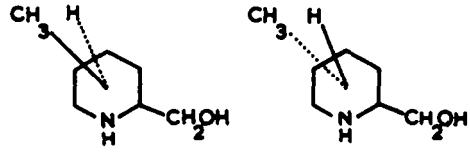


II



III

of the formals II and III by the action of formaldehyde. II and III were then obtained pure by means of fractional recrystallization of their picrates.



IV V

IR spectra of 8-*oxa*-1-*azabicyclo*[4.3.0]*nonanes*

Bohlmann's work on quinolizidines[4] produced an extremely useful correlation between the IR spectra and the stereochemistry of these compounds. It was found that the IR spectra of *trans*-fused quinolizidines in which the N lone pair of electrons is *trans*- to at least two axial hydrogens on α-C atoms exhibits a prominent band between 2700–2800 cm^{-1}. these bands being absent in the corresponding *cis*-fused

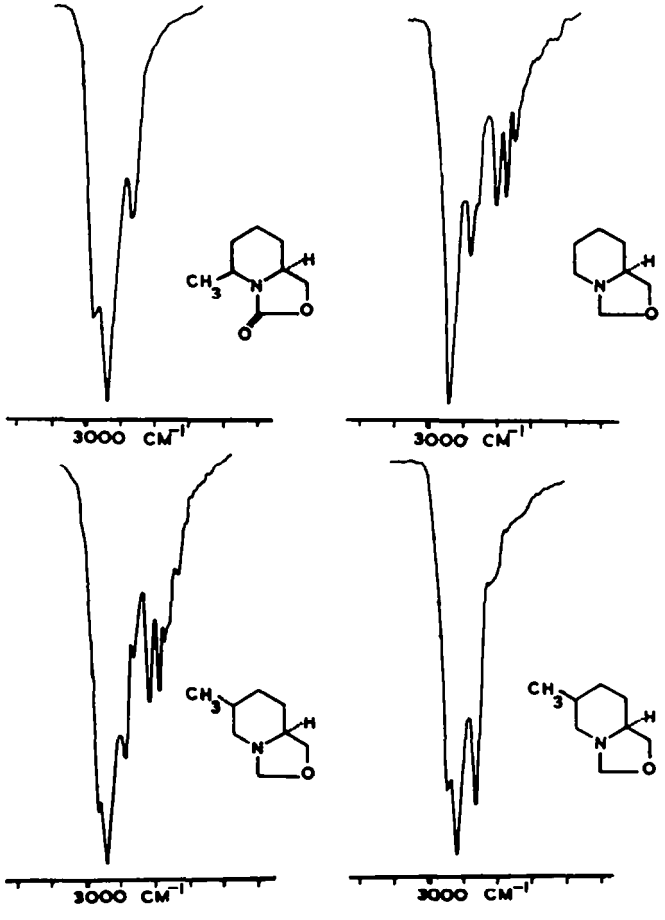


FIG. 2. C-H stretching region of the IR spectra.

compounds. This important correlation has been used extensively in stereochemical studies on compounds having a bridgehead N atom.

Wiewiorowski and Skolik[5] undertook a qualitative examination of these bands in some C_{15} lupin alkaloids. The dilactam 17-oxalupanine was taken as a reference compound having no bands in the 2850–2500 cm^{-1} region (termed the T band) and α isosparteine. possessing a double *trans*-quinolizidine system. as a second reference regarded as exhibiting 100% T bands. From a comparison of the areas of the absorptions between 2850 and 2500 cm^{-1} it was shown that the *cis*-fused quinolizidine system also exhibits some absorptions in this area.

In the present study the α lactams 9-oxo-8-oxa-1-azabicyclo[4.3.0]nonane and *cis*-2.6-H-2-methyl 9-oxo-8-oxa-1-azabicyclo[4.3.0]nonane have been used as reference compounds exhibiting no T bands. The results of the IR studies of the Me substituted 8-oxa-1-azabicyclo[4.3.0]nonanes shown in Table 2 and in Fig. 2 divide the compounds into two distinct groups.

TABLE 2. IR SPECTRA OF 8-OXA-1-AZABICYCLO[4.3.0]NONANES

Compound	cm^{-1}	ε^a
cis-2,6-H-2-Methyl 8-oxa-1-azabicyclo[4.3.0]nonane	2805	104
	2777	84
	2747	71
	2741	74
	2718	43
trans-3,6-H-3-Methyl 8-oxa-1-azabicyclo[4.3.0]nonane	2808	150
	2778	146
	2762	107
	2754	96
	2727	71
	2710	46
cis-4.6-H-4-Methyl 8-oxa-1-azabicyclo[4.3.0]nonane	2808	126
	2780	118
	2765	87
	2752	87
	2730	62
trans-5,6-H-5-Methyl 8-oxa-1-azabicyclo[4.3.0]nonane	2806	146
	2776	142
	2765	107
	2749	97
	2735	71
8-Oxa-1-azabicyclo[4.3.0]nonane	2803	97
	2776	97
	2752	62
cis-3,6-H-3-Methyl 8-oxa-1-azabicyclo[4.3.0]nonane	2830	57
	2777	30
trans-4,6-H-4-Methyl 8-oxa-1-azabicyclo[4.3.0]nonane	2835	80
	2810	65
	2780	51
cis-5,6-H-5-Methyl 8-oxa-1-azabicyclo[4.3.0]nonane	2838	87
	2807	57
	2775	46

TABLE 3. NMR OF *trans*-FUSED 8-OXA-1-AZABICYCLO[4.3.0]NONANES

	Coupling Constants (c/s)[a]				Chemical Shifts (τ)[b]					
	$J_{H_{9\alpha}H_{9\beta}}$	$J_{H_{7\alpha}H_{7\beta}}$	$J_{H_{7\alpha}H_{6\alpha}}$	$J_{H_{7\beta}H_{6\alpha}}$	$H_{9\beta}$	$H_{9\alpha}$	$H_{7\alpha}$	$H_{7\beta}$	$H_{6\alpha}$	$H_{2\alpha}$
cis-2,6-H-2-Methyl 8-oxa-1-azabicyclo[4.3.0]nonane	−0·7	−6·5	5·6	10·4	5·43	6·37	6·15	6·71	7·85(*m*)	—
trans-3,6-H-3-Methyl 8-oxa-1-azabicyclo[4.3.0]nonane	−0·8	−6·8	6·5	9·5	5·55	6·34	6·17	6·65	7·85(*m*)	7·05(*d*)
cis-4,6-H-4-Methyl 8-oxa-1-azabicyclo[4.3.0]nonane	−0·8	−6·4	6·0	9·6	5·55	6·30	6·15	6·65	7·90(*m*)	7·05(*d*)
trans-5.6-H-5-Methyl 8-oxa-1-azabicyclo[4.3.0]nonane	−0·8	−6·7	6·4	9·2	5·52	6·35	6·10	6·60	7·90(*m*)	7·08(*d*)
8-Oxa-1-azabicyclo[4.3.0]nonane	−2·4	−6·8	6·3	10·0	5·65	6·23	6·29	6·68	7·70(*m*)	7·20(*m*)

(*d*) doublet. measured from centre
(*m*) multiplet. measured from centre
[a] ± 0·3 c/s. [b] ± 0·05 τ

TABLE 4. NMR OF *cis*-FUSED 8-OXA-1-AZABICYCLO[4.3.0]NONANES

Compound	Coupling Constants (c/s)[a]				Chemical Shifts (τ)[b]			
	$J_{H_9H_9'}$	$J_{H_{2\alpha}H_{2\alpha}}$	$J_{H_{2\alpha}H_{3\alpha}}$	$J_{H_{2\alpha}H_{3\alpha}}$	H_9	$H_{9'}$	$H_{2\alpha}$	$H_{2\beta}$
cis-3.6-H-3-Methyl 8-oxa-1-azabicyclo[4.3.0]nonane	−5·0	−10·5	10·5	4·1	5·75	5·94	7·42	7·75
trans-4,6-H-4-Methyl 8-oxa-1-azabicyclo[4.3.0]nonane	−5·0	−9·0	8·5	5·0	5·67	5·86	7·42	7·73
cis-5,6-H-5-Methyl 8-oxa-1-azabicyclo[4.3.0]nonane	−5·0	—	—	—	5·72	5·90	4·45(*m*)	

(*m*) = centre of multiplet
[a] ± 0·3 c/s [b] ± 0·05 (τ)

The first group of compounds show an intense T band and to these predominantly *trans*-fused ring conformations have been assigned. Characteristic features of this T band are peaks at about 2805 cm^{-1} (ε_A 104–150). 2780 cm^{-1} (ε_A 84–146) and at 2750 cm^{-1} (ε_A 74–97). Additional peaks are present which vary from compound to compound.

The second group, to which predominantly *cis*-fused ring conformations have been assigned, show a T band of much lower intensity with a prominent band at about 2835 cm^{-1} (ε_A 57–87) and at 2780 cm^{-1} (ε_A 30–51). No peaks occur at 2750 cm^{-1} showing that the T bands of the *cis*-conformers are not the same as that of the *trans*-conformers on a reduced scale. A comparison between the IR spectra of the lactams and *cis*-fused ring conformers (Fig. 2) shows that the latter exhibit a T band of appreciable area.

The unsubstituted parent compound exhibits the three peaks characteristic of the *trans*-fused ring conformer T band. A comparison of the integrated T band areas in these compounds shows that the unsubstituted parent compound has a T band intensity intermediate between that of the *cis*- and the *trans*-fused ring conformers. The T band is only 81% as intense as that of a *trans*-fused ring conformer suggesting that the unsubstituted parent compound exists as approximately 30% of the *cis*-fused ring conformer and 70% of the *trans*-fused ring conformer in equilibrium at room temperature.

NMR spectra of 8-oxa-1-azabicyclo[4.3.0]*nonanes*

Tables 3 and 4 and Figs 3 and 4 summarize the NMR spectra of the compounds in this present study and show the dramatic differences in the spectra between those compounds existing in predominantly *cis*-fused ring conformations (Table 4) and those in *trans*-fused ring conformations (Table 3).

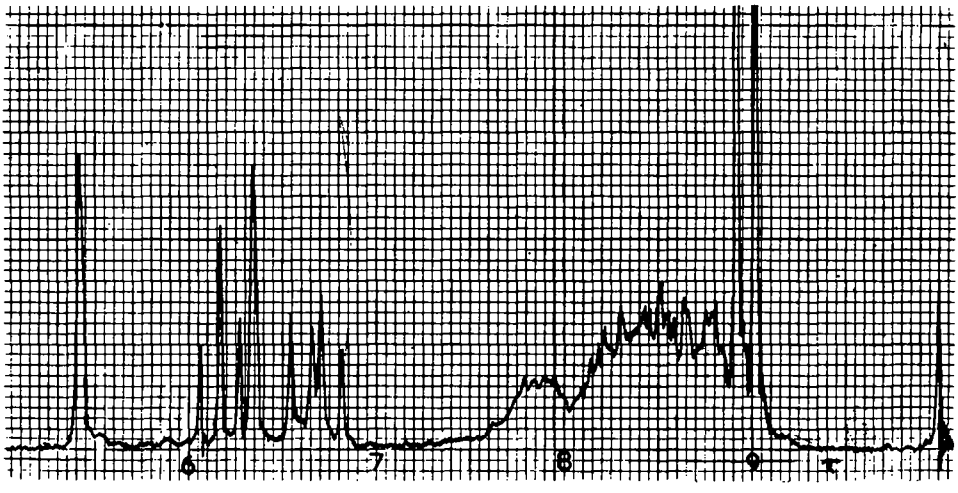


FIG. 3. NMR spectra of *cis*-2, 6-H-2-Methyl-8-oxa-1-azabicyclo[4.3.0]nonane.

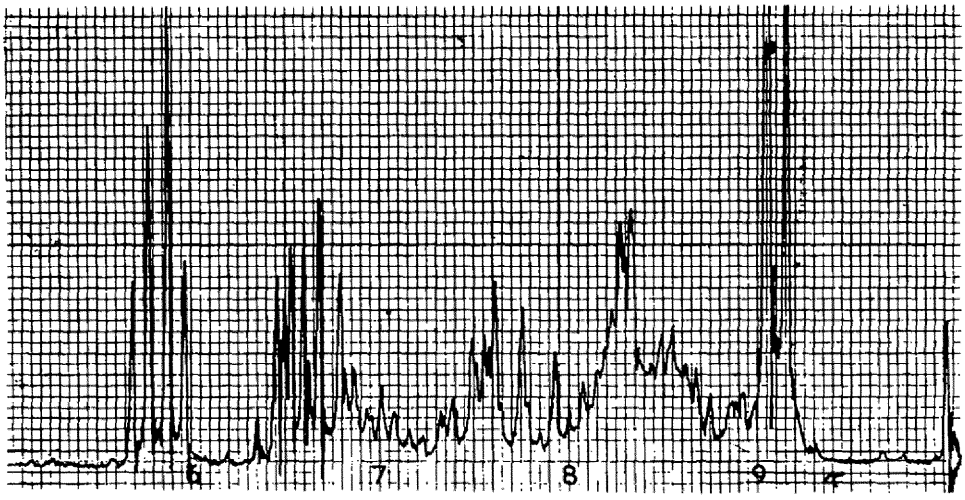
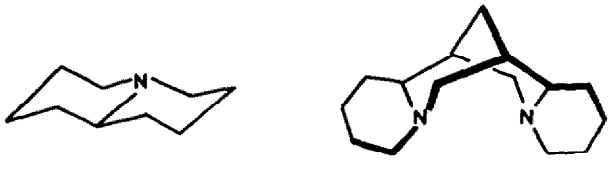


FIG. 4. NMR spectra of *cis*-3, 6-H-3-Methyl-8-oxa-1-azabicyclo[4.3.0]nonane.

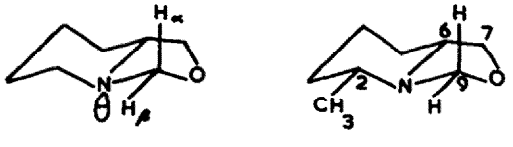
trans-Fused conformers

C_9-Methylene protons. In oxazolidines the O—CH_2—N protons normally give rise to signals in the region of 5·2 to 5·8τ.[6] In all of the *trans*-fused ring compounds under discussion one of the C_9 protons absorbs normally at ca. 5·5 τ whereas the other is abnormally shielded and gives a signal at ca. 6·3τ. the difference in chemical shift between them varying from 0·77 to 0·92 ppm.

In order to explain the large difference in chemical shift (0·93 ppm) between the methylene protons adjacent to N in quinolizidine (VI) is has been suggested[7] that partial participation of the N lone pair in a $\sigma^*C—H_{ax}$ orbital on the adjacent C atom occurs and this leads to an increase in the electron density at the axial proton with a corresponding increase in the shielding of this proton. This shielding should be greatest when the N lone pair and the adjacent C—H bond have a *trans*-diaxial relationship to each other and it is this relationship which should produce the maximum difference in chemical shift between the methylene protons adjacent to N.



VI VII



VIII IX

In support of this Bohlmann[8] found the chemical shifts of the C_6 and C_{11} protons in β-isosparteine (VII) which are *cis*- to the N lone pair to be 7 τ. Work on benzoquinolizidines[9] has also indicated that a CH—N-proton gauche to the N lone pair is deshielded whereas when the CH is *trans* to the lone pair shielding is observed.

From an examination of Dreiding models of the Me substituted 8-oxa-1-azabicyclo[4.3.0]nonanes. it can be seen that the α-C_9—H bond in the *trans*-fused ring conformers (VIII) is able to become nearly *trans*-diaxial to the N lone pair and in the light of the above discussion should be abnormally shielded. The β-C_9 proton making a dihedral angle of ca. 40° will then absorb at much lower field and so the large chemical shift difference between the C_9 methylene protons is then explained.

Support for the above assignment can be obtained from the NMR spectra of the 2-Me substituted compound. As is seen in Table 3 the β-C_9 proton absorbs at 0·15 ppm to lower field than in the other isomer. If as indicated in IX the β-C_9 proton and the C_2-Me have a near 1:3-diequatorial relationship then deshielding of this proton is expected by the van der Waals interaction.[10]

Recent work[1,2] has shown the importance of the influence of lone pair orbitals of heteroatoms on the J of adjacent methylene groups. Transfer of electrons from lone pairs into the antisymmetric molecular orbital of an adjacent methylene group produces a positive change in *J* and this is expected to be maximal when the orbitals eclipse adjacent CH bonds.

The extremely small value of −0·8 c/s for the geminal coupling constant between the C_9 methylene protons in the *trans*-fused ring compounds therefore implies a conformation with the O lone pairs of electrons eclipsing the C_9 methylene bonds. The inductive removal of the electrons from the symmetric C_9 methylene molecular orbital by the N and O atoms. combined with the transfer of the lone pairs of electrons on O into the antisymmetric CH_2 molecular orbital cannot be entirely responsible for the value of −0·8 c/s for J since J for dioxolans is ca. 0 c/s.[1] It must therefore be concluded that the N lone pair of electrons is also being transferred into the antisymmetric C_9 methylene orbitals. The above mentioned near *trans*-diaxial relationship of the N lone pair and the C_9-H perhaps aids this process. Anteunis[11] has recently proposed that J_{gem} in a methylene group next to a N atom becomes more positive when the lone pair on the N atom is parallel to the α C—H. Alternatively because of the strained nature of the *trans*-fused ring compounds some flattening of the molecule in the region of the N atom may be responsible for the very positive value of J_{gem}.

C_7 methylene protons. The C_7 methylene protons may be treated as the AB part of an ABX spectrum. The X proton (H_6) is further coupled to the H_5 protons. however the chemical shift of H_{6a} (ca. 8τ) is considerably different from those of the C_7 protons (ca. 6·1 and 6·6τ) and so the approximation in taking this treatment should not produce serious errors.

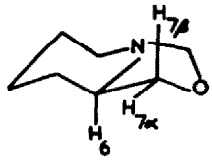
The results of the analysis of the AB pattern are summarized in Table 3.

The values of the vicinal coupling constants $J_{7\alpha 6a}$. $J_{7\beta 6a}$ allow assignments of signals to the C_7 methylene protons to be made. From a consideration of Dreiding models (X) and application of the Karplus equation describing the dependence of J_{vic} on dihedral angle between adjacent C—H bonds a value of ca. 7·5 c/s for $7_\alpha 6_a$ ($\phi \simeq 30°$) and ca. 12 c/s for $7_\beta 6_a$ ($\phi \simeq 150°$) is suggested.

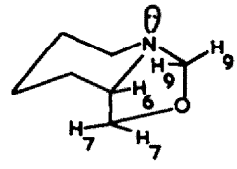
Recent work[12] has shown that lone pair orbitals on heteroatoms contribute towards

vicinal coupling constants and of course the well known electronegativity effect of substituents on J_{vic} must also be considered. Thus too exact an application of the $\cos.^2 \phi$ law in studying detailed conformation of the 5-membered ring cannot be made with any certainty. However $7_\beta 6_a$ might be expected to be greater than $7_\alpha 6_a$.

The 100 Mc/s spectrum of *trans*-5,6-H-5-methyl 8-oxa-1-azabicyclo[4.3.0]nonane for example, could be treated by first order methods. One of the protons showed a 1:2:1 triplet centred at $\tau = 6{\cdot}17$. $J_{gem} = -6{\cdot}5$ c/s., $J_{76a} = 6{\cdot}5$ c/s. and the other a quartet centred at $\tau = 6{\cdot}68$ giving $J_{gem} = -6{\cdot}5$ c/s. $J_{76a} = 9{\cdot}5$ c/s. Therefore $H_{7\alpha}$ must give rise to the signals centred at $\tau = 6{\cdot}17$ and $H_{7\beta}$ to those at $\tau = 6{\cdot}68$. The geminal coupling constant of $-6{\cdot}5$ c/s is very positive for a methylene group next to O in a 5-membered ring and so a conformation with the O lone pairs eclipsing the adjacent CH_2 must be postulated.



X



XI

C_2 methylene protons. In the NMR spectra of the 3, 4, and 5-methyl-8-oxa-1-azabicyclo[4.3.0]nonane *trans*-fused ring compounds, a doublet showing evidence of further coupling is observed at ca. 7τ. This is assigned to the C_2 equatorial proton by analogy with the NMR spectra of quinolizidine[8] and piperidine.[13] This signal is absent in the NMR spectra of the 2-Me compound since this has no equatorially situated CH-N proton. The C_2 and C_6 axial protons are abnormally shielded and appear at 7·6–8 τ. A 100 Mc/s spectrum of the 5-Me compound resolves the C_2 equatorial proton signal into two 1:2:1 triplets, first order analysis of these giving $J_{2e2a} = -9{\cdot}5$ c/s. $J_{2e3e} \approx J_{2e3a} = 3$ c/s. The value of $-9{\cdot}5$ for the geminal coupling constant between the C_2 methylene protons is unusually positive, J for similarly situated protons in N-methyl piperidine being -12 c/s.[14] As was suggested in the case of the C_9 methylene J_{gem} this value may be more positive than normal if flattening of the molecule occurs around the N atom. In sparteins[8] with *trans*-fused ring junctions J_{gem} of the CH_2-N methylene protons is also more positive (-10 to $-11{\cdot}5$ c/s) than in piperidines.

cis-Fused conformers

C_9 methylene protons. These protons absorb in the normal range for O—CH_2—N protons[6] between $\tau = 5{\cdot}65$ and 5·93. The chemical shift difference between them is about 0·22 ppm. Examination of Dreiding models shows that in the *cis*-fused ring conformers XI neither of the C_9 methylene protons is able to become *trans*-diaxial to the N lone pair of electrons and are therefore not abnormally shielded by them. The J_{gem} of $-5{\cdot}0$ c/s for the C_9 methylene protons in the *cis*-fused ring compounds is much more negative than J_{gem} for the *trans*-fused ring conformers. This means that transfer of electrons into the antisymmetric molecular orbitals of the methylene group is less efficient in the *cis*-fused ring compounds. This implies a conformation

of the 5-membered ring in which there is much less eclipsing of the lone pairs of electrons on the adjacent heteroatoms. in particular the O atom.

C_7 methylene protons. In the 60 Mc/s spectra of the *cis*-fused ring conformers the coupling constants of the C_7 methylene protons are of the same order as the chemical shifts and no parameters can be extracted. In the 100 Mc/s spectrum* of *cis*-3.6-H-3-methyl 8-oxa-1-azabicyclo[4.3.0]nonane however. the signals due to the C_7 methylene protons approximate to the AB part of an ABX system and was analyzed as such. One of the protons absorbed at $\tau = 6{\cdot}58$. with a J_{gem} of $-7{\cdot}0$ c/s and a vicinal coupling constant with the C_6 proton of 7·7 c/s and the other absorbed at $\tau = 6{\cdot}67$. with a J_{gem} of $-7{\cdot}0$ c/s and a $J_{H_7H_6}$ of 10·3 c/s.

The J_{gem} of $-7{\cdot}0$ c/s is still very positive, the normal range for CH_2—O in 5-membered ring being $-7{\cdot}0$ c/s to $-9{\cdot}0$ c/s.[1] As discussed for the *trans*-compounds the many factors affecting J_{vic} make application of the Karplus relationship to decisions regarding the conformation of the 5-membered ring dangerous.

C_2 methylene protons. In the 100 Mc/s spectrum of *cis*-3.6-H-3-methyl 8-oxa-1-azabicyclo[4.3.0]nonane the C_2 methylene protons signal approximates to the AB part of an ABX spectrum and was treated as such. The C_2 equatorial proton (H_{2e}) absorbed at $\tau = 7{\cdot}42$. with J_{gem} of $-10{\cdot}5$ c/s and J_{H2e3a} of 4·1 c/s with each peak arising from H_{2e} having an additional long range coupling of 1·5 c/s. The axial C_2 proton absorbed at $\tau = 7{\cdot}75$. with J_{gem} of $-10{\cdot}5$ c/s and a J_{H2aH3a} of 10·5 c/s.

The C_2 methylene signals for *trans*-4.6-H-4-methyl 8-oxa-1-azabicyclo[4.3.0] nonane are very similar to the above with the signals showing evidence of a further small vicinal coupling.

In *cis*-5.6-H-5-methyl 8-oxa-1-azabicyclo[4.3.0]nonane the C_2 equatorial and C_2 axial protons both appear as a multiplet lying between $\tau = 7{\cdot}3$ and $\tau = 7{\cdot}6$ and since the chemical shifts and the coupling constants are comparable in magnitude these values cannot be obtained from the spectra.

It is interesting to note that in the 3- and 4-Me substituted *cis*-fused conformers the difference in chemical shift between H_{2e} and H_{2a} is ca. 0·33 ppm and in the 5-Me conformer even smaller. This would appear to be evidence against a chair conformation for the 6-membered ring in which the normal axial and equatorial arrangement of the C—H bonds adjacent to the axially situated lone pair of electrons on the N atom should produce a chemical shift difference of ca. 0·8 ppm. Eliel[15] however. has suggested that in *cis*-hydrindane the 6-membered ring may be in a partially deformed chair and perhaps such a conformation in these compounds would produce these anomalous chemical shifts. Another possible explanation is the shielding effects of the 5-membered ring structure on the chemical shifts of the C_2 methylene protons.

Further work is in progress to obtain more evidence regarding the conformation of the 6-membered ring in the *cis*-fused ring conformers.

NMR of 8-oxa-1-azabicyclo[4.3.0]nonane

C_9 methylene protons. The unsubstituted parent compound has a geminal coupling constant for the C_9 methylene protons of $-2{\cdot}4$ c/s intermediate between that found

* We thank Dr. J. Feeney of Varian Associates for running the spectrum for us.

for the *cis*- and *trans*-fused conformers, showing that it exists at room temperature as a mixture of *cis*- and *trans*-fused conformations.

Assuming that the compounds assigned *cis*- and *trans*-fused ring conformations are nearly conformationally pure, a reasonable assumption since the value of −0·8 c/s observed for J_{gem} in the *trans*-fused conformers is the most positive one reported for a methylene group situated between N and O, and assuming a linear relationship between the value of J_{gem} and conformation, then the unsubstituted parent compound is calculated to exist as an equilibrium mixture of ca. 40% of the *cis*- and ca. 60% of the *trans*-fused ring conformation.

The difference in chemical shift between the C_9 protons, 0·58 ppm, is intermediate between that of a *trans*-fused conformer ca. 0·8 ppm and a *cis*-fused conformer ca. 0·2 ppm and this also indicates a similar conformational equilibrium.

C_7 *methylene protons.* As in the *trans*-fused ring conformers the C_7 methylene protons approximate to the AB part of an ABX spectrum. The coupling constants and chemical shifts are similar to those obtained for the *trans*-fused ring compounds.

C_2 *and* C_6 *methylene protons.* The C_2 and C_6 protons both have similar chemical shifts to the corresponding protons in the *trans*-fused ring conformers.

General discussion of results

The sterochemistry of 8-oxa-1-azabicyclo[4.3.0]nonane should be roughly analogous to that of hydrindane with the additional feature of the conformationally unstable bridgehead N atom and the possibility of dipole-dipole interactions[16] between the two heteroatoms. For the *cis*-hydrindane ⇌ *trans*-hydrindane equilibrium ΔG° has been calculated to be only −0·3 kcal.mole.$^{-1}$ at 25°.[17] Recent work[18] has shown that quinolizidine is more stable in the *trans*-ring fusion relative to the *cis*-than is decalin. This is attributed to the two non-bonded 1.3-diaxial hydrogen interactions (≡ 2·1 kcal.mole.$^{-1}$) present in *trans*-decalin which disappear when the bridgehead C—H is replaced by a tertiary N atom as in quinolizidine. If we apply a similar argument to the case of indolizidine we would expect the *trans*-fused ring conformer to be more stable relative to the *cis*-than is *trans*-hydrindane relative to *cis*-hydrindane. This is borne out by Aaron's observation[19] that in the 7 and 8 hydroxy indolizidines no *cis* ring fusion could be detected showing that ΔG° for the *cis*-indolizidine ⇌ *trans*-indolizidine equilibrium must be much more negative than the value of −0·3 kcal.mole.$^{-1}$ for hydrindane, since if there was no significant energy barrier to the establishment of the equilibria this would correspond to ca. 40% of the *cis*-fusion in the equilibrium mixture.

Since 8-oxa-1-azabicyclo[4.3.0]nonane appears to exist as an equilibrium mixture containing ca. 40% *cis*-fused ring conformer the *trans*-fused ring conformer must be appreciably less stable relative to the *cis*- than is *trans*-fused ring indolizidine relative to *cis*-indolizidine. The destabilising influence would appear to be dipole-dipole interactions between the heteroatoms which will be smaller in the *cis*-conformation than in the *trans*-conformation.

EXPERIMENTAL

All elemental analyses were carried out by Dr. F. Pascher and E. Pascher, Micro-analytical Laboratory, Bonn, Germany. M.ps are uncorrected. IR spectra were recorded on a Perkin–Elmer 237 grating instru-

ment and on a Unicam SP.100 as 0·2 M solns in CCl_4 using 0·1 mm matched cells. The NMR spectra were determined on a Perkin-Elmer R.10 and Varian H.A.60 and H.A.100 spectrometers as 10% solns in CCl_4 with TMS as internal reference.

Catalytic hydrogenation of 2-pyridyl carbinols

General procedure. The Me substituted 2-pyridyl carbinols (0·2 M), glacial AcOH (200 ml) and PtO_2 (1 g) were shaken with H_2 under atm press until reduction ceased. The soln was filtered, basified with NaOH aq and ether extracted 3 times. The dried (Na_2SO_4) ether extract was evaporated and the residue distilled to give a mixture of *cis*- and *trans*-Me substituted 2-piperidyl carbinols.

Hydrogenation of 2-pyridyl carbinol. 2-piperidyl carbinol (22·5 g, 87%) b.p., 95–97°/0·6 mm was obtained from 2-pyridyl carbinol (25 g) as a white crystalline solid m.p., 68–70° from ether (lit.[20] 64–67°). The picrate crystallized from EtOH as plates m.p. 133–134°. (Found: C, 41·81; H, 4·52; N, 16·26 calc for $C_{12}H_{16}O_8N_4$: C, 41·62; H, 4·24; N, 16·18%).

Hydrogenation of 6-methyl 2-pyridyl carbinol. cis-6,2-H-6-Methyl 2-piperidyl carbinol (18·2 g, 71%) b.p., 70–71°/0·9 mm was obtained from 6-methyl 2-pyridyl carbinol (24·5 g) as white crystals m.p., 76° from ether (lit.[21] 75°). This was the sole product.

Hydrogenation of 5-methyl 2-pyridyl carbinol. A mixture of *cis*- and *trans*-5,2-H-5-methyl 2-piperidyl carbinol (20 g, 75%) was obtained from 5-methyl 2-pyridyl carbinol (26 g) as a colourless oil b.p., 76–80°/0·45 mm. (Found: C, 65·31; H, 11·87; N, 10·60. $C_7H_{15}ON$ requires: C, 65·13; H, 11·63; N, 10·85%). The NMR spectra in CCl_4 showed the mixture to be 55% *cis*- and 45% *trans*-5,2-H-5-methyl 2-piperidyl carbinol. τ values for the Me doublet of the *cis*-isomer were 8·94 and 9·05 and 9·10 and 9·21 for the *trans*-isomer. The calculated amount of picric acid in EtOH was added to a soln of the alcohol mixture in EtOH. The resultant crystals were filtered and recrystallized twice from EtOH to give the picrate of *cis*-5,2-H-5-methyl 2-piperidyl carbinol as orange needles m.p., 136–137°. (Found: C, 43·52; H, 4·96; N, 15·47. $C_{13}H_{18}O_8N_4$ requires: C, 43·58; H, 5·03; N, 15·64%). Concentration of the mother liquors yielded a mixture of the epimeric picrates which on repeated recrystallization from EtOH yielded the picrate of trans-5,2-H-5-*methyl 2-piperidyl carbinol* as orange needles m.p., 151–152°. (Found: C, 43·61; H, 4·94; N, 15·88. $C_{13}H_{18}O_8N_4$ requires: C, 43·58; H, 5·03; N, 15·64%).

Hydrogenation of impure 4-methyl 2-pyridyl carbinol. A mixture of *cis*- and *trans*-4,2-H-4-methyl 2-piperidyl carbinol (24·5 g, 63%) was obtained from impure 4-methyl 2-pyridyl carbinol (37 g) as a colourless oil b.p., 101–105°/5·5 mm. (Found: C, 64·68; H, 11·57; N, 10·71. $C_7H_{15}ON$ requires: C, 65·13; H, 11·63; N, 10·85%). In addition an unexamined compound (10·5 g) probably 2-methyl 4-piperidyl carbinol was also obtained. The percentage of each isomer was estimated from the spectra of the 4-methyl 8-oxa-1-azabicyclo[4.3.0]nonanes prepared directly from the mixture which showed there was 90% of the *trans*-isomer and 10% of the *cis*-isomer present. When reduction was carried out at 60 p.s.i. in a Parr hydrogenator the percentage of each isomer was 50%.

Hydrogenation of 3-methyl 2-pyridyl carbinol. A mixture of *cis*- and *trans*-3,2-H-3-methyl 2-piperidyl carbinol (10 g, 80%) was obtained from 3-methyl 2-pyridyl carbinol (23·0 g) as a colourless oil b.p., 75–76°/0·35 mm. (Found: C, 64·78; H, 11·91; N, 10·70. $C_7H_{15}ON$ requires: C, 65·13; H, 11·63; N, 10·85%). The NMR spectra of the mixture in CCl_4 showed one Me doublet at 9·09 and 9·19 τ, so the percentage composition of the mixture was estimated from the spectra of the 5-methyl 8-oxa-1-azabicyclo[4·3·0] nonanes directly prepared from it. This showed the mixture to be 90% of the *cis*-isomer and 10% of the *trans*-isomer (estimated from the intensities of the signal due to the C_9 methylene protons).

Sodium-ethanol of 2-pyridyl carbinols

General procedure. The Me substituted 2-pyridyl carbinol (0·2 M) was refluxed in EtOH (500 ml) and Na (60 g) was added. The reaction mixture was refluxed for 2 hr, the soln was acidified with dil HCl and excess EtOH removed. The soln was then basified with NaOH aq and ether extracted. The ether extract was dried (Na_2SO_4) and concentrated and the residue distilled to give a mixture of the *cis*- and *trans*-Me substituted 2-piperidyl carbinols.

Sodium-ethanol reduction of 6-methyl 2-pyridyl carbinol

cis-6.2-H-6-Methyl 2-piperidyl carbinol (13·4 g, 53%) was obtained from 6-methyl 2-pyridyl carbinol (24·0 g) was white crystals m.p. 76° from ether (lit.[21] 75°) b.p., 70–71°/0·9 mm. The NMR spectra showed this to be the sole product with the Me doublet at 8·87 and 8·97 τ.

Sodium-ethanol reduction of 5-methyl 2-pyridyl carbinol

A mixture of *cis*- and *trans*-5.2-H-5-methyl 2-piperidyl carbinol (9·0 g. 36%) was obtained from 5-methyl 2-pyridyl carbinol (24·0 g) as a colourless oil b.p., 10·5–107°/6 mm. The NMR spectra showed the mixture to contain 30% of the *cis*-isomer and 70% of the *trans*-isomer. estimated from the comparative intensities of the Me doublet.

Sodium-ethanol reduction of impure 4-methyl 2-pyridyl carbinol

A mixture of *cis*- and *trans*-4.2-H-4-methyl 2-piperidyl carbinol (10·0 g. 30%) was obtained from impure 4-methyl 2-pyridyl carbinol (31·5 g) as a colourless oil b.p., 90–93°/0·8 mm. an unexamined compound (8·5 g) of higher b.p., was also obtained. probably 2-methyl 4-piperidyl carbinol. NMR spectra of the 4-methyl 8-oxa-1-azabicyclo[4.3.0]nonanes directly prepared from the above showed there to be 70% of the *cis*- and 30% of the *trans*-isomer present.

Sodium-ethanol reduction of 3-methyl 2-pyridyl carbinol

A mixture of *cis*- and *trans*-3.2-H-3-methyl 2-piperidyl carbinol (9 g. 45%) was obtained from 3-methyl 2-pyridyl carbinol (20·0 g) as a colourless oil b.p., 83–84°/0·7 mm. The NMR spectra showed one Me doublet at 9·09 and 9·19 τ. The percentage composition was estimated from the spectra of the 5-methyl 8-oxa-1-azabicyclo[4.3.0]nonanes prepared directly from the carbinols. this showed the mixture to contain 10% of the *cis*- and 90% of the *trans*-isomer.

Preparation of methylsubstituted 8-oxa-1-*azabicyclo*[4.3.0]*nonanes*

General procedure. The Me substituted 2-piperidyl carbinol was shaken with an excess of 36% aqueous formaldehyde soln for ½ hr. The mixture was basified with NaOH aq and ether extracted 3 times. The ether was dried (Na_2SO_4) and evaporated and the residue distilled to give the Me substituted 8-oxa-1-azabicyclo[4.3.0]nonane.

8-*oxa*-1-*azabicyclo*[4.3.0]*nonane* (8·2 g. 74%) was obtained from 2-piperidyl carbinol (10·0 g) as a colourless oil b.p., 66–68°/16 mm n_D^{20} 1·4709. (Found: C, 65·56; H, 10·15; N, 10·95. Calc. for $C_7H_{13}ON$: C, 66·1; H, 10·20; N, 11·00%). It formed a picrate m.p., 178–179°. (Found: C, 43·83; H, 4·37; N, 15·93. $C_{13}H_{16}O_8N_4$ requires: C, 43·82; H, 4·49; N, 15·73%). The m.p. reported in the lit.[20] 135–137° actually corresponds to the m.p. of the picrate of 2-piperidyl carbinol. 134–136°.

cis-2.6-H-2-*Methyl* 8-oxa-1-*azabicyclo*[4.3.0]*nonane* (4·2 g. 76%) was obtained from 6-methyl 2-piperidyl carbinol (5·0 g) as a colourless mobile oil b.p., 81–82°/16 mm n_D^{21} 1·4699. The picrate formed dark yellow crystals from EtOH. m.p., 176°. (Found: C, 45·1; H, 4·77; N, 15·21. $C_{14}H_{18}O_8N_4$ requires: C, 45·40; H, 4·86; N, 15·14%).

cis- and *trans*-3,6-H-3-methyl 8-oxa-1-azabicyclo[4.3.0]nonane (21 g, 98%) were obtained from 5-methyl 2-piperidyl carbinol (20 g) as a colourless oil b.p., 100–105°/40 mm. The epimeric mixture (21 g) in abs EtOH was added to picric acid (36 g) in abs EtOH (500 ml). The soln was left overnight then filtered to give a picrate (38 g) m.p., 140–145°. This was recrystallized twice from EtOH to give the picrate of *cis*-3,6-H-3-methyl 8-oxa-1-azabicyclo[4.3.0]nonane (25 g) m.p., 150–151° as yellow needles. (Found: C, 45·25; H, 4·77; N, 14·87. $C_{14}H_{18}O_8N_4$ requires: C, 45·41; H, 4·86; N, 15·17%). Excess cold NaOH aq was added to the picrate (25 g) and the mixture was immediately ether extracted 3 times. The ether extract was dried (Na_2SO_4) and concentrated. The residue was distilled to give cis-3,6-H-3-*methyl* 8-*oxa*-1-*azabicyclo*[4.3.0]*nonane* (4·5 g, 47%) as a colourless oil, b.p., 103–104°/41 mm $n_D^{19.5}$ 1·4718. Concentration of the mother liquors yielded a mixture of picrates (27 g) m.p., 155–157°. Repeated recrystallization from EtOH gave the picrate of *trans*-3,6-H-methyl 8-oxa-1-azabicyclo[4.3.0]nonane (20 g) as yellow plates m.p., 165–166°. (Found: C, 45·38; H, 4·86; N, 15·42. $C_{14}H_{18}O_8N_4$ requires: C, 45·41; H, 4·86; N, 15·17%). The picrate (20 g) was decomposed as above to give trans-3,6-H-3-*methyl* 8-oxa-1-*azabicyclo*[4.3.0]*nonane* (5·4 g, 75%) as a colourless mobile oil b.p., 94–95° (31 mm $n_D^{19.5}$ 1·4651.

trans-4.6-H-4-*Methyl* 8-*oxa*-1-*azabicyclo*[4.3.0]*nonane*

The 4-methyl 2-piperidyl carbinol (20·0 g) prepared by catalytic reduction gave an epimeric mixture of *cis*- and *trans*-4.6-H-4-methyl 8-oxa-1-azabicyclo[4.3.0]nonanes (18·5 g. 95%) as a colourless mobile oil b.p., 48–50°/2.5 mm. This mixture (12·4 g) was reacted with a soln of picric acid (20·4 g) in EtOH. Fractional recrystallization gave the pure picrate of *trans*- 4.6-H-4-methyl 8-oxa-1-azabicyclo[4.3.0]nonane (5·3 g) as yellow needles m.p., 171–172°. (Found: C, 45·35; H, 4·69; N, 14·55. $C_{14}H_{18}O_8N_4$ requires: C, 45·40; H,

4·85; N, 15·17%). Decomposition of the picrate gave *trans*-4.6-H-4-methyl 8-oxa-1-azabicyclo[4.3.0]nonane (1·9 g, 94%) as a colourless mobile oil b.p., 97–98°/35 mm $n_D^{22.5}$ 1·4707.

cis-4.6-H-*Methyl* 8-*oxa*-1-*azabicyclo*[4.3.0]*nonane*

The 4-methyl 2-piperidyl carbinol (11·0 g) obtained by Na and EtOH reduction gave an epimeric mixture of *cis*- and *trans*-4.6-H-4-methyl 8-oxa-1-azabicyclo[4.3.0]nonanes (10·2 g, 80%) as a colourless oil b.p., 92–95°/30 mm. This mixture was converted to the picrate and fractionally recrystallized from EtOH to give the pure picrate of *cis*-4.6-H-4-methyl 8-oxa-1-azabicyclo[4.3.0]nonane (7·8 g) as yellow plates m.p., 143–145°. (Found: C, 45·14; H, 4·93; N, 14·65. $C_{14}H_{18}O_8N_4$ requires: C, 45·41; H, 4·86; N, 15·17%). The picrate was decomposed as above to give *cis*-4.6-H-4-methyl 8-oxa-1-azabicyclo[4.3.0] nonane (2·7 g, 93%) as a colourless oil b.p., 87–89°/28 mm $n_D^{22.5}$ 1·4654.

cis-5.6-H-5-*Methyl* 8-*oxa*-1-*azabicyclo*[4.3.0]*nonane*

The 3-methyl 2-piperidyl carbinol (16·0 g) prepared by catalytic reduction gave an epimeric mixture of *cis*- and *trans*-5.6-H-5-methyl 8-oxa-1-azabicyclo[4.3.0]nonane (16 g, 91%) as a colourless mobile oil b.p., 104–105°/37 mm. This mixture (6·2 g) was added to picric acid (10·2 g) in EtOH and the resultant picrate recrystallized 3 times to give the picrate of *cis*-5.6-H-5-methyl 8-oxa-1-azabicyclo[4.3.0]nonane (9·0 g) as yellow needles m.p., 187–189°. (Found: C, 45·15; H, 4·85; N, 15·22. $C_{14}H_{18}O_8N_4$ requires: C, 45·40; H, 4·85; N, 15·17%). The picrate was decomposed with NaOH and yielded *cis*-5.6-H-5-methyl 8-oxa-1-azabicyclo[4.3.0]nonane (3·2 g, 94%) as a colourless oil b.p., 103–104°/40 mm $n_D^{19.3}$ 1·4732.

trans-5.6-H-5-*Methyl* 8-*oxa*-1-*azabicyclo*[4.3.0]*nonane*

The 3-methyl 2-piperidyl carbinol (9·0 g) obtained by reduction with Na and EtOH gave an epimeric mixture of *cis*- and *trans*-5.6-H-5-methyl 8-oxa-1-azabicyclo[4.3.0]nonane (9 g, 90%) as a colourless mobile oil b.p., 96–98°/37 mm. This mixture (6·1 g) was converted to the picrate as before and recrystallized 3 times to give the picrate of *trans*-5.6-H-5-methyl 8-oxa-1-azabicyclo[4.3.0]nonane (8·5 g) as yellow needles m.p., 150–151°. (Found: C, 45·01; H, 5·15; N, 14·90. $C_{14}H_{18}O_8N_4$ requires: C, 45·40; H, 4·86; N, 15·17%). Decomposition of the picrate with NaOH aq gave *trans*-5.6-H-5-methyl 8-oxa-1-azabicyclo [4.3.0]nonane (2·8 g, 87%) as a colourless mobile oil b.p., 100–101°/39 mm $n_D^{19.2}$ 1·4692.

9-Oxa-8-oxa-1-azabicyclo[4.3.0]nonane was prepared according to the method of Rink and Eich[20] and was obtained from 2-piperidyl carbinol (2·3 g) as a colourless oil (2·1 g, 74%) b.p., 104–106°/0·6 mm. (Found: C, 59·85; H, 8·15; N, 9·98. Calc. for $C_7H_{11}O_2N$: C, 59·55; H, 7·85; N, 9·92%).

cis-2.6-H-2-*Methyl*-9-*oxo*-8-*oxa*-1-*azabicyclo*[4.3.0]nonane

6-methyl 2-piperidyl carbinol (5 g) in abs benzene (50 ml) was heated on a water bath with Na (0·91 g). When all the Na had dissolved a further 50 ml benzene was added and the mixture was warmed. Ethyl chloroformate (5·4 g) in benzene (20 ml) was added to the hot soln which was refluxed for 4 hr. The soln was filtered and the filtrate basified with Na_2CO_3. Excess benzene was removed *in vacuo* and the soln was extracted 3 times with $CHCl_3$ (50 ml). The $CHCl_3$ extract was dried over Na_2SO_2 and concentrated. The crude product was distilled to give *cis*-2.6-H-2-methyl 9-oxo-8-oxa-1-azabicyclo[4.3.0]nonane (4·1 g, 69%) as a colourless oil b.p., 105–107°/0·55 mm. (Found: C, 61·60; H, 8·71; N, 8·88. $C_8H_{13}O_2N$ requires: C, 61·91; H, 8·44; N, 9·03%).

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