MAGNETIC RESONANCE IN CHEMISTRY, VOL. 25, 696-706 (1987)

Compounds with Bridgehead Nitrogen 52*—NMR Spectra and Stereochemistry of the 2-Alkylperhydroimidazolo[3,4-*a*]pyridines

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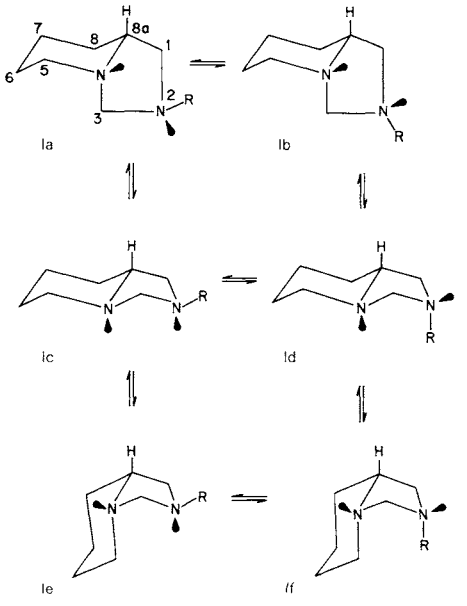
In contrast to perhydro-oxazolo[3,4-*a*]pyridine and perhydrothiazolo[3,4-*a*]pyridine, which adopt equilibria in $CDCl_3$ solution at room temperature containing *ca* 70% *trans*-fused conformers in equilibria with *O*- or *S*-inside *cis*-fused conformers, 2-alkylperhydroimidazolo[3,4-*a*]pyridines are found to adopt equilibria containing >98% *trans*-fused conformers. Comparison of NMR parameters of 2-methylperhydroimidazolo[3,4-*a*]pyridine with those of the two isomers of 1,2-dimethylperhydroimidazolo[3,4-*a*]pyridine indicates an equilibrium for the former compound between the two *trans*-fused conformers, with *ca* 83% of that conformation containing a *trans* arrangement of nitrogen lone pairs of electrons. These observations are explained in terms of the generalized anomeric effect.

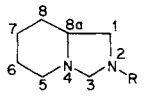
KEY WORDS Perhydroimidazolo[3,4-*a*]pyridine Conformational equilibria ^1H and ^{13}C NMR

INTRODUCTION

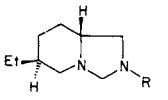
2-Alkylperhydroimidazolo[3,4-*a*]pyridine (I) may exist in solution as an equilibrium between *trans*-fused conformers Ic and Id, *N*-outside *cis*-fused conformers Ia and Ib and *N*-inside *cis*-fused conformers Ie and If, interconvertible by N-inversion and ring inversion (Scheme 1). Previous work[2] has shown the predominance of the *trans*-fused conformers Ic and Id, but no estimate of the *trans* ⇌ *cis* conformational equilibrium could be made since the 60 MHz NMR data was essentially limited to the chemical shifts and coupling constants of the C-3 methylene protons. Accordingly, a reinvestigation of the equilibrium was undertaken using 270 MHz ^1H NMR and ^{13}C NMR spectroscopy and compounds **1–7** were synthesized. For comparison purposes the NMR spectra of the *trans*-(H-6,H-8a)-2-alkyl-6-ethylperhydroimidazolo[3,4-*a*]pyridines **8–10** were recorded. The equilibria in these compounds are expected to be biased even more towards the *trans*-fused conformers IIc and IId (Scheme 2) than the equilibria for the parent 2-alkylperhydroimidazolo[3,4-*a*]pyridines (I), since the *N*-inside-*cis*-fused conformers IIe and IIf are further destabilized by the additional non-bonded interactions between the axial 6-ethyl and *syn*-axial H-8 and N-4 lone pair of electrons. In addition, since the early work[2] could not provide information on which to base an estimate of the position of the Ic ⇌ Id equilibrium, the 2-alkyl-1-methylperhydroimidazolo[3,4-*a*]pyridines III and IV were synthesized.



Scheme 1. Conformational equilibrium of 2-alkylperhydroimidazolo[3,4-*a*]pyridine (I). The *N*-inside/outside designation of stereochemistry has been defined in Ref. 11. Conformers Ia and Ib allow the nitrogen atom in the five-membered ring to occupy the hindered 'inside' position, and are therefore termed *N*-inside conformers. In the *N*-outside conformers Ie and If this nitrogen atom is in the unhindered 'outside' position.



I R=alkyl
1 R=methyl
2 R=*n*-propyl
3 R=*n*-hexyl
4 R=3,7-dimethyloctyl
5 R=i propyl
6 R=cyclohexyl
7 R=*t*-butyl



II R=alkyl
8 R=methyl
9 R=cyclohexyl
10 R=*t*-butyl

Examination of non-bonded interactions (Schemes 3 and 4) as evidenced by Dreiding models of these compounds indicates that III should favour conformer IIIb and IV should favour conformer IVa. Comparison of

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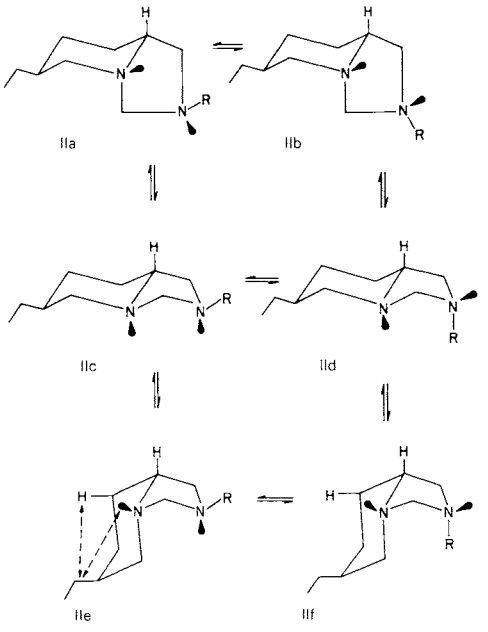
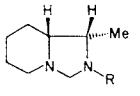
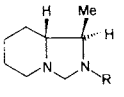
0749-1581/87/080696-11$05.50

Received 11 December 1986
Accepted 4 March 1987



Scheme 2. Conformational equilibrium in the *trans*-(H-6,H-8a)-2-alkyl-6-ethylperhydroimidazolo[3,4-*a*]pyridine (II).





III R=alkyl
11 R=methyl
12 R=hexyl
13 R=cyclohexyl

IV R=alkyl
14 R=methyl
15 R=hexyl
16 R=cyclohexyl

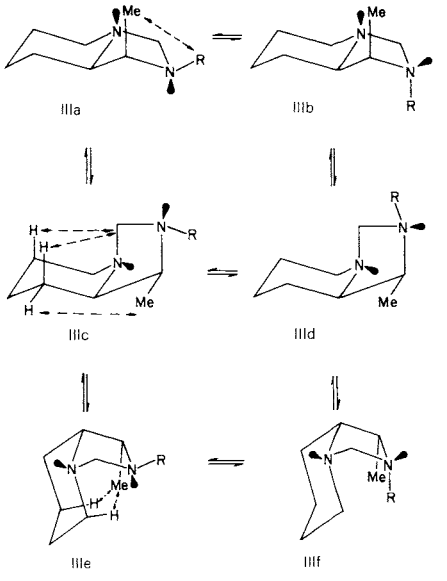
NMR data obtained on I with those from III and IV should then provide an indication of the position of the Ic ⇄ Id equilibrium.

RESULTS AND DISCUSSION

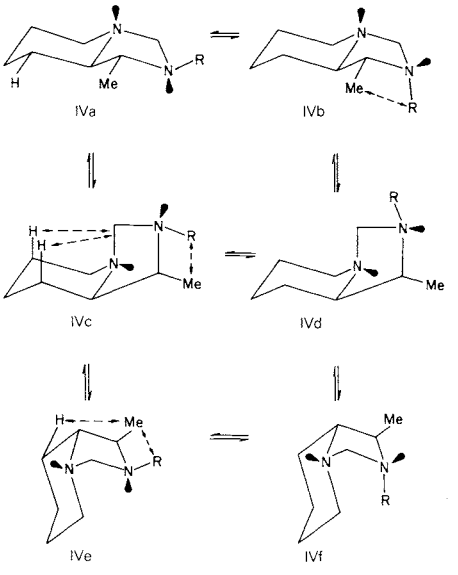
NMR spectra of the 2-alkyl- and 2-alkyl-6-ethyl-perhydroimidazolo[3,4-*a*]pyridines

The 270 MHz ^{1}H NMR data obtained on the 2-alkylperhydroimidazolo[3,4-*a*]pyridines **1–7** are summarized in Table 1. The spectra of all the compounds showed seven clear signals arising from protons adjacent to nitrogen. The lowest field signals (δ *ca* 3.1–3.9; $J = -4$ to -5 Hz) were assigned to the C-3 methylene protons, since these are situated between the two nitrogen atoms. The remaining discernible signals appeared as a broadened doublet (δ *ca* 2.9, $J \approx 10$ Hz), a doublet of doublets (δ *ca* 2.9; $J = 5.6$ Hz, $J = 8.0$–9.0 Hz), a near triplet (δ *ca* 2.45; $J = 8.0$–9.0 Hz) and two multiplets at δ 2.1–2.2 and δ *ca* 2.0. The signals due to the α-protons of the alkyl substituent, where present, were variable in position and multiplicity.

By analogy with the ^{1}H NMR spectra of indolizidine[3] (Fig. 1), known to adopt the *trans* conformation,[4] the broadened doublet at δ *ca* 2.9 and the multiplet at δ *ca* 2.0 were assigned to H-5eq and H-5ax, respectively.



Scheme 3. Conformations of *cis*-(H-1,H-8a)-2-alkyl-1-methylperhydroimidazolo[3,4-*a*]pyridine (III).



Scheme 4. Conformations of the *trans*-(H-1,H-8a)-2-alkyl-1-methylperhydroimidazolo[3,4-*a*]pyridines (IV).

Decoupling experiments on **1** and **7** permitted assignment of the signals from the C-1 methylene protons. Decoupling of the multiplet at δ 2.17 in the spectrum of **7** collapsed the downfield doublet of doublets at δ 2.89 to a doublet ($J = 8.1$ Hz) by removing the smaller coupling, and the near triplet at δ 2.53 to a doublet ($J = 8.1$ Hz) on removing a large coupling. This decoupling is consistent with removal of a J(ax,eq) (= *ca* 5.6 Hz) from the signals at δ *ca* 2.89 and a larger J(ax,ax) (= 9.8 Hz) from the signals at δ 2.53. This enabled assignment of H-leq′ downfield of H-lax′ and this, together with the reverse decoupling experiment (i.e. irradiation of the δ 2.89 doublet of doublets), confirmed the assignment of H-8a to the signals at δ *ca* 2.2 in the spectra of **1–7**.

Table 1. 270 MHz ^{1}H NMR spectra of the 2-alkylperhydroimidazolo[3,4-*a*]pyridines

	Chemical shift, δ (ppm)							Coupling constants, J (Hz)					
Compound	H-1ax'	H-1eq'	H-3ax'	H-3eq'	H-5ax	H-5eq	H-8a	J(3eq', 3ax')	J(1eq', 1ax')	J(1eq', 8a)	J(1ax', 8a)	J(5eq, 5ax)	Others
1	2.45	2.95	3.19	3.70	2.04	2.97	2.21	−5.0	−8.75	5.6	—	—	—
2	2.43	2.95	3.16	3.74	2.03	2.98	2.19	−5.0	−8.1	5.6	9.4	—	—
3	2.44	2.95	3.17	3.75	2.04	2.97	2.19	−5.0	−8.5	5.6	8.5	—	—
4	2.43	2.96	3.18	3.75	2.04	2.96	2.19	−5.0	−8.1	5.6	8.1	—	—
5	2.49	2.91	3.19	3.83	2.05	2.96	2.23	−4.6	−8.5	5.6	8.5	—	—
6	2.51	2.93	3.18	3.75	2.04	2.96	2.21	−4.5	−8.75	5.6	8.75	—	—
7	2.53	2.89	3.14	3.85	2.03	2.96	2.17	−4.4	−8.1	5.6	9.8	—	J(8ax, 8a)=9.8; J(8ax, 8a)=9.8;
8	2.41	2.98	3.18	3.69	1.66	3.01	2.20	−5.0	−8.25	5.6	8.25	−10.0	J(6ax, 5ax)=10.0; J(6ax, 5eq)=2.0
9	2.49	2.94	3.16	3.86	1.58	3.01	2.15	−4.4	−8.2	5.6	8.2	−10.65	J(6ax, 5ax)=10.0
10	2.52	2.89	3.13	3.85	1.65	3.01	2.12	−4.4	−8.1	5.7	8.1	−10.0	J(6ax, 5ax)=10.0

Decoupling difference spectroscopy[5] located the C-6 methylene protons, allowing assignment of the chemical shifts of both H-6ax and H-6eq at δ *ca* 1.65. The irradiation of the H-8a signals located the C-8 methylene protons at δ *ca* 1.78 and δ *ca* 1.26 which were assigned as H-8eq and H-8ax, respectively. Integration indicated signals for two protons at δ *ca* 1.2 and for two at δ *ca* 1.7. Hence, by elimination, the signal at δ *ca* 1.7 was assigned to H-7eq and that at δ *ca* 1.2 to H-7ax (cf. cyclohexane Heq δ 1.6, Hax δ 1.1).[6]

The ^{1}H NMR spectra of the series were analysed by comparison. The ^{1}H NMR spectra of the *trans*-(H-6,H-8a)-2-alkyl-6-ethylperhydroimidazolo[3,4-*a*]pyridines showed marked resemblances to the spectra of the parent 2-alkylperhydroimidazolo[3,4-*a*]pyridines. The triplet at δ *ca* 1.6 (H-5ax) and the doublet at δ 3.01 (J = 10.0, 2.0 Hz (H-5eq) indicate the *trans*-fused conformation wih an equatorial ethyl group.

^{13}C NMR spectra of the 2-alkylperhydroimidazolo[3,4-*a*]pyridines

The ^{13}C NMR spectra of the 2-alkylperhydroimidazolo[3,4-*a*]pyridines **1–7** were assigned on the basis of electronegativity effects on chemical shifts and by a comparison with the ^{13}C NMR spectrum of indolizidine[7] (see Fig. 1). All these assignments are shown in Table 2, and were supported by APT (Attached Proton Test)[8] experiments and by a two-dimensional ^{13}C/^{1}H correlated shift NMR experiment which permitted all proton-proton couplings with the exception of geminal couplings to be removed by decoupling. The ^{13}C NMR spectra of the *trans*-(H-6,H-8a)-2-alkyl-6-ethylperhydroimidazolo[3,4-*a*]pyridines **8–10** resembled closely those of **1–7** (allowing for the ethyl substituent effect).

^{1}H NMR spectra of the 2-alkyl-1-methylperhydroimidazolo[3,4-*a*]pyridines

The ^{1}H NMR spectra of the *trans*-(H-1,H-8a)-2-methyl-, -2-hexyl- and -2-cyclohexyl-1-methylperhydroimidazolo[3,4-*a*]pyridines **14–16** are summarized in Table 3. The spectra showed AB quartets δ *ca* 3.2–3.9 ($J \approx -5.2$ to −5.6 Hz) due to the C-3 methylene protons. The broadened doublet at δ *ca* 2.9 ($J \approx 10.6$ Hz) and the triplet of doublets at δ *ca* 1.9–2.0 ($J \approx -10.5, 10.5, 2.5$ Hz) closely resemble signals from the 5-methylene protons in the spectra of the 2-alkylperhydroimidazolo[3,4-*a*]pyridines and can be assigned similarly.

The symmetrical eight-line multiplet at δ *ca* 2.3–2.7 yields, by first-order analysis, three equal couplings ($J \approx$ 6.25 Hz) and one larger coupling ($J \approx 8$ Hz). This absorption is consistent with that expected for the C-1 proton. The coupling of $J \approx 6.25$ Hz is the observed splitting of the signal at δ 1.07, assigned to the C-1-methyl, and the larger coupling is the order of magnitude of a *trans*-diaxial vicinal coupling [J(H-1,H-8a) (cf. 2-alkylperhydroimidazolo[3,4-*a*]pyridine, J(lax',8a) ≈ 8 Hz]. The signals at δ *ca* 2.3–2.7 are therefore assigned to H-lax', confirming a pseudo-equatorial 1-methyl group.

Irradiation of the doublet at δ 1.07 in the spectrum of **15** caused the symmetrical eight-line multiplet at δ 2.42 to collapse to a doublet (J = 8.1 Hz), consistent with the removal of J(1, Me) leaving a residual J(1,8a) vicinal coupling. Irradiation of the H-1 signal at δ 2.42, and the use of decoupling difference spectroscopy, confirmed the absorption of the 1-methyl protons (δ 1.07) and located the H-8a signal at δ 1.75. The equivalent angular proton in the spectrum of the parent 2-hexylperhydroimidazolo[3,4-*a*]pyridine (**3**) occurs at δ 2.19, representing a shielding by the pseudo-equatorial methyl group of 0.44 ppm (cf. shielding of 0.47 ppm in the cyclohexane system[9]).

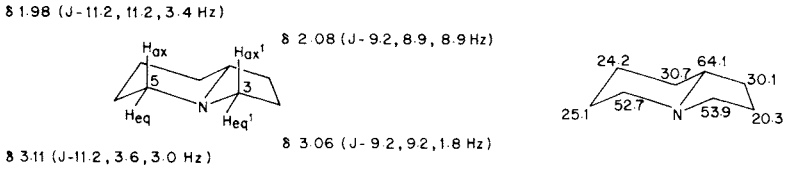


Figure 1. ^{1}H[3] and ^{13}C[7] NMR spectral parameters of indolizidine.

Table 2. ^{13}C NMR spectra ($CDCl_3$) of the 2-alkyl and 2-alkyl-6-ethyl-perhydroimidazolo[3,4-*a*]pyridines

	Chemical shift, δ (ppm)														
Compound	C-1	C-3	C-5	C-6	C-7	C-8	C-8a	Side-chain	^{13}C shifts						
1	60.30	78.02	49.90	24.92	23.95	28.33	63.17	Me 43.42							
2	59.04[a]	76.62	50.02	25.00	24.04	28.50	62.74	C-1′ 58.65[a]	C-2′ 22.63	C-3′ 11.82					
3	58.69[b]	76.63	50.00	25.00	24.03	29.42[c]	62.71	C-1′ 57.18[b]	C-2′ 28.50[c]	C-3′ 27.10	C-4′ 31.80	C-5′ 22.62	C-6′ 14.10		
4	58.72	76.73	50.03	25.03	24.06	28.54	62.75	C-1′ 55.21	C-2′ 36.48	C-3′ 31.08	C-4′ 37.44	C-5′ 24.69	C-6′ 39.31	C-7′ 27.97	
		76.62						55.10	35.54		37.38	C-7′Me 22.62, 22.71		C-3′ Me 19.2	
5	55.95	74.09	50.05	25.01	24.07	28.58	62.71	C-1′ 53.74	Me 22.18, 21.50						
6	55.55	73.73	50.08	25.14[d]	24.11	28.63	62.17	C-1′ 62.49	C-2′ (C-6′) 31.66, 32.64	C-3′ (C-5′) 26.17, 24.81[d]	C-4′ 24.73				
7	51.23	70.10	50.22	25.08	24.11	28.60	63.17	C-1′ 52.41	Me 26.17						
8	60.38	79.10	55.51	37.55	31.04	28.28	63.44								
9	55.50[e]	73.24	55.37[e]	37.57	30.93	28.33	62.35								
10	51.17	70.84	55.84	37.52	31.03	28.43	63.27								

[a,b,c,d,e] Values interchangeable.

Table 3. 270 MHz ^{1}H NMR spectral data (chemical shifts, $CDCl_3$) of the 2-alkyl-1-methylperhydroimidazolo[3,4*a*]pyridines III and IV

	Chemical shift, δ (ppm)							Coupling constants, J (Hz)				
Compound	H-1	Me	H-3eq'	H-3ax'	H-5eq	H-5ax	H-8a	J(5eq', 3ax')	J(5eq, 5ax)	J(1, 8a)	J(1, Me)	Others
14	*ca* 2.35	1.07	3.63	3.50	2.92	2.00	*ca* 1.8[a]	−5.25	−10.6	8.1	6.25	J(5ax, 6ax) = 10.6 J(6eq, 5ax) = 3.75
11	2.63	0.99	3.92	2.73	3.05	2.01	2.17	−3.75	−10.6	6.5	6.5	J(8ax, 8a) = 10.5 J(8eq, 8a) = 2.5 J(8eq, 8ax) = −12.3
15	2.42	1.07	3.69	3.40	2.93	1.99	1.75[b]	−5.6	−10.9	8.1	6.25	J(6ax, 5ax) = 10.9 J(6eq, 5ax) = 3.75
12	*ca* 2.45	0.99	3.97	2.68	3.06	1.97	2.10	−3.9	−10.0	6.5	6.5	J(8ax, 8a) = 10.5 J(8eq, 8a) = 2.5
16	2.69	1.07	3.89	3.20	2.90	1.92	*ca* 1.8[a]	−5.6	−10.6	8.1	5.8	—
13	2.90	0.99	3.96	2.78	3.06	*ca* 1.8	1.97	−3.75	−10.0	6.5	6.5	J(8ax, 8a) = 10.5 J(8eq, 8a) = 2.5

[a] Signal obscured.
[b] Located by decoupling experiment.

The spectra of the *cis*-(H-1,H-8a)-2-alkyl-1-methylperhydroimidazolo[3,4-*a*]pyridines **11–13** show an AB quartet at δ 3.92–3.97 and δ 2.68–2.78 ($J = -3.75$ to 3.88 Hz) assigned to the C-3 methylene protons. The proton absorbing at δ 3.92 and 3.97 has a chemical shift comparable to that of H-3eq' of the parent compounds (δ 3.69–3.86) and is assigned to H-3eq'. The second half of the AB quartet, due to the H-3ax', is at much higher field than in the spectra of the parent compounds by *ca* 0.41–0.46 ppm. The broadened doublet at δ 3.05 ($J \approx$ 10 Hz) is similar to the signal for H-5eq in the spectra of the 2-alkylperhydroimidazolo[3,4-*a*]pyridines (δ *ca* 2.97, $J \approx 10.0$ Hz).

The symmetrical quintuplet at δ 2.45–2.9 ($J \approx 6.5$ Hz) is consistent with a proton adjacent to nitrogen with couplings from a geminal methyl [J(1,Me) = 6.5 Hz] and a vicinal coupling to an adjacent proton of *ca* 6.5 Hz—the magnitude of J(1eq',8a) = 5.63 Hz in the 2-alkylperhydroimidazolo[3,4-*a*]pyridines. This multiplet was therefore assigned to H-1eq' and the methyl group to the pseudo-axial orientation.

Following from this assignment, the chemical shift of H-8a in the spectra of **11–13** can be established, since a vicinal axial methyl is known[9] to shield an axial proton in a cyclohexane system by *ca* 0.1–0.2 ppm. The H-8a in the spectra of the parent compounds **1–7** absorbs at δ *ca* 2.2, so the expected chemical shift of H-8a for the isomers III is δ 2.0–2.1. In addition, the H-8a signals in the spectra of isomers III are expected to show a large vicinal coupling to H-8ax of the order of 10.0 Hz [J(8ax,8a) = 9.8 Hz in 2-*tert*-butylperhydroimidazolo[3,4-*a*]pyridine (**7**)], a smaller vicinal coupling of *ca.* 2.5 Hz to the H-8eq and a slightly larger vicinal coupling of *ca* 5.6 Hz to the H-1eq' [J(8eq,8a) = 2.5 Hz, J(1eq', 8a) = 5.6 Hz for 2-*tert*-butylperhydroimidazolo[3,4-*a*]pyrdine (**7**)]. These expectations are consistent with the observed multiplet ($J \approx 10.5$, 6.5, 2.5 Hz) at δ *ca* 2.1, and this is therefore assigned to H-8a.

The spectra of **11** and **12** show a triplet of doublets at δ *ca* 2.0 and a broadened doublet at δ *ca* 2.9 which, by analogy with the spectra of the 2-alkylperhydroimidazolo[3,4-*a*]pyridines, are assigned to H-5ax and H-5eq, respectively.

In the spectra of the 2-alkylperhydroimidazolo[3,4-*a*]pyridines **1–7** H-6eq, H-7eq and H-8eq absorb at δ 1.65, 1.70 and 1.78, respectively. Hence H-8eq is probably responsible for the signal at δ *ca* 1.8 in the spectra of **11** and **12**. The slightly deshielded position, relative to the parent, is consistent with a pseudo-equatorial methyl group.

Irradiation of the high-field doublet at δ 1.09 in the spectrum of the *cis*-(H-1,H-8a)-1-hexyl-1-methyl derivative **12** caused a decoupling of a signal at δ *ca* 2.45 only, confirming this as arising from H-1. A decoupling difference experiment was carried out by irradiation of the H-1' signal at δ 2.45, resulting in the location of the H-8a signal at δ 2.1. Irradiation of the broadened doublet at δ 3.06, assigned to H-5eq, and a decoupling difference experiment located H-5ax at δ 1.97 and the C-6 methylene protons at δ *ca* 1.58.

^{13}C NMR spectra of the 2-alkyl-1-methylperhydroimidazolo[3,4-*a*]pyridines

The ^{13}C NMR spectra of the 2-alkyl-1-methylperhydroimidazolo[3,4-*a*]pyridines are summarized in Table 4. The assignments were made by comparison with the ^{13}C shifts of the parent unsubstituted systems (Table 2), and were partially confirmed by APT eperiments[8] where appropriate. The ^{13}C NMR shifts of C-5 and C-7 in the spectra of both isomers are expected to be very similar to those signals in the parent systems, since the methyl

Table 4. ^{13}C NMR chemical shifts ($CDCl_3$) of the 2-alkyl-1-methylperhydroimidazolo[3,4-*a*]pyridines

	Chemical shift, δ (ppm)							
Compound	C-1	C-3	C-5	C-6	C-7	C-8	C-8a	1-Me
14	66.44	77.45	50.14	24.92	23.99	27.22	70.34	16.19
11	62.44	78.31	50.36	24.54	24.27	25.60	65.44	16.31
15	65.25	75.95	50.33	24.89	24.03	27.76	69.94	16.98
12	61.08	77.17	50.68	24.78	24.38	25.73	65.39	17.50
16	61.30	71.80	50.08	25.46	23.95	27.68	70.29	18.12
13	57.89	75.36	51.01	25.03	24.35	25.03	65.77	18.99

substituent is too remote to exert any influence. The greater deshielding of the C-8a by the pseudo-equatorial methyl group in IV (βeq effect) than by the pseudo-axial group in III (βax effect) confirms the stereochemistry assigned from ^{1}H NMR data.

NMR spectra and the *cis* ⇌ *trans* conformational equilibria in perhydroimidazolo[3,4-*a*]pyridines

The chemical shift differences between protons adjacent to the bridgehead N-4 in the perhydroimidazolo[3,4-*a*]pyridines I is expected to provide a reliable indication[10,11] of the predominant ring-fused conformer in the *cis*- ⇌ *trans*-fused conformational equilibrium mixture. Accordingly, an assessment of the predominant conformer in the equilibrium mixture of I can be made by comparison of the Δ(5ax,5eq) values with indolizidine,[3] which adopts[4] an equilibrium containing at least 98% *trans*-fused conformer (see Fig. 1).

In indolizidine the Δ(5eq,5ax) value is 1.13 ppm, which compares with a value for Δ(5eq,5ax) in **1**–**7** of 0.91–0.95 ppm and indicates a strong preference for the *trans*-fused conformer.

The predominance of the *trans*-fused ring conformer is also indicated by the signal at δ *ca* 2.2 in the spectra of **1**–**7** assigned to the angular 8a-proton. Coupling constant data extracted from the spectrum of 2-*tert*-butylperhydroimidazolo[3,4-*a*]pyridine (**7**) (J = 9.8, 9.8, *ca* 5.6, 2.5 Hz) are consistent with two large vicinal coupling constants [J(lax',8a), J(8ax,8a)] and two smaller couplings [J(1eq',8a), J(8eq,8a)]. The appearance of the H-8a signal remained constant throughout the series **1**–**7**.

The availability of J(5eq,5ax) as an indication of the conformational equilibrium in the 2-alkylperhydroimidazolo[3,4-*a*]pyridines I was restricted by the second-order nature of the C-5 proton signals, due to the very small difference between the chemical shifts of the C-6 protons. As the size of the 2-substituent was increased from methyl in **1** to *tert*-butyl in **7** the H-5ax signal became distorted from a near triplet of doublets in **1** to a non-first-order multiplet in **7**.

Comparison of the ^{1}H NMR spectra of 2-methylperhydroimidazolo[3,4-*a*]pyridine (**1**) and *trans*-(H-6,H-8a)-6-ethyl-2-methylperhydroimidazolo[3,4-*a*]pyridine (**8**) (Table 1) shows very close correspondences, except for the shielding of H-5ax by the equatorial ethyl group[9] in **8**. Since the equilibrium for the ethyl-substituted compound is expected to be very heavily biased towards the *trans*-conformations (IIc and IId in Scheme 2), the similarities of the shifts, particularly of H-8a and of the 1-methylene protons, indicate a similar heavy bias towards the *trans* conformation (Ic and Id in Scheme 1) for **1**.

The close correspondence between the ^{13}C NMR shifts of 2-methylperhydroimidazolo[3,4-*a*]pyridine (**1**) (Table 2) and indolizidine (Fig. 1), apart from the differences caused by the presence of the second heteroatom, confirms the predominance of the *trans*-fused conformers. In particular, the presence of the *cis*-conformers Ia, Ib, Ie and If (Scheme 1) would be indicated by marked upfield shifts of C-7 in Ie and If and of C-6 and C-8 in Ia and Ib, respectively, due to the γax interactions. The C-7 shift (δ 23.95) in **1** is, however, very close to the value (δ 24.2) in indolizidine, ruling out the presence of appreciable amounts of Ie and If. The C-6 shifts in both compounds also compare closely, but the C-8 and C-5 shifts are to high field in **1**. The upfield shift of both these signals relative to those in the spectrum of indolizidine does not indicate the *N*-outside *cis*-conformer, but is due to the antiperiplanar relationship between C-3—N and C-5—N and between C-3—N and C-8—N in the *trans*-conformers (Ic ⇌ Id).[12]

Comparison (Table 2) of the ^{13}C NMR shifts of **1**–**7** and of the 6-ethyl compounds **8**–**10** shows very close similarities (apart from the ethyl substituent effects) and, as in the case of the ^{1}H NMR comparison discussed above, indicates the predominance of the *trans*-conformations (Ic and Id) for **1**–**7**. Similarly, the ^{13}C NMR shifts of the 2-alkyl-1-methylperhydroimidazolo[3,4-*a*]pyridines (Table 4) are very similar (apart from methyl substituent effects) to those of the 2-alkylperhydroimidazolo[3,4-*a*]pyridines (Table 2), again demonstrating the predominance of the *trans*-fused conformers IIIa and IIIb (Scheme 3) and IVa and IVb (Scheme 4).

Conformational equilibria about N-2

Attention was focused above on the position of the *cis* ⇌ *trans* conformational equilibria for the perhydroimidazolo[3,4-*a*]pyridines, and in Schemes 1–4 relating to this problem the five-membered ring was depicted, for convenience of representation, in a particular envelope conformation. In order to obtain some estimate of the equilibrium position involving N-2 (e.g. the c ⇌ d equilibria in Schemes 1–2), some discussion is necessary on the five-membered ring conformation.

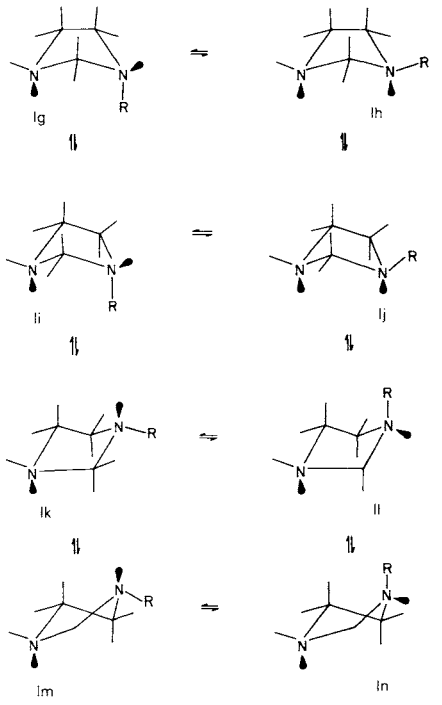
Cyclopentane exists in puckered forms, to relieve the unfavourable eclipsing of the C—H bonds (Pitzer strain) in the planar structure. In minimizing this eclipsing the angle strain increases, although this is more than compensated for by the relief of the Pitzer strain.[13] When the five-membered ring is fused to a six-membered ring, as in the hydrindanes, the pseudo-rotation is restricted. Theoretical analysis of 6/5-fused sytems present as the C/D rings in steroids shows the preferred conformation as intermediate between the C-14 envelope and the half-chair. It has been reported[14] that calculated parameters for the steroid systems analysed are in good agreement with X-ray diffraction results.

Similar restrictions of the pseudo-rotation of the five-membered ring must occur in the 6/5-fused nitrogen bridgehead systems such as indolizidine. An x-ray diffraction study[15] of *trans*-fused indolizidine alkaloids showed that C-1, C-2, C-3 and C-8a are essentially coplanar (within ±0.17 Å). ^{1}H NMR analysis[3] indicates that indolizidine itself exists in solution between the N-4 envelope and a half-chair conformer, similar to that present in the steroidal systems.

The presence of the N-2 atom in the imidazolidine ring of the 2-alkylperhydroimidazolo[3,4-*a*]pyridines further complicates the conformational picture but, by taking account of the generalized anomeric effect[16] arising from the presence of N-4 and N-2 and the nature of the N-2 substituent, the most favourable five-

membered ring conformation in the *trans*-fused conformations can be predicted.

The various conformations of the five-membered ring in the *trans*-fused conformers of 2-alkylperhydroimidazolo[3,4-*a*]pyridine are depicted in Scheme 5.



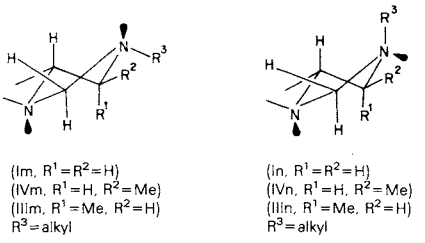
Scheme 5. Possible conformations of the imidazolidine ring in 2-alkylperhydroimidazolo[3,4-*a*]pyridine.

The classical envelope structures Ig and Ih may be discounted on the basis of unfavourable eclipsing about the C-1—C-8a bond and, in addition, Ih suffers from an unfavourable generalized anomeric effect. The alternative envelopes Ii and Ij suffer from eclipsing *N*-alkyl group–H-1 interactions, but the eclipsing lone pair–H-1 interaction may be less than CH–CH eclipsing present in Ig and Ih (cf. rotational barriers:[13] ethane 2.9 kcal mol^{-1}, methylamine 1.98 kcal mol^{-1}). However, Ij may be discounted owing to the unfavourable generalized anomeric effect. The extreme C-1 flap envelopes Ik and Il necessitate flattening around the ring fusion, giving rising to unacceptable ring fusion strain.

This analysis of the envelopes suggests an energy minimum somewhere between Ii and Ij, best achieved in the half-chair type conformations Im and In which permit a staggered arrangement of the bonds attached to C-1, C-8a and N-2. Such an arrangement is in accord[17] with the magnitudes of J(1eq′,8a) and J(1ax′,8a) extracted from the ^{1}H NMR spectra of the 2-alkylperhydroimidazolo[3,4-*a*]pyridines.

An examination of Dreiding models suggests that the equatorial C-1-methyl group in the *trans*-(H-1,H-8a)-2-alkyl-1-methylperhydroimidazolo[3,4-*a*]pyridines (IV) will not alter the preferred conformation of the imidazolidine ring from that of the parent system (I), and this is confirmed by the similarity of J(1ax′,8a) values in the ^{1}H NMR spectra of the two sets of compounds (Tables 1 and 3).

The half-chair conformation Im with *trans*-nitrogen lone pairs is expected to predominate in an equilibrium mixture between Im and In, since this is favoured by the generalized anomeric effect. An examination of Dreiding models of the analogous conformers IVm and IVn of the *trans*-(H-1,H-8a)-2-alkyl-1-methylperhydroimidazolo[3,4-*a*]pyridines IV (Scheme 6) shows



Scheme 6. Half-chair conformations of the imidazolidine ring in 2-alkyl- and 2-alkyl-1-methyl-perhydroimidazolo[3,4-*a*]pyridine.

different interactions between the C-1-methyl and the 2-alkyl substituent. The near eclipsing interaction between the two alkyl groups in IVn makes this conformer relatively disfavoured, and so IVm is expected to be the predominant conformer of IV. The suggested similarity of conformations (Im and IVm) for I and IV is supported by the similar C-3 methylene geminal coupling constants of −5.0 Hz and −5.25 Hz, respectively, since this parameter is dependent on the dihedral angle between the C—H bonds and the nitrogen lone pairs of electrons.[11,18]

The orientation of nitrogen lone pairs with respect to C—H bonds is also known to alter the $^1J(^{13}CH)$ value.[11,19] The values for $^1J(^{13}C\text{-}3, H)$ in 2-methylperhydroimidazolo[3,4-*a*]pyridine (**1**) were extracted from a proton coupled ^{13}C NMR spectrum by first-order analysis and were shown to be equal (J = 145.0 Hz). The observed values for *trans*-(H-1,H-8a)-1,2-dimethylperhydroimidazolo[3,4-*a*]pyridine (**14**) were both 145.5 Hz, confirming conformation IVm to be predominant. The values for J(3eq′,3ax′) and $^1J(^{13}C\text{-}3, H)$ for the 2-hexyl derivative **15** indicate the same conformational preferences as for **14**.

Examination of Dreiding models suggests that the pseudoaxial C-1-methyl group in *cis*-(H-1,H-8a)-2-alkyl-1-methylperhydroimidazolo[3,4-*a*]pyridines III does not alter the preferred conformation of the five-membered ring from that for the parent unsubstituted system. This is confirmed by the similarities of the J(1,8a) values in the two series of compounds. Thus III can be expected to exist as an equilibrium between the half-chair forms IIIm and IIIn (Scheme 6). The approach to eclipsing interactions between the two alkyl substituents that occurs in IIIm destabilizes it relative to the almost *anti*-periplanar arrangement found in IIIn, and therefore IIIn is expected to be the predominant conformer in the IIIm ⇌ IIIn equilibrium.

As discussed above for the *trans*-(H-1,H-8a)-2-alkyl-1-methyl isomers IV, J(3eq′,3ax′) can provide a good indication of changes in the nitrogen lone pair orientation with respect to the C-3—methylene bonds. The value for J(3eq′,3ax′) for the *cis*-(H-1,H-8a)-1,2-dimethyl isomer **11** is −3.75 Hz, a larger value than

that (−5.0 Hz) of 2-methylperhydroimidazolo[3,4-*a*]pyridine (**1**), indicating different preferred conformations of the 2-methyl substituents.

The different orientation of the lone pairs indicated by J(3eq′,3ax′) values in the *cis*-(H-1,H-8a)-1,2-dimethyl isomer **11** should also be reflected in the $^1J(^{13}C$-3, H) values. The observed values for this system are 134.0 151.0 Hz compared with the two equal values of 145.0 Hz in the parent compound. A two-dimensional NMR $^{13}C/^1H$ shift correlation experiment assigned the larger coupling of 151.0 Hz to $^1J(^{13}C$,H-3eq′) and the smaller 134.0 Hz to $^1J(^{13}C$,H-3ax′). The assignment is consistent with the proposed orientation of the nitrogen lone pairs in conformer IIIn. In IIIn, two nitrogen lone pairs of electrons nearly overlap with the C—H-3eq′ bond, whereas in IIIm the lone pairs of N-2 and N-4 eclipse the C—H-3ax′ and C—H-3eq′ bonds, respectively.

Since it has been determined that *cis*-(H-1,H-8a)-1,2-dimethylperhydroimidazolo[3,4-*a*]pyridine (**11**) exists predominantly as conformation IIIn (R^3 = Me), and the *trans*-(H-1,H-8a)-1,2-dimethyl isomer **14** predominantly as conformation IVm (R^3 = Me), these two systems can provide models for the extreme conformations of the Ic ⇌ Id (Scheme 1) equilibrium for the parent system **1**. Comparison (Figure 2) of the J(3eq′,3ax′) value for **1** with those of the biased systems **11** and **14** gives the equilibrium position for **1** as *ca* 83% N-Me equatorial conformer in equilibrium with the N-Me axial conformer.

General discussion of the conformational equilibrium for 2-alkylperhydroimidazolo[3,4-*a*]pyridines

The ^{1}H 270 MHz NMR and ^{13}C NMR spectral data described in this paper indicate an extreme preference (>98%) for the *trans*-fused ring conformers in the 2-alkylperhydroimidazolo[3,4-*a*]pyridines **1**–**7**. This is in sharp contrast to the related perhydro-oxazolo[3,4-*a*]pyridine,[20] which adopts an equilibrium containing *ca* 68% *trans*-fused conformer **17a** in equilibrium with 32% *O*-inside *cis*-fused conformer **17b** in a variety of solvents at 298 K.

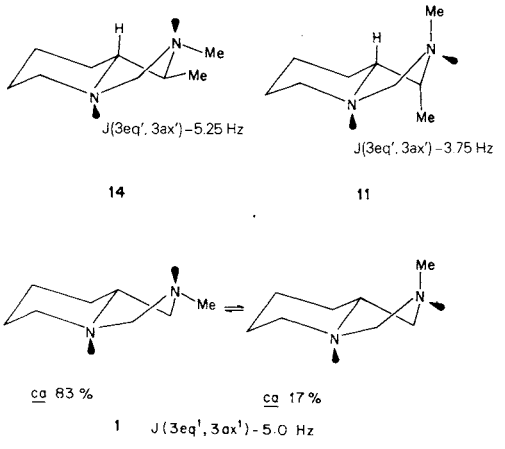
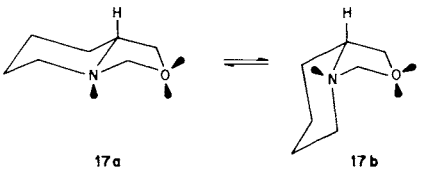


Figure 2. J(3eq′, 3ax′) values and conformational equilibria for *trans*-(*H*-1,*H*-8*a*)- (**14**) and *cis*-(H-1,H-8a)-1,2-dimethyl- (**11**) and 2-methyl-perhydroimidazolo[3,4-*a*]pyridines (**1**).



Since indolizidine adopts the *trans*-fused conformation (Fig. 1) in solution (>98%), the shift in equilibria for **17** must be a result of the generalized anomeric effect[16] disfavouring the *trans*-conformer **17a**, and the replacement in *cis*-indolizidine of the unfavourable C-2–C-5 methylene interactions by the less unfavourable heteroatom–C-5 methylene interactions in **17b**. That the equilibrium in 2-methylperhydroimidazolo[3,4-*a*]pyridine (**1**) shifts back towards the *trans*-conformation (>98%) must be due to the stabilization of the *trans*-fused conformer Id by a favourable generalized anomeric effect, which may be brought about by the N-2 inversion in Ic without resorting to N-4 inversion to give the *cis*-conformer Ie or If. This is supported by the position of the N-2 equilibria in **1**, which favours the conformation with the *trans* arrangement of nitrogen lone pairs (Fig. 2).

EXPERIMENTAL

Elemental analyses were carried out by the Butterworth Microanalytical Consultancy, Teddington, Middlesex. Melting points are uncorrected.

The ^{1}H NMR spectra were recorded as 10% solutions in deuteriochloroform, with tetramethylsilane (TMS) as internal reference, on a Bruker WH270 spectrometer at 293 K. Accumulated scans over 4K data points were normally 100 and the resultant FID was Fourier transformed over 8K data points after application of a trapezoidal window filter to the FID signal; the resultant peak-to-peak resolution was 0.1 Hz, with an error of ±0.7 Hz when the sweep width was *ca* 3 kHz (3012 Hz). The ^{13}C NMR spectra were recorded on a Jeol FX90Q (22.5 MHz), Fourier transform) spectrometer, as *ca* 10% deuteriochloroform solutions with TMS as internal reference: pulse length 6 μs, pulse interval 2 s, 2000 scans. ^{13}C chemical shifts are considered accurate to ±0.05 ppm and ^1J(CH) values to ±1.0 Hz.

General procedure for the synthesis of 2-(*N*-alkylaminomethyl)pyridines

Method (a). A solution of 2-aminomethylpyridine (0.1 mol, 10.8 g) and the appropriate aldehyde or ketone (0.11 mol) in sodium-dried benzene (100 ml) was boiled under reflux using a Dean and Stark apparatus to separate the water produced in the reaction. When the calculated amount of water had been collected (0.1 mol, 1.8 ml), the benzene was removed under reduced pressure. The residual crude 2-(*N*-alkyliminomethyl)pyridine was then taken up in dry methanol (200 ml) and placed in a 500-ml conical flask. Sodium borohydride (0.1 mol, 3.78 g) was added

gradually to a stirred solution of the imine, causing a gentle refluxing. The reaction mixture was stirred for 2–3 h. The excess sodium borohydride was treated dropwise with concentrated hydrochloric acid until the pH of the solution reached 7.0. Sodium hydroxide was added to the stirred solution until the pH reached 11.0 or greater. The methanolic solution was then evaporated under reduced pressure using a rotary evaporator, and the residue was taken up in the minimum volume of distilled water and extracted four times with an equal volume of diethyl ether. The ethereal extract was dried (Na_2SO_4), filtered, the ether removed *in vacuo* and the residue distilled *in vacuo* to yield the required 2-(*N*-alkylaminomethyl)pyridine.

Alternative procedure, method (b). A solution of 2-pyridine carboxyaldehyde (0.11 mol, 10.7 g) and the appropriate amine (0.1 mol) in sodium-dried benzene (100 ml) was boiled under reflux using a Dean and Stark apparatus to separate the water produced (0.1 mol, 1.8 ml). The benzene was removed under reduced pressure and the residual crude 2-(*N*-alkyliminomethyl)pyridine was treated with sodium borohydride as described in method (a). The crude product was purified as in method (a) to yield the required 2-(*N*-alkylaminomethyl)pyridine.

The following compounds were obtained: 2-(*N*-methylaminomethyl)pyridine (65%), b.p. 33–36 °C at 0.18 mmHg; found, C 68.8, H 8.2, N 22.9; $C_7H_{10}N_2$ requires C 68.8, H 8.25, N 22.9%; 2-(*N*-propylaminomethyl)pyridine (60%), b.p. 68–70 °C at 0.12 mmHg; found, C 71.8, H 9.3, N 18.65; $C_9H_{14}N_2$ requires C 71.95, H 9.4, N 18.65%; 2-(*N*-hexylaminomethyl)pyridine (75%), b.p. 90 °C at 0.10 mmHg; found, C 74.8, H 10.4, N 14.6; $C_{12}H_{20}N_2$ requires C 74.95, H 10.5, N 14.6%; 2-(*N*-3,7-dimethylocta-2,6-dienylaminomethyl)pyridine (40%), b.p. 105 °C at 0.02 mmHg; found, C 78.6, H 10.1, N 11.3; $C_{16}H_{24}N_2$ requires C 78.6, H 9.9, N 11.3%; 2-(*N*-3,7-dimethylocta-6-enylaminomethyl)pyridine (56%), b.p. 108–110 °C at 0.02 mmHg; found, C 77.95, H 10.7, N 11.4, $C_{16}H_{26}N_2$ requires C 77.9, H 10.6, N 11.4%; 2-(*N*-isopropylaminomethyl)pyridine (72%), b.p. 46 °C at 0.15 mmHg (lit.,[2] b.p. 97–99 °C at 10 mmHg); found, C 71.9, H 9.4, N 18.7; $C_9H_{14}N_2$ requires C 71.95, H 9.4, N 18.65%; 2-(*N*-cyclohexylaminomethyl)pyridine (60%), b.p. 128 °C at 1.2 mmHg (lit.,[2] b.p. 131–133 °C at q.3 mmHg); found,. C 75.7, H 9.5, N 14.7; $C_{12}H_{22}N_2$ requires C 75.7, H 9.5, N 14.7%; 2-(*N*-*tert*-butylaminomethyl)pyridine (84%), b.p. 52 °C at 0.15 mmHg (lit.,[2] b.p. 79–80 °C at 0.6 mmHg); found, C 73.2, H 9.8, N 17.0; $C_{10}H_{16}N_2$ requires C 73.1, H 9.8, N 17.1%.

General procedure for the synthesis of 2-(*N*-alkylaminomethyl)piperidines

The 2-(*N*-alkylaminomethyl)pyridine (0.05 mol) was dissolved in glacial acetic acid (170 ml), yielding a bright red to bright yellow solution. To the solution was added Adams platinum oxide catalyst (500 mg) and the mixture was shaken under hydrogen in a Parr hydrogenator, at 60 lb in^{-2} of hydrogen, until the calculated uptake was completed. The hydrogenation was normally completed in *ca* 24–48 h to give a clear, colourless solution. The solution was filtered, the acetic acid removed *in vacuo* and the residue basified with saturated sodium carbonate solution followed by sodium hydroxide pellets until the pH of the solution was greater than 11.0. This solution was then extracted three times with diethyl ether (200 ml aliquots) and the dried (Na_2SO_4) ethereal extract was filtered, concentrated and the residue distilled *in vacuo* to give the required 2-(*N*-alkylaminomethyl)piperidine.

The following compounds were obtained: 2-(*N*-methylaminomethyl)piperidine (51%), b.p. 38 °C at 0.08 mmHg (lit.,[2] b.p. 76–78 °C at 15 mmHg); found, C 65.6, H 12.5, N 21.8; $C_7H_{16}N_2$ requires C 65.6, H 12.6, N 21.85%; 2-(*N*-propylaminomethyl)piperidine (60%), b.p. 48 °C at 0.15 mmHg; found, C 69.1, H 13.0, N, 18.1; $C_9H_{20}N_2$ requires C 69.2, H 12.9, N 17.9%; 2-(*N*-hexylaminomethyl)piperidine (47%), b.p. 63–64 °C at 0.02 mmHg; found, C 72.65, H 13.2, N 14.1; $C_{12}H_{26}N_2$ requires C 72.7, H 13.2, N 14.1%; 2-(*N*-3,7-dimethyloctylaminomethyl)piperidine (41%), b.p. 130–132 °C at 2.0 mmHg; found, C 75.4, H 13.4, N 10.9; $C_{16}H_{34}N_2$ requires C 75.5, H 13.5, N 11.0%; 2-(*N*-isopropylaminomethyl)piperidine (76%), b.p. 58 °C at 0.15 mmHg (lit.,[2] b.p. 96–98 °C at 15.0 mmHg); found, C 68.9, H 13.25, N 17.7, $C_9H_{20}N_2$ requires C 69.2, H 12.9, N 17.9%; 2-(*N*-cyclohexylaminomethyl)piperidine (70%), b.p. 104–106 °C at 0.6 mmHg (lit.,[2] b.p. 104–106 °C at 0.55 mmHg); found, C 73.2, H 12.5, N 14.5; $C_{12}H_{24}N_2$ requires C 73.4, H 12.3, N 14.3%, 2-(*N*-*tert*-butylaminomethyl)piperidine (88%), b.p. 42 °C at 0.03 mmHg (lit.,[2] b.p. 73–74 °C at 1.30 mmHg); found, C 70.3, H 13.2, N 16.3; $C_{10}H_{22}N_2$ requires C 70.5, H 13.0, N 16.5%.

General procedure for the synthesis of 2-alkylperhydroimidazolo[3,4-*a*]pyridines

The 2-(*N*-alkylaminomethyl)piperidine (0.01 mol) was shaken with a weight equivalent of aqueous formaldehyde (48%), when an exothermic reaction ensued. The mixture was shaken for 0.5–0.75 h and then strongly basified with aqueous sodium hydroxide (30%) and extracted with diethyl ether (3 × 200 ml). The ethereal solution was dried (Na_2SO_4), filtered, concentrated and the residual oil distilled *in vacuo* to yield the required 2-alkylperhydroimidazolo[3,4-*a*]pyridine.

The following compounds were obtained: 2-methylperhydroimidazolo[3,4-*a*]pyridine (87%), b.p. 130 °C at 2.8 mmHg (lit.,[2] b.p. 86–87 °C at 27.0 mmHg); found, C 61.2, H 11.6, N 19.2; $C_8H_{16}N_2$ requires C 68.5, H 11.5, N 19.9%; 2-propylperhydroimidazolo[3,4-*a*]pyridine (80%), b.p. 42–43 °C at 0.02 mmHg; found, C 71.1, H 12.0, N 16.6; $C_{10}H_{20}N_2$ requires C 71.4, H 12.0, N 16.65%; 2-hexylperhydroimidazolo[3,4-*a*]pyridine (90%), b.p. 89 °C at 0.5 mmHg; found, C 74.3, H 12.4; N 13.3; $C_{13}H_{26}N_2$ requires C 74.2, H 12.5, N 13.3%, 2-(3,7-dimethyloctyl)perhydroimidazolo[3,4-*a*]pyridine (62%), b.p. 106–108 °C at 0.05 mmHg; found, C 75.4, H 13.4, N 11.0; $C_{17}H_{34}N_2$ requires C 76.6, H 12.9, N 10.5%; 2-isopropylperhydroimidazolo[3,4-*a*]pyridine (90%), b.p. 58 °C at 0.15 mmHg; found, C 71.3, H 11.9, N 16.7; $C_{10}H_{20}N_2$ requires C 71.4,

H 12.0, N 16.65%; 2-cyclohexylperhydroimidazolo[3,4-*a*]pyridine (86%), b.p. 120–121 °C at 1.3 mmHg (lit.,[2] b.p. 120–121 °C at 1.3 mmHg); found, C 74.9, H 11.6, N 13.4; $C_{13}H_{24}N_2$ requires C 74.9, H 11.6, N 13.5%; 2-*tert*-butylperhydroimidazolo[3,4-*a*]pyridine (94%), b.p. 40–41 °C at 0.07 mmHg (lit.,[2] b.p. 107–108 °C at 13.0 mmHg); found, C 72.2, H 12.3, N 15.3; $C_{11}H_{22}N_2$ requires C 72.5, H 12.2, N 15.4%.

2-Alkyl-6-ethylperhydroimidazolo[3,4-*a*]pyridines. The synthesis follows that described for the 2-alkylperhydroimidazolo[3,4-]pyridines. The following 5-ethyl-2-(*N*-alkylaminomethyl)pyridines were obtained: 5-ethyl-2-(*N*-methylaminomethyl)pyridine (66%), b.p. 56–57 °C at 0.03 mmHg; found, C 72.0, H 9.5, N 18.9; $C_9H_{14}N_2$ requires C 71.95, H 9.4, N 18.65%; 5-ethyl-2-(*N*-cyclohexylaminomethyl)pyridine (75%), b.p. 97–98 °C at 0.03 mmHg; found, C 77.0, H 10.2, N 12.8; $C_{14}H_{22}N_2$ requires C 77.0, H 10.2, N 12.8%; 5-ethyl-2-(*N*-*tert*-butylaminomethyl)pyridine (86%), b.p. 63–64 °C at 0.05 mmHg; found, C 71.2, H 14.8, N 13.8; $C_{12}H_{30}N_2$ requires C 71.2, H 14.9, N 13.8%.

The following 5-ethyl-2-(*N*-alkylaminomethyl)-piperidines were obtained: 5-ethyl-2-(*N*-methylaminomethyl)piperidine (73%), b.p. 48–50 °C at 0.1 mmHg; found, C 69.0, H 12.9, N 17.8; $C_9H_{20}N_2$ requires C 69.2, H 12.9, N 17.9%; 5-ethyl-2-(*N*-cyclohexylaminomethyl)piperidine (87.5%), b.p. 120 °C at 0.03 mmHg; found, C 74.8, H 12.35, N 12.4; $C_{14}H_{28}N_2$ requires C 74.9, H 12.6, N 12.5%; 5-ethyl-2-(*N*-*tert*-butylaminomethyl)piperidine (69.5%), b.p. 49–50 °C at 0.03 mmHg; found, C 72.7, H 13.2, N 14.1; $C_{12}H_{26}N_2$ requires C 72.7, H 13.2, N 14.1%.

The individual isomers of 2-alkyl-6-ethylperhydroimidazolo[3,4-*a*]pyridine were obtained in a pure state by column chromatography. A mixture of isomers (2 g) was chromatographed over neutral alumina (250 g, Woelm grade IV) using a 98 : 2 mixture of light petroleum (b.p. 40–60 °C) and diethyl ether as eluent. The first isomer eluted was the *cis*-(H-6,H-8a)-2-alkyl-6-ethylperhydroimidazolo[3,4-*a*]pyridine, and the second the *trans*-(H-6,H-8a)-2-alkyl-6-ethylperhydroimidazolo-[3,4-*a*]pyridine.

The following compounds were obtained: *cis*-(H-6,H-8a)-6-ethyl-2-methylperhydroimidazolo[3,4-*a*]pyridine, b.p. 32–33 °C at 0.03 mmHg; found, C 71.4, H 12.2, N 16.6; $C_{10}H_{20}N_2$ requires C 71.4, H 12.0, N 16.7%; *trans*-(H-6,H-8a)-6-ethyl-2-methylperhydroimidazolo[3,4-*a*]pyridine, b.p. 32–33 °C at 0.03 mmHg; found, C 71.3, H 12.2, N 16.6; $C_{10}H_{20}N_2$ requires C 71.4, H 12.0, N 16.7%; *cis*-(H-6,H-8a)-2-cyclohexyl-6-ethylperhydroimidazolo[3,4-*a*]pyridine, b.p. 122–123 °C at 0.15 mmHg; found, C 76.5, H 12.0, N 12.0, $C_{15}H_{28}N_2$ requires C 76.2, H 11.9, N 11.85%; *trans*-(H-6,H-8a)-2-cyclohexyl-6-ethylperhydroimidazolo[3,4-*a*]pyridine, b.p. 122–123 °C at 0.15 mmHg; found, C 76.5, H 12.1, N 12.0; $C_{15}H_{28}N_2$ requires C 76.2, H 11.9, 11.85%; *cis*-(H-6,H-8a)-2-*tert*-butyl-6-ethylperhydroimidazolo[3,4-*a*]pyridine, b.p. 56 °C at 0.03 mmHg; found, C 74.4, H 12.2, N 13.4; $C_{13}H_{26}N_2$ requires C 74.2, H 12.5, N 13.3; and *trans*-(H-6,H-8a)-2-*tert*-butyl-6-ethylperhydroimidazolo[3,4-*a*]pyridine, b.p. 56 °C at 0.03 mmHg; found, C 74.4, H 12.2, N 13.0; $C_{13}H_{26}N_2$ requires C 74.2, H 12.5, N 13.3%.

Synthesis of the 2-alkyl-1-methylperhydroimidazolo[3,4-*a*]pyridines

***N*-Alkyl-1-(2-pyridyl)ethylamine.** A solution of 2-acetylpyridine (0.15 mol, 18.2 g) in dry benzene (100 ml) containing a grain of *p*-toluenesulphonic acid and the appropriate amine (0.15 mol) was boiled under reflux, using a Dean and Stark water separator to remove the water produced by the reaction and to give a solution of the Schiff base. (The Schiff base from methylamine was obtained by passing methylamine gas into the benzene solution of the 2-acetylpyridine and drying the solution over anhydrous sodium carbonate. The extent of the reaction was monitored by IR spectroscopy.) The resultant benzene solution was shaken with saturated sodium carbonate solution, separated from the aqueous layer, dried (Na_2SO_4) and the benzene removed by distillation *in vacuo*. The crude Schiff base was dissolved in dry methanol (150 ml) and treated with sodium borohydride (0.15 mol, 5.7 g). The excess sodium borohydride was destroyed by the careful addition of hydrochloric acid (0.1 M). The solution was then basified using sodium hydroxide and the excess solvents removed *in vacuo*. The solid residue was taken up in the minimum volume of water and extracted with diethyl ether. The ethereal extracts were dried (Na_2SO_4), filtered and the ether removed by distillation. The resultant oil was distilled *in vacuo* to give the required *N*-methyl-1-(2-pyridyl)ethylamine (7 g, 34%), b.p. 116 °C at 43 mmHg; found, C 71.0, H 8.9, N 20.7; $C_8H_{12}N_2$ requires C 70.55, H 8.9, N 20.6%; *N*-hexyl-1-(2-pyridyl)ethylamine (22.6 g, 73%), b.p. 76–78 °C at 0.15 mmHg; found, C 75.5, H 10.8, N 13.7; $C_{13}H_{22}N_2$ requires C 75.7, H 10.75, N 13.6%; and *N*-cyclohexyl-1-(2-pyridyl)ethylamine (22.4 g, 73%), b.p. 77 °C at 0.05 mmHg; found, C 76.35, H 9.8, N 13.6; $C_{13}H_{20}N_2$ requires C 76.4, H 9.9, N 13.7%.

***N*-Alkyl-1-(2-piperidyl)ethylamines.** The synthesis of the *N*-alkyl-1-(2-piperidyl)ethylamines was effected by catalytic reduction of the *N*-alkyl-1-(2-pyridyl)ethylamines over Adams catalyst following the procedure used for the synthesis of the 2-(*N*-alkylaminomethyl)piperidines.

The following compounds were obtained: *N*-methyl-1-(2-piperidyl)ethylamine (58%) b.p. 32–34 °C at 0.09 mmHg; found, C 67.5, H 12.8, N 19.6; $C_8H_{18}N_2$ requires C 67.66, H 12.8, N 19.7%; *N*-hexyl-1-(2-piperidyl)ethylamine (89%), b.p. 80 °C at 0.05 mmHg; found, C 73.2, H 13.1, N 13.8; $C_{13}H_{28}N_2$ requires C 73.5, H 13.3, N 13.8%; and *N*-cyclohexyl-1-(2-piperidyl)ethylamine (88%), b.p. 80–83 °C at 0.08 mmHg; found, C 74.5, H 12.35, N 13.25; $C_{13}H_{26}N_2$ requires C 74.2, H 12.5, N 13.3%.

2-Alkyl-1-methylperhydroimidazolo[3,4-*a*]pyridines. The preparation of the 2-alkyl-1-methylperhydroimidazolo-[3,4-*a*]pyridines from the *N*-alkyl-1-(2-piperidyl)-ethylamines is similar to the synthesis of the 2-alkylperhydroimidazolo[3,4-*a*]pyridines from the 2-(*N*-alkylaminomethyl)piperidines. The individual isomers of the 2-alkyl-1-methylperhydroimidazolo[3,4-*a*]pyridines were obtained by chromatographic separation over neutral alumina (Woelm grade IV). The first isomer, eluted with light petroleum (b.p. 40–60 °C),

was the *trans*-(H-1,H-8a)-2-alkyl-1-methylperhydroimidazolo[3,4-*a*]pyridine and the second, eluted with a 90:10 mixture of light petroleum (b.p. 40–60 °C) and 10% diethyl ether, was the *cis*-(H-1,H-8a)-2-alkyl-1-methylperhydroimidazolo[3,4-*a*]pyridine.

The following compounds were obtained: *trans*-(H-1, H-8a)-1, 2-dimethylperhydroimidazolo [3,4-*a*]pyridine, b.p. 93 °C at 300 mmHg; found, C 70.1, H 11.65, N 18.2; $C_9H_{18}N_2$ requires C 70.1, H 11.7, N 18.2%; *cis*- (H-1, H- 8a)- 1, 2- dimethylperhydroimidazolo[3, 4-*a*]pyridine, b.p. 93 °C at 300 mmHg; found, C 70.0, H 11.5, N 18.15; $C_9H_{18}N_2$ requires C 70.1, H 11.7, N 18.2%; *trans*-(H-1,H-8a)-2-hexyl-1-methylperhydroimidazolo[3,4-*a*]pyridine, b.p. 74 °C at 0.03 mmHg; found, C 74.9, H 12.55, N 12.5; $C_{14}H_{28}N_2$ requires C 74.9, H 12.6, N 12.5%; *cis*-(H-1,H-8a)-2-hexyl-1-methylperhydroimidazolo[3,4-*a*]pyridine, b.p. 74 °C at 0.03 mmHg; found, C 74.8, H 12.5, N 12.45; $C_{14}H_{28}N_2$ requires C 74.9, H 12.6, N 12.5%; *trans*-(H-1,H-8a)-2-cyclohexyl-1-methylperhydroimidazolo[3,4-*a*]pyridine, b.p. 80–82 °C at 0.03 mmHg; found, C 75.4, H 11.8, N 12.7; $C_{14}H_{26}N_2$ requires C 75.6, H 11.8, N 12.6%; and *cis*-(H-1,H-8a)-2-cyclohexyl-1-methylperhydroimidazolo[3,4-*a*]pyridine, b.p. 80–82 °C at 0.03 mmHg; found, C 75.4, H 11.8, N 12.7; $C_{14}H_{26}N_2$ requires C 75.6, H 11.8, N 12.6%.

Acknowledgements

This work was carried out with the support of the Ministry of Defence, Procurement Executive. We thank the SERC for the ^{13}C NMR spectra.

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