Tetrahedron Vol 26, pp. 701 to 713 Pergamon Press 1970 Printed in Great Britain

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

CONFIGURATIONAL AND CONFORMATIONAL STUDIES WITH DERIVATIVES OF 1,3-DIAZABICYCLO[4.4.0]DECANES

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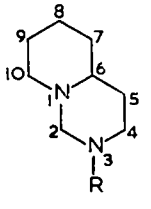
(*Received in the UK* 15 *August* 1969; *Accepted for publication* 23 *October* 1969)

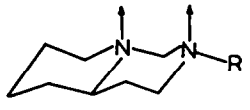
Abstract—The configurations and preferred conformations of a number of 1,3-diazabicyclo[4.4.0]decanes have been assigned on the basis of their NMR spectra. Dipolar interactions are shown to be important in determining the position of conformational equilibria.

OUR previous work on the conformational preferences of bicyclic bridgehead N compounds with one extra heteroatom has indicated that dipole-dipole interactions between 1,3-heteroatoms may be important in determining preferred conformations in these systems.[1, 2]

In order to obtain more information regarding the nature and magnitude of this effect it was decided to study the position of conformational equilibria in substituted 1,3-diazabicyclo[4.4.0]decanes (I). In this system unfavourable dipole-dipole interactions in the *trans*- fused ring conformation (II) may be relieved by inversion of the 3N atom (III), and this will be reflected in the value of the geminal coupling constant (J_{gem}) for the C2 methylene group.[2]



I



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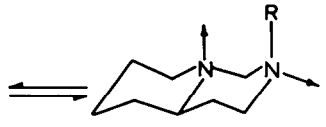


III

Synthesis

The N-alkyl substituted 1,3-diazabicyclo[4.4.0.]decanes and the 5 and 10-Me N-substituted compounds were synthesized from the corresponding 2-vinylpyridines (Fig. 1) by reaction with the appropriate amine to yield the 2-aminoethylpyridine. Sodium-ethanol reduction, followed by cyclization of the resultant piperidine with formaldehyde, afforded the required bicyclic product. The two diasteroisomers†

* Part X. P. J. Chivers, T. A. Crabb and R. O. Williams, *Tetrahedron* **25**, 2921 (1969).

† All 1,3-diazabicyclo[4.4.0]decanes described in this paper exist as racemates.

possible for the 5 and 10-Me substituted compounds were separated by preparative GLC.

3-phenyl-1,3-diazabicyclo[4.4.0]decane was synthesized by refluxing aniline and α-(2-bromoethyl)-piperidine hydrobromide together to give 2-phenylamino-1-(α-piperidyl)-ethane. Reaction of the latter compound with formaldehyde yielded the bicyclic product.

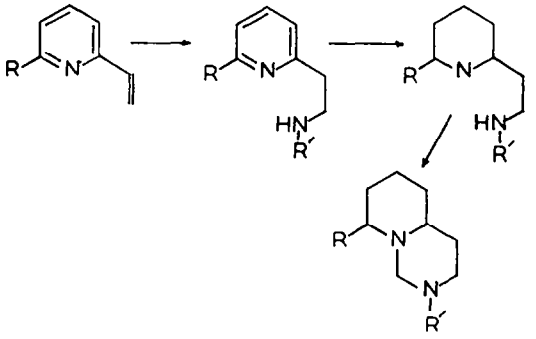


FIG. 1.

The 4-Me substituted compounds were synthesized from the corresponding substituted pyridyl ethanols, as shown in Fig. 2. The latter compound was catalytically reduced to yield an epimeric mixture of the 1-(α-piperidyl)-2-propanols which was then oxidized to the ketone using chromium trioxide. Shaking with an excess of methylamine or ethylamine in MeOH in the presence of H_2 and Adams catalyst reductivity alkylated the ketone, and gave a mixture of the epimeric 2-ethylamino and 2-methylamino-1-(β-piperidyl)-propanes. After reaction with formaldehyde, the epimeric 4-ethyl and 4-methyl-1,3-diazabicyclo[4.4.0]decanes were separated by preparative GLC.

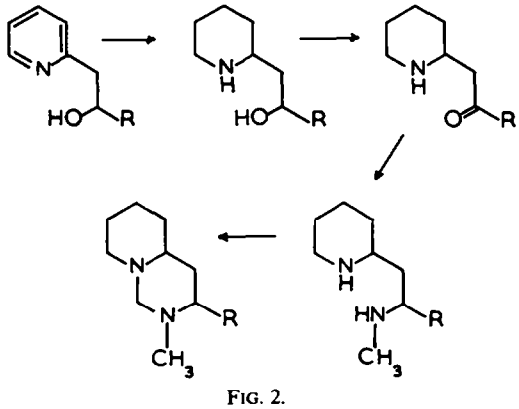


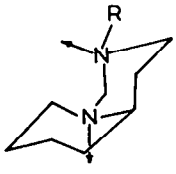
FIG. 2.

NMR spectra

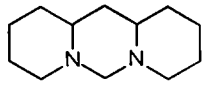
Previous papers in this series have shown that the value of the J_{gem} of a methylene group α to a heteroatom depends upon the orientation of the CH bonds with respect to the heteroatom lone pairs of electrons. Thus compounds (I) existing in the *trans*-fused ring conformation (II) with an equatorially situated N-alkyl group are expected

to have a larger* J_{gem} for the C2 methylene group than those compounds in which either the ring fusion is *trans*- and the N-alkyl group is axial (III) or the ring fusion is *cis* (IV). This was discussed more fully in connection with the 3-oxa-1-azabicyclo-[4.4.0]decanes.[2]

It may be predicted that 3-t-butyl-1,3-diazabicyclo[4.4.0]decane will exist predominantly in conformation II, since the conformational free energy of the 3-t-butyl group is too great to allow appreciable amounts of conformation III, with an axial t-Bu group, to be present. In those compounds with less sterically demanding 3-alkyl groups, however, the destabilizing dipole-dipole interaction between the N atoms might be sufficiently severe to induce the N-alkyl group to adopt an axial position. It can be seen from Table 1 that all of the unsubstituted 3-alkyl-1,3-diazabicyclo-[4.4.0]decanes have a J_{gem} for the C2 methylene group of between −8·4 and −8·6 Hz. In compound V which possesses the *trans syn trans* stereochemistry[5] J_{gem} for the methylene group situated between the heteroatoms is − 8·9 Hz and this will be taken as representative for compounds of this type in which both of the N lone pairs of electrons are situated anti-coplanar with a C—H bond of the C2 methylene group.



IV



V

It follows therefore that all of the unsubstituted 3-alkyl-1,3-diazabicyclo[4.4.0]-decanes must exist predominantly in a *trans*-fused ring conformation with an equatorial N-alkyl group. Further evidence for the correctness of these assignments is the large chemical shift difference between the C2 methylene protons, with the axial C2 proton shielded by both the equatorial N-alkyl group and the C10 methylene group[3] and perhaps by both nitrogen lone pairs of electrons.[4] The equatorial C2 protons of these compounds all show a long range coupling of ca. 1·8 Hz, which spin decoupling experiments prove to be due to coupling with the equatorial C4 proton. The J_{gem} for the C2 methylene group in 3-phenyl-1,3-diazabicyclo[4.4.0]decane is − 10·5 Hz showing that the conformation must be such that the lone pair of electrons on the 3N atom can overlap the MO of the Ph group. The N lone pair is thus less readily available for donation into the antisymmetric MO of the C2 methylene group. The other features of the NMR spectrum of this compound are unexceptional and support a *trans*-fused ring conformation (Table 1).

The 3,5-dimethyl-1,3-diazabicyclo[4·4·0]decanes exhibit values of J_{gem} of − 8·4 Hz and − 8·7 Hz indicating that both compounds also exist in predominantly *trans*-fused ring conformations with equatorial N-Me groups. In quinolizidines[6] and in other related heterocyclic systems, equatorial C-Me group resonances come to higher field and have smaller apparent coupling constants with the vicinal CH proton than

* J_{gem} is assumed to be negative.

TABLE 1. NMR SPECTRA ($CDCl_3$ SOLN) OF 1,3-DIAZABICYCLO[4.4.0]DECANES

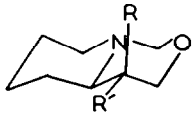
Compound	Coupling constants (Hz.)[a]			Chemical shifts (τ)[b]					
	$J_{H2_{eq}H2_{ax}}$	$J_{H2_{eq}H4_{eq}}$	$J_{CH\text{-}CH_3}$	$H2_{eq}$	$H2_{ax}$	$H4_{eq}$	$H10_{eq}$	$N\text{-}CH_3$	$C\text{-}CH_3$
3-Methyl-1,3-diazabicyclo[4.4.0]decane	−8·4	1·6	—	6·47	7·62	7·2	7·2	7·76	—
3-Ethyl-1,3-diazabicyclo[4.4.0]decane	−8·4	1·7	—	6·37	7·60	7·2	7·2	—	—
3-Isopropyl-1,3-diazabicyclo[4.4.0]decane	−8·6	1·8	—	6·35	7·39	7·2	7·2	—	—
3-t-Butyl-1,3-diazabicyclo[4.4.0]decane	−8·5	2·0	—	6·19	7·46	7·2	7·2	—	—
3-Phenyl-1,3-diazabicyclo[4.4.0]decane	−10·5	2·0	—	5·71	6·88	6·38	7·2	—	—
cis-4,6-*H*-3,4-Dimethyl-1,3-diazabicyclo[4.4.0]decane	−8·8	—	6·6	6·51	7·47	—	7·2	7·81	8·91
trans-4,6-*H*-3,4-Dimethyl-1,3-diazabicyclo[4.4.0]decane	(−10·8)[c]	<0·5	5·2	6·82	6·82	7·2	7·2	7·54	8·94
cis-4,6-*H*-3-Methyl-4-ethyl-1,3-diazabicyclo[4.4.0]decane	−8·8	—	—	6·44	7·38	—	7·3	7·76	—
trans-4,6-*H*-3-Methyl-4-ethyl-1,3-diazabicyclo[4.4.0]decane	(−11·4)[c]	<0·5	—	6·79	6·79	7·4	7·4	7·43	—
cis-5,6-*H*-3,5-Dimethyl-1,3-diazabicyclo[4.4.0]decane	−8·7	2·0	6·7	6·44	7·82	7·2	7·2	7·78	8·90
trans-5,6-*H*-3,5-Dimethyl-1,3-diazabicyclo[4.4.0]decane	−8·4	2·0	5·6	6·47	7·60	7·2	7·2	7·82	9·19
cis-10,6-*H*-3,10-Dimethyl-1,3-diazabicyclo[4.4.0]decane	−8·5	1·7	5·8	6·03	7·82	7·15	—	7·73	8·93
trans-10,6-*H*-3,10-dimethyl-1,3-diazabicyclo[4.4.0]decane	−9·9	2·0	6·4	6·32	7·21	6·9	—	7·82	8·97
cis-10,6-*H*-3-t-Butyl-10-methyl-1,3-diazabicyclo[4.4.0]decane	−8·6	1·8	—	5·70	7·70	6·9	—	—	—
trans-10,6-*H*-3-t-Butyl-10-methyl-1,3-diazabicyclo[4.4.0]decane	−9·8	1·8	—	6·09	7·0	6·9	—	—	—

[a] ±0·2 Hz

[b] ±0·05 τ

[c] The values of $J_{H2_{eq}H2_{ax}}$ were extracted from spectra obtained on 10% solns in benzene in which the C2 methylene protons did not have identical chemical shifts (e.g. Fig. 4)

their axial counterparts, and configurational assignments were therefore made to the 3,5-dimethyl-1,3-diazabicyclo[4.4.0]decanes on the basis of the chemical shift and apparent coupling constant of the C5-Me group. In one of the isomers the C5-Me absorbs at 9·19 τ and J C*H*—Me = 5·6 Hz whereas in the other the corresponding chemical shift and coupling constant are 8·90 τ and 6·7 Hz. The latter compound is therefore assigned the *cis*-5, 6-*H*-5-methyl configuration and the chemical shift of the axial C2 proton in this compound confirms the assignment. This proton absorbs 0·22 τ to higher field than the corresponding proton in the epimer. A similar chemical shift difference was observed in the pair of compounds VI (R′ = H, R = Me) and VI (R′ = Me, R = H)[8], the configurations of these having been determined by their different rates of reaction with methyl iodide.



VI

The NMR spectra of the 3,4-dimethyl and 3-methyl, 4-ethyl-1,3-diazabicyclo-[4.4.0]decanes show very interesting variations. One of the 3,4-dimethyl-1,3-diazabicyclo[4.4.0]decanes showed a J_{gem} of − 8·8 Hz (Fig. 3) indicating a *trans*-fused ring conformation with an equatorial N-alkyl group. The C2 methylene chemical shifts in this compound are similar to those in 3-methyl-1,3-diazabicyclo[4.4.0]decane.

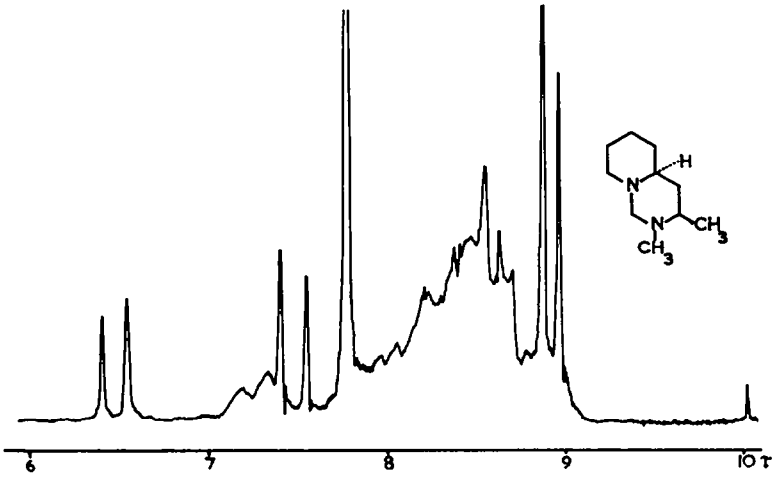


FIG. 3.

This leads to the assignment of the *cis*-4, 6-H-3,4-dimethyl configuration with an equatorial N-Me group to this isomer since an axial Me group at C4 is expected[2] to deshield C2Hax and shield C2Heq relative to the unsubstituted compound. This conclusion is supported by the lack of any appreciable long range coupling of the equatorial C2 proton with the C4 equatorial proton (observed in II) and the presence of only one equatorial proton adjacent to nitrogen at ca. 7·2 τ (C10eq).

trans-4,6-*H*-3,4-Dimethyl-1,3-diazabicyclo[4.4.0]decane has a J_{gem} for the C2 methylene group of −10·8 Hz, 2 Hz more negative than that observed in the other isomer. The NMR spectrum also indicates the presence of two CH equatorial protons next to N at ca. 7·2 τ and a long range coupling between the C2 and C4 equatorial protons (Fig. 4). These results are interpreted in terms of a *trans*-fused ring conformation with an axial N-Me group (VIII) since although there are two *cis*-fused ring

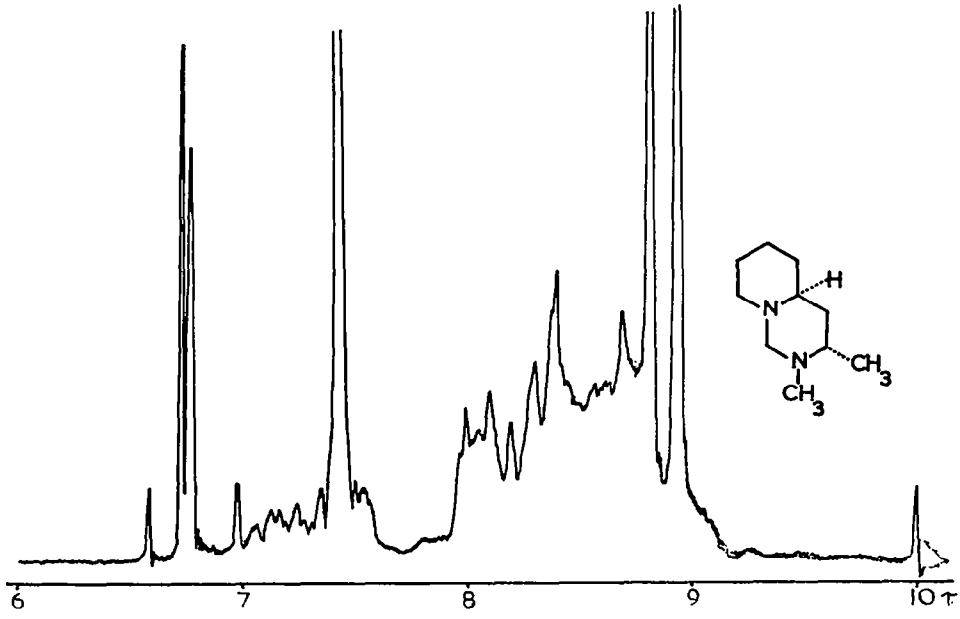
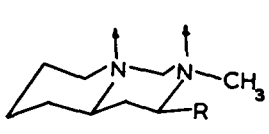
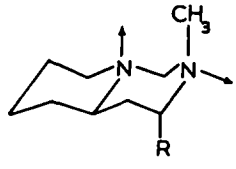


FIG. 4.

conformations which might possess a J_{gem} of ca. − 10·8 Hz, they would not give rise to all of the other spectral characteristics and models indicate that both contain an excessive number of non-bonded interactions. The axial nature of the N-Me group in this compound is further indicated by its chemical shift, 0·27 τ to lower field than the corresponding signal in the *cis*-4,6-*H*-3,4-dimethyl compound (VII). Similar arguments apply to the epimeric 3-methyl-4-ethyl-1,3-diazabicyclo[4.4.0]decanes. It is notable that in this case the *trans*-4,6-*H*-3-methyl-4-ethyl compound has a J_{gem} for the C2 methylene group of − 11·4 Hz, 0·6 Hz more negative than in VIII. A further



VII



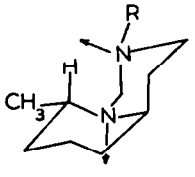
VIII

point of interest with regard to the *trans*-4, 6 :*H*-4-substituted compounds is the much reduced value of the long range coupling $|J_{H2eq\ H4eq}|$ compared with the other members of the series. The difference is probably attributable to the equatorial position of

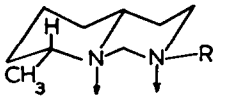
the nitrogen lone pair of electrons. Cookson and Crabb[9] noticed a similar variation during a study of tetrahydro-1,3-oxazines and found that when the N lone pair was equatorial with respect to the equatorial C2 and C4 protons the coupling $|J_{H2eq\,H4eq}|$ was smaller than when the lone pair was axially orientated.

It is well known that sodium-ethanol reduction normally gives the thermodynamically most stable product and the reduction of 2-alkylamino-1-(6-methyl-α-pyridyl)-ethanes is thus expected to give mainly the diequatorially substituted piperidine. The bicyclic product obtained in greatest yield by the route shown in Fig. 1 is therefore assumed to be the *cis*-10,6-*H*-10-methyl-1,3-diazabicyclo[4.4.0]decane.

The epimers assigned the *cis*-10, 6-*H*-10-methyl configuration on the basis of chemical evidence are both found to exist in a predominantly *trans*-fused ring conformation with an equatorial N-alkyl group, the J_{gem} for the C2 methylene group of the N-Me and N-t-Bu compounds being − 8·5 and − 8·6 Hz respectively. As expected, the chemical shift difference between the C2 protons is very large, since in addition to preferential shielding of the axial C2 proton by the N-alkyl group and the C10 methyl group the equatorial 10-Me group also deshields the equatorial C2 proton and shields the axial C2 proton. This results in a chemical shift difference of 2·0 τ in the case of the *cis*-10,6-*H*-10-methyl-3-t-butyl compound. The 3-methyl and 3-t-butyl compounds, assigned the *trans*-10,6-*H*-10-methyl configuration on the basis of chemical evidence, have J_{gem} for the C2 methylene protons of − 9·9 Hz and 9·8 Hz respectively. The ca. 1 Hz difference between this and the corresponding parameter in the *cis*-10,6-H-10-methyl epimers suggests that the former exist as conformational mixtures containing appreciable amounts of the *cis*- and *trans*-fused ring conformations (IX and X). In order to gain further information regarding this mixture low temperature NMR experiments were carried out, but no variations in the spectra were observed at temperatures down to − 100°.



IX



X

Conformational analysis

The NMR results given above enable some deductions to be made regarding the severity of dipole interactions between the N atoms in this system. Since 3-methyl-1,3-diazabicyclo[4.4.0]decane exists in the *trans*-fused ring conformation with an equatorial N-Me group the destabilising dipole-dipole interaction in this compound must be less than the conformational free energy of the 3-Me group. This is expected to be ca. 1·7 k cal/mole since an axial 3-Me group would introduce a *gauche*-butane (0·85 k cal/mole) and a *gauche*-n-propylamine interaction into the molecule which may be assumed to be of the same order of magnitude as a *gauche*-butane interaction.[10]

Conformation VII with the 3-Me group equatorial, is expected to be the preferred conformation for the *cis*-4, 6-*H*-3,4-dimethyl compound since an axially orientated 3-Me group would remove the unfavourable dipole interaction only at the expense of introducing a *gauche*-butane and a *gauche*-n-propylamine interaction into the molecule. The *trans*-4, 6-*H*-3,4-dimethyl compound might however be predicted to exist as a conformational mixture containing appreciable amounts of conformation VIII with an axial N-Me group.

A comparison of the number of non-bonded interactions in the conformation with an equatorial N-Me group with conformation VIII reveals that the latter, with an axial N-Me group, has an extra *gauche*-n-propylamine interaction. Since the *trans*-4,6-*H*-3,4-dimethyl compound has been found to exist as a conformational mixture containing appreciable amounts of conformation VIII, it follows that the dipole-dipole interaction is in the region 0·8 kcal/mole.

Similar reasoning explains the position of the conformational equilibrium in the *trans*-10,6-*H*-10-methyl compounds. The dipole-dipole interaction present in the *trans*-fused ring conformation (X) is relieved in the *cis*-fused ring conformation (IX). This latter conformation however is destabilised relative to the *trans*-fused ring conformation (X), by a *gauche*-n-propylamine interaction.

Infrared spectra

The application of Bohlmann's IR criterion to these compounds is greatly complicated both by the presence of two N atoms and in some cases α-H atoms of the 3-alkyl group. The IR results are summarized in Table 2 and Fig. 5 and although not definitive the general trends support the configurational and conformational assignments already made. The decrease in the intensity of the absorption between 2850 and 2500 cm^{-1} on going from 3-methyl to 3-t-butyl-1,3-diazabicyclo[4.4.0]decane clearly shows the contribution to Bohlmann bands from the α C–H bonds of the N-alkyl groups.

It can be seen from Fig. 5 that the *cis*-10,6-H-10-methyl compounds, which exist in the *trans*-fused ring conformation (X), both exhibit more intense bands in the

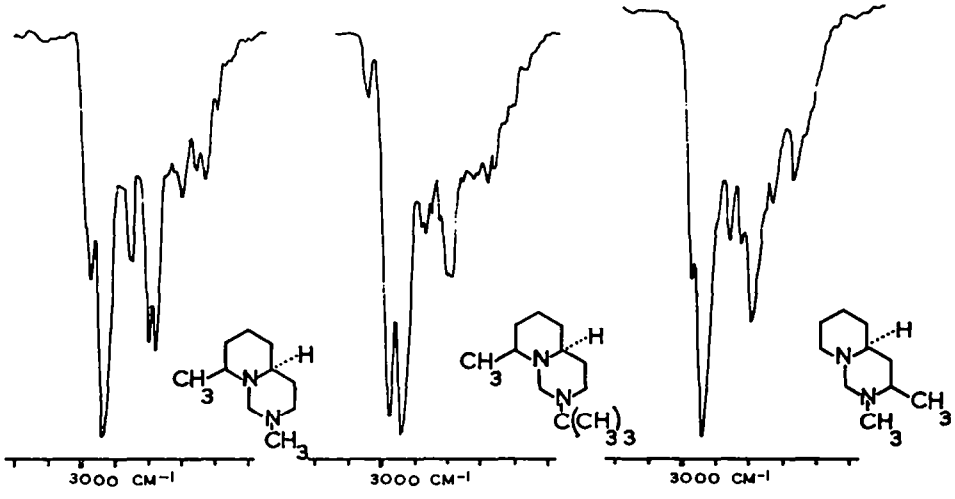


FIG. 5.

TABLE 2. IR SPECTRA OF 1,3-DIAZABICYCLO[4.4.0]DECANES

Compound	$cm^{-1}(\varepsilon_a{}^*)$
3-Methyl-1,3-diazabicyclo[4.4.0]decane	2803(100), 2778(115), 2740(50), 2721(50), 2658(49)
3-Ethyl-1,3-diazabicyclo[4.4.0]decane	2824(77), 2793(115), 2732(60), 2668(51)
3-Isopropyl-1,3-diazabicyclo[4.4.0]decane	2824(75), 2792(105), 2728(58), 2680(45), 2658(47)
3-t-Butyl-1,3-diazabicyclo[4.4.0]decane	2822(51), 2785(70), 2740(41), 2720(41), 2677(46)
3-Phenyl-1,3-diazabicyclo[4.4.0]decane	2818(85), 2785(76), 2764(77), 2728(50), 2675(48)
cis-4,6-*H*-3,4-Dimethyl-1,3-diazabicyclo[4.4.0]decane	2825(71), 2795(110), 2750(60), 2732(50), 2670(45)
trans-4,6-*H*-3.4-Dimethyl-1,3-diazabicyclo[4.4.0]decane	2801(50), 2775(55), 2734(35), 2670(25)
cis-4,6-*H*-3-Methyl-4-ethyl-1,3-diazabicyclo[4.4.0]decane	2802(80), 2777(120), 2743(55), 2664(45), 2628(30)
trans-4,6-*H*-3-Methyl-4-ethyl-1,3-diazabicyclo[4.4.0]decane	2793(71), 2777(70), 2668(43)
cis-5,6-*H*-3,5-Dimethyl-1,3-diazabicyclo[4.4.0]decane	2806(85), 2778(104), 2755(57), 2718(47), 2657(40)
trans-5,6-*H*-3,5-Dimethyl-1,3-diazabicyclo[4.4.0]decane	2805(90), 2777(115), 2728(58), 2670(42), 2657(42), 2620(32)
cis-10,6-*H*-3,10-Dimethyl-1,3-diazabicyclo[4.4.0]decane	2800(125), 2774(128), 2740(45), 2700(51), 2660(42), 2635(45)
trans-10,6-*H*-3,10-Dimethyl-1,3-diazabicyclo[4.4.0]decane	2800(100), 2780(80), 2705(30), 2685(25)
cis-10,6-*H*-3-t-Butyl-10-methyl-1,3-diazabicyclo[4.4.0]decane	2821(51), 2790(78), 2720(43), 2680(43), 2660(40)
trans-10,6-*H*-3-t-Butyl-10-methyl-1,3-diazabicyclo[4.4.0]decane	2821(49), 2800(55), 2760(28), 2600(26)

* Apparent extinction coefficient.

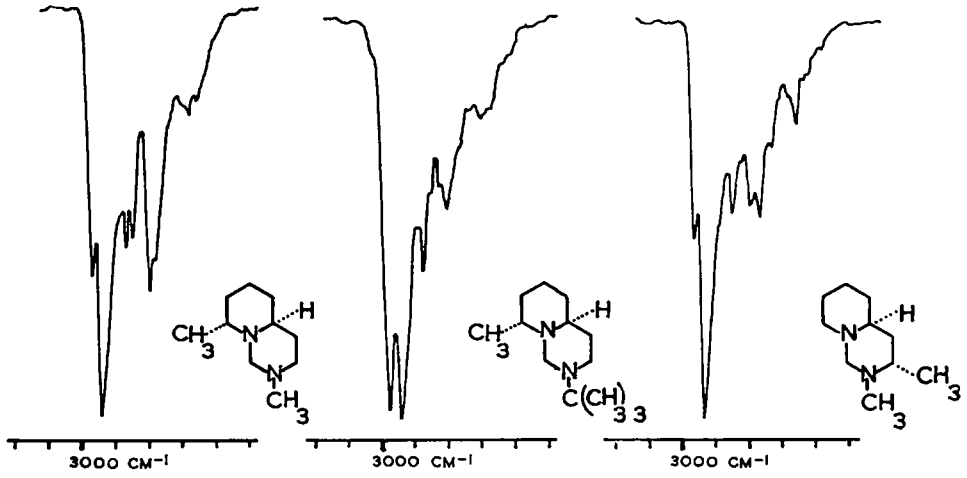


FIG. 6.

Bohlmann region of their IR spectra than do the *trans*-10,6-*H*-10-methyl compounds which contain appreciable amounts of the *cis*-fused ring conformation (IX) in their equilibrium. The *cis*-4,6-*H*-4-methyl compounds exhibit bands in this region from *trans*-axial C-H bonds α to both the N atoms and from the N-alkyl group. In the *trans*-4,6-*H*-4-methyl compounds, in which no bonds will arise between 2850 and 2500 cm^{-1} from *trans*-axial C-H bonds α to the 3N atom, a marked decrease in the intensity of the absorption is observed.

EXPERIMENTAL

Elemental analyses were carried out by Dr. F. Pascher and E. Pascher, Micro-Analytical Laboratory, Bonn, Germany. IR spectra were recorded on a Perkin Elmer 237 grating instrument as 0·075 M solns in $CDCl_3$ using 0·5 mm matched cells. The NMR spectra were determined on a Perkin Elmer R.10 spectrometer as 10% solns in $CDCl_3$ with TMS as internal reference.

Preparation of 2-alkylamino-1-(α-pyridyl)-ethanes

General procedure. The 2-vinylpyridine (0·2 M) in abs MeOH (60 ml) was refluxed with either (a) t-$BuNH_2$ (0·2 M) and glacial AcOH (12 g) for 4 days or (b) $MeNH_2$.HCl (0·2 M) or $EtNH_2$.HCl for 8 hr. The solvents were removed *in vacuo* and the residue was strongly basified with NaOH aq. The reaction mixture was ether extracted 3 times and the extract was dried (Na_2SO_4), concentrated and distilled to give the 2-alkylamino-1-(α-pyridyl)-ethane.

2-*Methylamino*-1-(α-*pyridyl*)-*ethane* (14·6 g, 52%) was obtained from 2-vinylpyridine (21·6 g) as a colourless mobile oil b.p., 114–116°/26 mm (Lit.[11] 117–118°/25 mm).

2-*Ethylamino*-1-(α-*pyridyl*)-*ethane* (21·4 g, 71%) was obtained from 2-vinylpyridine (21·6 g) as a colourless mobile oil b.p., 106–108°/13 mm (Lit.[11] 109–110°/12 mm).

2-*t-Butylamino*-1-(α-*pyridyl*)-*ethane*[11] (10·6 g, 29%) was obtained from 2-vinylpyridine (21·6 g) as a colourless mobile oil b.p., 120–122°/16 mm.

2-*Methylamino*-1-(6-*methyl*-α-*pyridyl*)-*ethane* (25 g, 83%) was obtained from 6-methyl-2-vinylpyridine (24 g) as a colourless mobile oil b.p., 117–118°/23 mm.(Found: C, 72·07; H, 9·47; N, 18·78. $C_9H_{14}N_2$ requires: C, 71·95; H, 9·39; N, 18·65%).

2-*t-Butylamino*-1-(6-*methyl*-α-*pyridyl*)-*ethane* (17·5 g, 46%) was obtained from 6-methyl-2-vinylpyridine (24 g) as a colourless mobile oil b.p., 95–98°/3 mm. (Found: C, 75·25; H, 10·52; N, 14·98. $C_{12}H_{20}N_2$ requires: C, 74·95; H, 10·48; N, 14·57%).

3-*Methylamino*-2-(α-*pyridyl*)-*propane* (10·1 g, 55%) was obtained from 2-(α-pyridyl)-propane (14·5 g) by method b, however refluxing for four days in the presence of glacial AcOH was necessary to make the reaction work. The product was a colourless mobile oil b.p., 97–100°/12 mm.

2-*Isopropylamino*-1-(α-*pyridyl*)-*ethane*. 2-amino-1-(α-pyridyl)-ethane (16 g) and acetone (20 g) were refluxed together for 1 hr. Distillation of the reaction mixture gave 2-isopropylimino-1-(α-pyridyl)-ethane (21·0 g, 91%) as a colourless mobile oil b.p., 91–92°/1·6 mm. To the Schiff's base (20 g) in abs MeOH (150 ml) was added $NaBH_4$ (10 g). When the reaction ceased the mixture was acidified with dil HCl, basified with NaOH aq and ether extracted 3 times. The ethereal solution was concentrated and distilled to give 2-isopropylamino-1-(α-pyridyl) ethane (16·5 g, 79%) as a colourless mobile oil b.p., 84–86°/1·2 mm $n_D^{20.0}$ 1·5059. (Found: C, 72·97; H, 9·82; N, 16·80. $C_{10}H_{16}N_2$ requires: C, 73·12; H, 9·82; N, 17·06%).

Sodium-ethanol reduction of 2-*alkylamino*-1-(α-pyridyl)-*ethanes*

General procedure. To a stirred soln of the 2-alkylamino-1-(α-pyridyl) ethane (15 g) in abs EtOH (400 ml) was added Na (40 g) at such a rate that the reaction mixture refluxed. When all the Na had dissolved the reaction mixture was refluxed for 1 hr and then acidified with conc HCl. Excess EtOH was removed *in vacuo* and the crude mixture was basified with NaOH aq and ether extracted 3 times. The extract was dried (Na_2SO_4) and concentrated and the crude product was distilled to give the 2-alkylamino-1-(α-piperidyl)-ethane.

2-*Methylamino*-1-(α-*piperidyl*)-*ethane* (7·9 g, 59%) was obtained from 2-methylamino-1-(α-pyridyl)-ethane (12·5 g) as a colourless mobile oil b.p., 93–94°/11 mm. (Found: N, 19·61. $C_8H_{18}N_2$ requires: N, 19·70%).

2-*Ethylamino*-1-(α-*piperidyl*)-*ethane* (16·3 g, 71%) was obtained from 2-ethylamino-1(α-pyridyl)-ethane (20 g) as a colourless mobile oil b.p. 104–106°/11 mm. (Found: C, 68·90; H, 12·64; N, 18·01. $C_9H_{20}N_2$ requires: C, 69·17; H, 12·90; N, 17·93%).

2-*Isopropylamino*-1-(α-*piperidyl*)-*ethane* (10·3 g, 79%) was obtained from 2-isopropylamino-1-(α-pyridyl)-ethane (11·5 g) as a colourless mobile oil b.p., 100–101°/ mm, n_D^{20} 1·4798. (Found: C, 69·93; H, 13·47; N, 16·66. $C_{10}H_{22}N_2$ requires: C, 70·53; H, 13·02; N, 16·45%).

2-*t-Butylamino*-1-(α-*piperidyl*)-*ethane* (13·2 g, 86%) was obtained from 2-t-buylamino-1-(α-pyridyl)-ethane (15 g) as a colourless mobile oil b.p., 98–101°/7 mm. (Found: C, 71·15; H, 12·94; N, 14·87. $C_{11}H_{24}N_2$ requires: C, 71·68; H, 13·13; N, 15·20%).

2-*Methylamino*-1-(6-*methyl*-α-*piperidyl*)-*ethane* (13·5 g, 73%) was obtained from 2-methylamino-1-(6-methyl α-pyridyl)-ethane (18 g) as a colourless mobile oil b.p., 96–99°/14 mm. (Found: C, 69·51; H, 12·66; N, 17·96. $C_9H_{20}N_2$ requires: C, 69·17; H, 12·90; N, 17·93%).

2-*t-Butylamino*-1-(6-*methyl*-α-*piperidyl*)-*ethane* (12·5 g, 80%) was obtained from 2-t-butylamino-1-(6-methyl-α-pyridyl)-ethane (15 g) as a colourless mobile oil b.p., 107–109°/7 mm. (Found: C, 72·47; H, 13·02; N, 14·98. $C_{12}H_{20}N_2$ requires: C, 72·66; H, 13·21; N, 14·12%).

3-*Methylamino*-2-(α-*piperidyl*)-*propane* (8·8 g, 77%) was obtained from 3-methylamino-2-(α-pyridyl)-propane (10 g) as a colourless mobile oil b.p., 101–105°/9 mm. (Found: C, 68·35; H, 12·56; N, 17·93. $C_9H_{20}N_2$ requires: C, 69·17; H, 12·90; N, 17·93%).

2-*Phenylamino*-1-(α-*piperidyl*)-*ethane*

A cooled soln of 2-piperidyl ethanol (30 g) in CCl_4 (150 ml) was saturated with HBr gas. The solvent was removed *in vacuo* and the crude viscous hydrobromide was treated with PBr_3 (35 g). A vigorous exothermic reaction ensued and dense clouds of HBr were evolved. When the reaction ceased the crude product was triturated with ether and recrystallized from abs EtOH to give the bromide hydrobromide (42 g, 97%) as white needles m.p., 162–164°. (Found: C, 30·80; H, 5·30; N, 4·88; Br, 59·07. $C_7H_{15}NBr_2$ requires: C, 30·76; H, 5·53; N, 5·12; Br, 58·57%). 2-bromoethylpiperidine hydrobromide (15 g) was refluxed with aniline (15 g) for 3 hr. The reaction mixture was cooled and triturated with ether to give a white crystalline solid. This was strongly basified with NaOH aq and ether extracted 3 times. The ether extract was dried (Na_2SO_4) and concentrated to give a white solid. Recrystallization from ether afforded 2-phenylamino-1-(α-piperidyl)-ethane (6·5 g, 58%) as white plates m.p., 67–68°. (Found: C, 75·98; H, 9·89; N, 13·52. $C_{13}H_{20}N_2$ requires: C, 76·42; H, 9·87; N, 13·71%).

Preparation of 2-*methylamino*-1-(α-*piperidyl*)-*propanes*

An epimeric mixture of the 1-(α-piperidyl)-2-propanols[12] was oxidized to 1-(α-piperidyl)-2-propanone by Meisenheimer's method.[13]

The ketone (10·3 g) was dissolved in abs MeOH (150 g) containing $MeNH_2$ (8 g) and the mixture was shaken with PtO_2 (1 g) and H_2 at 60 psi. After 2 hr the theoretical uptake of H_2 was complete, the soln

was filtered and the solvents were removed *in vacuo*. Distillation of the crude product afforded an epimeric mixture of the 2-methylamino-1-(α-piperidyl)-propanes (10·7 g, 92%) as a colourless mobile oil b.p., 97–98°/11 mm. (Found: C, 68·81; H, 12·88; N, 18·11. $C_9H_{20}N_2$ requires: C, 69·17; H, 12·90; N, 17·93%).

Preparation of 2-*methylamino*-1-(α-*piperidyl*)-*butanes*

An epimeric mixture of the 1-(α-piperidyl)-2-butanols was oxidized to 1-(α-piperidyl)-2-butanone by Meisenheimer's method.[13] Reductive alkylation of the ketone (8·0 g) as above gave an epimeric mixture of the 2-methylamino-1-(α-piperidyl)-butanes (5·0 g, 57%) as a colourless mobile oil b.p., 130–131°/30 mm. (Found: C, 70·84; H, 12·66. $C_{10}H_{22}N_2$ requires: C, 70·53; H, 13·02%).

Preparation of 3-*alkyl*-1,3-*diazabicyclo*[4.4.0]*decanes*

General procedure. The amine (10 g) was shaken with 40% aqueous formaldehyde (10 ml) for ½ hr. The mixture was basified with NaOH aq and ether extracted 3 times. The ethereal soln was dried (Na_2SO_4) and concentrated and the crude product was distilled.

3-*Methyl*-1,3-*diazabicyclo*[4.4.0]*decane* (3·0 g, 69%) was obtained from 2-methylamino-1-(α-piperidyl)-ethane (4 g) as a colourless mobile oil b.p. 92–94°/14 mm, n_D^{10} 1·4872. (Found: C, 70·32; H, 11·74; N, 17·91. $C_9H_{18}N_2$ requires: C, 70·07; H, 11·76; N, 18·16%).

3-*Ethyl*-1,3-*diazabicyclo*[4.4.0]*decane* (4·2 g, 77%) was obtained from 2-ethylamino-1-(α-piperidyl)-ethane (5 g) as a colourless mobile oil b.p. 112–113°/19 mm, $n_D^{10\,0}$ 1·4862. (Found: C, 71·40; H, 12·03; N, 16·79. $C_{10}H_{20}N_2$ requires: C, 71·37; H, 11·98; N, 16·65%).

3-*Isopropyl*-1,3-*diazabicyclo*[4.4.0]*decane* (4·1 g, 74%) was obtained from 2-isopropylamino-1-(α-piperidyl)-ethane (5 g) as a colourless mobile oil b.p., 116–117°/14 mm, $n_D^{20\,0}$ 1·4899. (Found: C, 71·99; H, 12·36; N, 15·13. $C_{11}H_{22}N_2$ requires: C, 72·47; H, 12·16; N, 15·37%).

3-*t-Butyl*-1,3-*diazabicyclo*[4.4.0]*decane* (4·8 g, 53%) was obtained from 2-t-butylamino-1-(α-piperidyl)-ethane (5 g) as a colourless mobile oil b.p. 113–114°/11 mm, n_D^{10} 1·4898. (Found: C, 71·15; H, 12·94; N, 14·87. $C_{11}H_{24}N_2$ requires: C, 71·68; H, 13·13; N, 15·20%).

3-*Phenyl*-1,3-*diazabicyclo*[4.4.0]*decane* (5·2 g, 98%) was obtained from 2-phenylamino-1-(α-piperidyl)-ethane (5 g) as a colourless viscous oil b.p., 130–132°/0·375 mm, $n_D^{19\,0}$ 1·5698. (Found: C, 77·78; H, 9·28; N, 13·09. $C_{14}H_{20}N_2$ requires: C, 77·73; H, 9·32; N, 12·95%).

cis- *and* trans-10,6-H-3,10-*Dimethyl*-1,3-*diazabicyclo*[4.4.0]*decane* (9·7 g, 87%) was obtained from an epimeric mixture of 2-methylamino-1-(6-methyl-α-piperidyl)-ethane (10 g) as a colourless mobile oil b.p., 105–107°/17 mm. (Found: C, 70·99; H, 12·00; N, 16·75. $C_{10}H_{20}N_2$ requires: C, 71·37; H, 11·98; N, 16·65%). Separation was achieved on a Pye 105 gas–liquid chromatograph using a carbowax column and N_2 carrier gas. *cis*-10,6-*H*-3,10-Dimethyl-1,3-diazabicyclo[4.4.0]decane (65% of the mixture) was the first isomer off the column and was obtained as a colourless mobile oil $n_D^{20\,0}$ 1·4800. *trans*-10,6-*H*-3,10-Dimethyl-1,3-diazabicyclo[4.4.0]decane (35% of the mixture) was the second isomer off the column as a colourless mobile oil $n_D^{20\,0}$ 1·4835. The percentage of each isomer was estimated from the intensities of the signal due to the C2 methylene protons in the NMR spectrum of the mixture.

cis- *and* trans-10,6-*H*-10-*Methyl*-3-*t-butyl*-1,3-*diazabicyclo*[4.4.0]*decane* (9·4 g, 89%) was obtained from an epimeric mixture of 2-t-butylamino-1-(6-methyl-α-piperidyl)-ethane (10 g) as a colourless mobile oil b.p., 122–124°/10 mm. (Found: C, 74·36; H, 12·37; N, 13·76. $C_{13}H_{26}N_2$ requires: C, 74·22; H, 12·46; N, 13·32%). Separation was achieved on an Aerograph Autoprep using a carbowax column and H-carrier gas. *cis*-10,6-*H*-10-Methyl-3-t-butyl-1,3-diazabicyclo[4.4.0]decane (65% of the mixture) was the first fraction off the column as a colourless mobile oil $n_D^{15\,0}$ 1·4827. *trans*-10,6-*H*-10-*Methyl*-3-t-butyl-1,3-diazabicyclo-[4.4.0]decane (34% of the mixture) was the second fraction off the column as a colourless mobile oil n_D^{22} 1·4830.

cis- *and* trans-4,6-*H*-3,4-*Dimethyl*-1,3-*diazabicyclo*[4.4.0]*decane* (8·1 g, 94%) was obtained from an epimeric mixture of 2-methylamino-1-(α-piperidyl)-propane (8 g) as a colourless mobile oil b.p., 94–95°/10 mm. (Found: C, 71·32; H, 12·01; N, 16·71. $C_{10}H_{20}N_2$ requires: C, 71·37; H, 11·98; N, 16·65%). Separation was achieved on an Aerograph autoprep gas–liquid chromatogram using a 20% carbowax column and H_2 carrier gas. *trans*-4,6-*H*-3,4-Dimethyl-1,3-diazabicyclo[4.4.0]decane was the first fraction off the column and was obtained as a colourless mobile oil n_D^{10} 1·4854 b.p. 100–101°/15 mm. *cis*-4,6-*H*-3,4-Dimethyl-1,3-diazabicyclo[4.4.0]decane was the second isomer off the column, on standing it solidified to a low melting white solid b.p., 101–102°/15 mm.

cis- *and* trans-4,6-H-3-*Methyl*-4-*ethyl*-1,3-*diazabicyclo*[4.4.0]*decane* (5·7 g, 92%) was obtained from an epimeric mixture of 2-methylamino-1-(α-piperidyl)-butane (6 g) as a colourless mobile oil b.p., 126–128°/

29 mm. (Found: C, 72·27; H, 12·05; N, 15·15. $C_{11}H_{22}N_2$ requires: C, 72·47; H, 12·16; N, 15·37%). The diastereoisomeric mixture was separated on a Pye 105 gas–liquid chromatograph using a carbowax column and N_2 carrier gas. *trans*-4,6-*H*-3-Methyl-4-ethyl-1,3-diazabicyclo[4.4.0]decane was the first isomer off the column as a colourless mobile oil $n_D^{10\cdot0}$ 1·4812. *cis*-4,6-*H*-3-Methyl-4-ethyl-1,3-diazabicyclo[4.4.0]-decane was the second fraction off the column $n_D^{15\cdot0}$ 1·4837.

cis- *and* trans-5,6-H-3,5-*Dimethyl*-1,3-*diazabicyclo*[4.4.0]*decane* 5·2 g, 79%) was obtained from an epimeric mixture of 2-methylamino-2-(α-piperidyl)-propane (6·0 g) as a colourless mobile oil b.p., 104–106°/15 mm. (Found: C, 70·76; H, 11·78; N, 16·63. $C_{10}H_{20}N_2$ requires: C, 71·37; H, 11·98; N, 16·65%). Separation of the isomers was achieved on an Aerograph autoprep gas–liquid chromatogram, using a 20% carbowax column and H_2 carrier gas. *cis*-5,6-*H*-3,5-Dimethyl-1,3-diazabicyclo[4.4.0]decane was the first isomer off the column as a colourless mobile oil n_D^{20} 1·4844. *trans*-5,6-*H*-3,5-Dimethyl-1,3-diazabicyclo-[4.4.0]decane was the second fraction off the column as a colourless mobile oil $n_D^{22\cdot0}$ 1·4822.

Acknowledgement—We are indebted to the Science Research Council for a grant enabling us to obtain the Pye Model 105 Automatic Preparative Chromatograph.

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