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PROTON MAGNETIC RESONANCE STUDIES OF COMPOUNDS WITH BRIDGEHEAD NITROGEN ATOMS—X[1]

CONFIGURATIONAL AND CONFORMATIONAL STUDIES WITH METHYL SUBSTITUTED PERHYDROPYRIDO [1,2-c]PYRROLO[2,1-e] IMIDAZOLES

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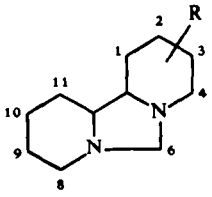
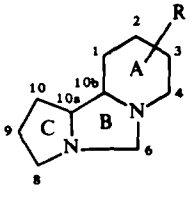
Abstract—A series of Me substituted perhydropyrido [1.2-*c*]pyrrolo [2.1-*e*] imidazoles have been synthesized and their configurations and preferred conformations assigned on the basis of the 2800–2700 cm^{-1} region of their IR spectra and from a study of their PMR spectra with particular reference to the geminal coupling constant of the C6 methylene protons. The influence of dipole interactions in determining conformational preferences in these compounds is discussed.

As A natural extension of our stereochemical studies on the perhydrodipyrido [1.2-*c* 2′1′-*e*] imidazoles (I)[2] we decided to study the related perhydropyrido [1.2-*c*]-pyrrolo[2.1-*e*] imidazoles (II). The presence of the 5-membered C ring should give rise to N—CH_2—N geometries differing from those in I and also affect the position of conformational equilibria in the various Me substituted isomers. These differences should be reflected in the observed values of the geminal coupling constant (J_{gem}) for the C6 methylene protons since J_{gem} has been demonstrated[3, 5–7] to be very sensitive to the orientation of adjacent heteroatom lone pairs of electrons.



I (R = H or Me)



II (R = H or Me)

Some of the possible conformations (chair conformations for ring A assumed) of *syn* and *anti*-perhydropyrido [1.2-*c*]pyrrolo[2.1-*e*] imidazoles are shown in Fig. 1; only conformations possessing a *cis* fusion of rings B and C have been considered. *trans* B:C Ring fused conformations have been neglected since *trans*-bicyclo[3.3.0]-octane is considerably strained[4] and a *trans* fusion of two 5-membered rings is therefore unlikely to be present in pyrrolizidine derivatives which possess the conformationally mobile bridgehead N atom. The conformation of the 5-membered ring C depicted in Fig. 1 has been chosen from a study of Dreiding models and represents a conformation in which non-bonded interactions are minimised; the exact conformations of the 5-membered rings cannot of course be defined.

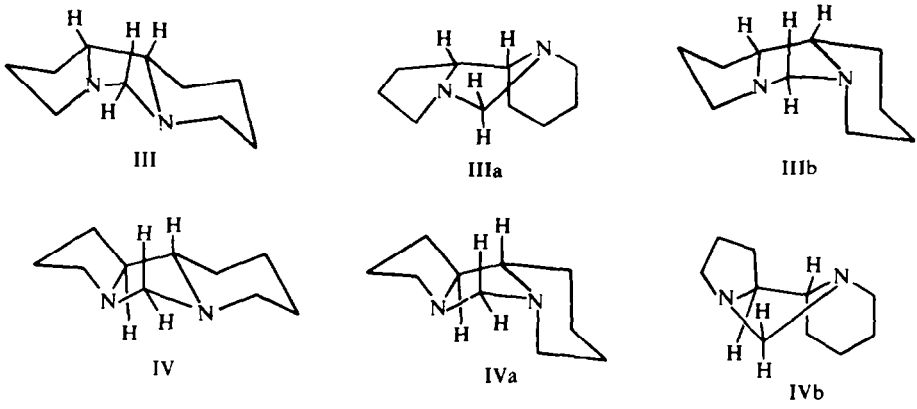


FIG. 1 Conformations of *syn* (III) and *anti* (IV) perhydropyrido [1.2-*c*] pyrrolo [2.1-*e*] imidazoles.

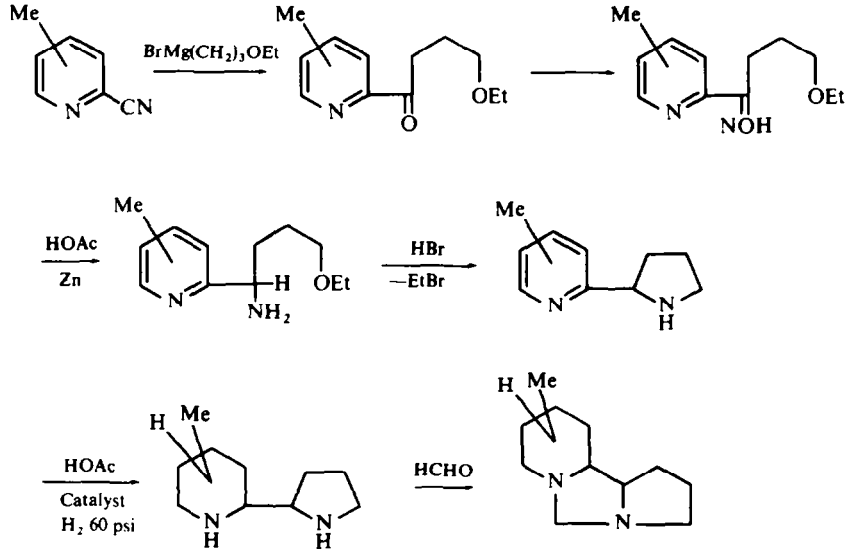


FIG. 2 Synthesis of methyl substituted perhydropyrido [1.2-*c*]pyrrolo [2.1-*e*] imidazoles

From an examination of non-bonded interactions present in the conformations shown in Fig. 1 the *cis* A:B conformations IIIa and IIIb of the *syn* isomer are very much destabilized with respect to the *trans* A:B conformation III whereas the three conformations of the *anti*-isomer (IV, IVa, IVb) are all relatively free of these interactions. Purely on the basis of steric grounds therefore one might expect the *syn* isomer to exist predominantly in the more favourable *trans syn cis* conformation III and the *anti* isomer as a possible equilibrium mixture of the *trans anti cis* (IV), and the two *cis anti cis* conformations (IVa and IVb).

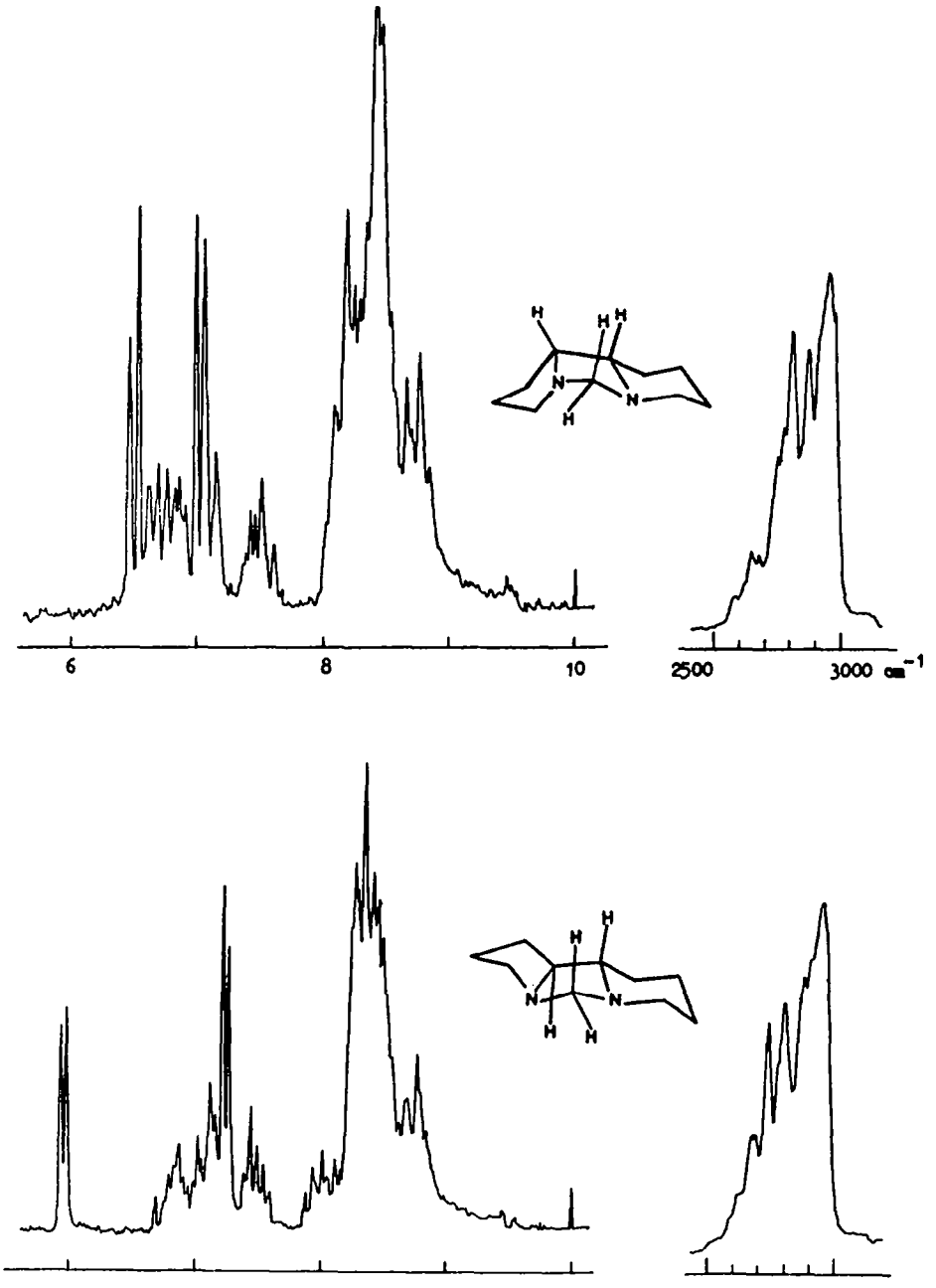
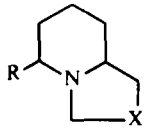
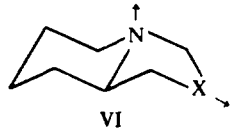


FIG. 3 NMR and IR spectra of *syn* and *anti* perhydropyrido [1.2-*c*] pyrrolo [2.1-*e*] imidazoles.

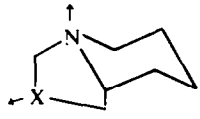
One of the most important factors expected to influence conformational equilibria in III and IV is the dipolar interactions arising from the presence of the two bridgehead N atoms. In previous papers in this series we have drawn attention to the destabilizing influence of parallel or near parallel arrangements of heteroatom electron pairs in 1,3-hetero-systems. For example, compounds V (X = S, R = H)[5] and V (X = O, R = H)[6] exist at room temperature as conformational mixtures containing approximately 50% of the *cis* fused ring conformations VII in which the unfavourable dipole interactions present in the *trans*-fused ring conformations VI have been relieved. *trans*-9,5*H*-9-Methyloctahydropyrido [1.2-*c*] 1,3-oxazine exists in the *cis*-fused conformation VIII and this, as discussed,[7] must also be due to the destabilizing influence of the *syn* axial lone pairs present in the *trans*-fused ring conformation.



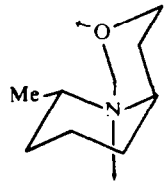
V



VI



VII



VIII

From a consideration of both steric and dipolar factors, *syn*-perhydropyrido [1.2-*c*]pyrrolo[2.1-*e*] imidazoles would be expected to preferentially adopt the *trans* A:B conformation III in which non-bonded interactions are at a minimum and the N lone pairs of electrons are *trans*-orientated. Similarly the *anti*-isomer might be expected to exist as an equilibrium mixture of the *trans* A:B conformation IV, in which an unfavourable dipole interaction involving the N atoms exists, and the *cis* A:B conformations IVa and IVb in which this interaction is absent.

The compounds II were synthesized by the route shown in Fig. 2. The preparation of the Me substituted 2,2'-pyridylpyrrolidines was based on the synthesis of α-nornicotine described by Craig.[8] Catalytic hydrogenation of the pyridyl-pyrrolidines in glacial acetic acid using Adams catalyst followed by treatment of the resultant mixture of piperidyl-pyrrolidines with formaldehyde gave the required mixture of Me substituted perhydropyrido [1.2-*c*]pyrrolo[2.1-*e*] imidazoles (II). These were separated by preparative GLC using a Carbowax on chromosorb packed column.

The IR and PMR spectra of *syn* and *anti*-perhydropyrido [1.2-*c*]pyrrolo[2.1-*e*] imidazoles* are shown in Fig. 3. The first isomer off the column (isomer 1) showed a strong peak in the IR at 2800 cm^{-1} with a set of descending maxima extending to 2500 cm^{-1} and the second isomer (isomer 2 showed moderate to strong peaks at 2800

* All the perhydropyrido [1.2-*c*]pyrrolo[2.1-*e*] imidazoles discussed in this paper exist as racemates.

cm^{-1} and 2740 cm^{-1} with the same type of tailing of absorption to 2500 cm^{-1}. The IR absorption pattern in this region (Bohlmann's bands) is evidence* for the presence of conformations with a *trans* A:B ring junction (i.e. III and IV).

The PMR spectral parameters for the C6 methylene protons are dramatically different: isomer I shows a J_{gem}† of −7·2 Hz and a difference in chemical shift between the methylene protons (ΔH6H6′) of 0·52 ppm whereas isomer II shows J_{gem} = −4 Hz and ΔH6H6′ = 1·30 ppm. The remainder of the PMR spectra of both isomers are very similar: isomer I shows a one proton multiplet centred at 7·5τ and a three proton multiplet centred at 6·8 τ, the corresponding signals in isomer 2 being at 7·5 τ and 7 τ; these signals must arise from the C10a, C8 and C4eq protons. The rest of the ring protons in both isomers absorb between 8 and 9 τ.

The PMR and IR spectra of the *syn* and *anti* isomers (with particular reference to the C6 proton parameters and Bohlmann region respectively) closely resembled the spectra of several of the monomethyl perhydropyrido [1.2-*c*]pyrrolo[2.1-*e*] imidazoles (Tables 1 and 2). This near identity of the spectral features of the parent compounds with certain corresponding Me substituted compounds provides clear evidence that the unsubstituted *syn* and *anti* isomers exist at room temperature predominantly in conformations III and IV respectively. If other conformations contributed appreciably to an equilibrium mixture clear differences should be

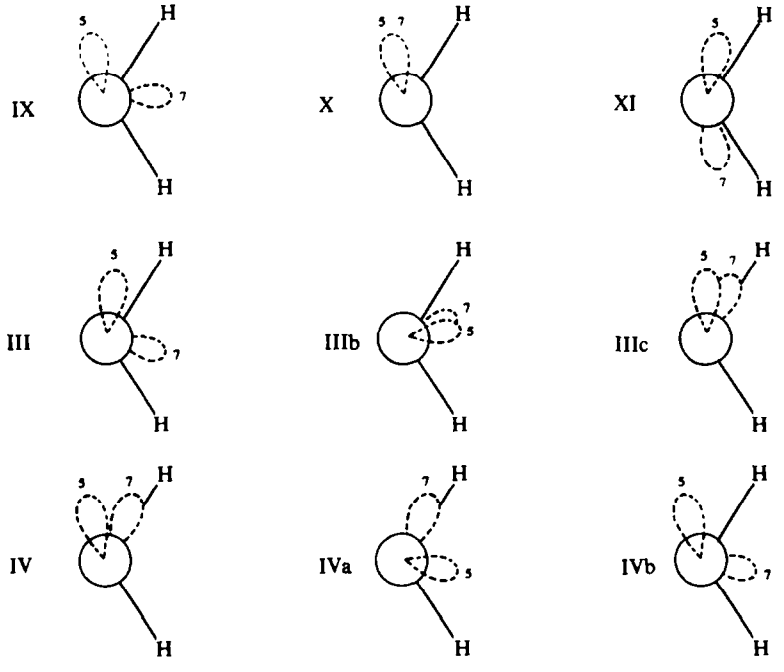
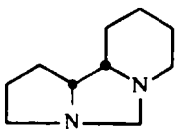
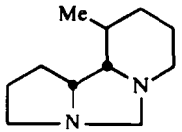
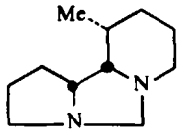


FIG. 4 Schematic representation of the dihedral angles between the nitrogen lone pair orbitals and the C6 methylene bonds in the various conformations of *syn* and *anti* perhydropyrido [1.2-*c*]pyrrolo[2.1-*e*] imidazoles (III and IV) and in certain perhydrodipyrido [1.2-*c* 2′1′-*e*] imidazoles (IX, X, XI).

* For a recent detailed discussion on the IR spectra of quinolizidine derivatives in the 2800–2700 cm^{-1} region see Ref 9 but this region has also been discussed in Refs 2, 5, 6.

† J_{gem} is assumed to be negative.

TABLE 1. PMR SPECTRA AND IR SPECTRA (BOHLMANN'S REGION) OF *syn* PERHYDROPYRIDO [1,2-*c*]PYRROLO[2.1-*e*] IMIDAZOLES

Compound	No.	PMR Spectra								IR spectra
		C6 Methylene protons				Centre of the Doublet and "J_{CH-Me}"				
						Equatorial		Axial		
		$-J$ (Hz)	H6 (τ)	H6′ (τ)	ΔH6H6′	τ	J	τ	J	
	III	7·2	6·42	6·94	0·52					2800 cm^{-1} (ε_a 148)
	XIII	7·3	6·41	6·96	0·55	9·13	5·3			2800 cm^{-1} (ε_a 141)
	XIV	7·3	6·36	7·00	0·64			8·92	7·0	2800 cm^{-1} (ε_a 124)

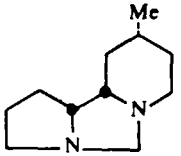
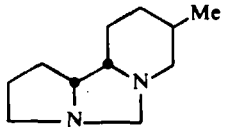
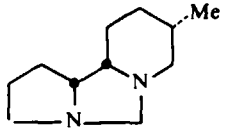
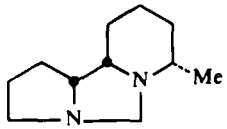
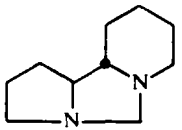
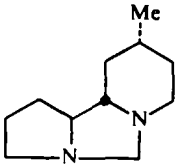
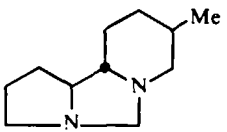
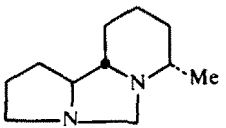
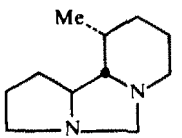
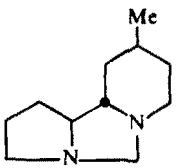
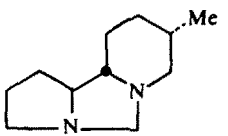
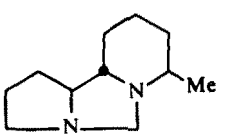
	XV	7·3	6·45	6·96	0·51	9·02	4·8			2800 cm^{-1} (ε_a 159)
	XVI	7·3	6·45	6·96	0·51	9·14	5·5			2800 cm^{-1} (ε_a 161)
	XVII	6·8	6·55	7·05	0·50			8·92	7·3	2800 cm^{-1} (ε_a 161)
	XVIII	7·2	6·25	6·98	0·73	8·96	6·0			2800 cm^{-1} (ε_a 144)

TABLE 2. PMR SPECTRA AND IR SPECTRA (BOHLMANN'S REGION) OF *anti* PERHYDROPYRIDO [1.2-*c*]PYRROLO[2.1-*e*] IMIDAZOLES

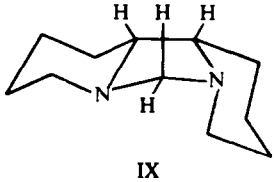
Compound	No.	PMR Spectra								IR spectra
		C6 Methylene protons				Centre of the Doublet and "J_{CH-Me}"				
						Equatorial		Axial		
		$-J$ (Hz)	H6 (τ)	H6′ (τ)	ΔH6H6′	τ	J	τ	J	
	IV	4·0	5·89	7·19	1·30					2800 cm^{-1} (ε_a 103) 2740 cm^{-1} (ε_a 89)
	XXV	4·0	5·87	7·22	1·35	9·02		4·5		2800 cm^{-1} (ε_a 102) 2740 cm^{-1} (ε_a 75)
	XXVI	4·0	5·88	7·23	1·35	9·15		5·6		2800 cm^{-1} (ε_a 91) 2740 cm^{-1} (ε_a 93)

	XXVII	4·0	5·68	7·27	1·59	8·95	6·0	2800 cm^{-1} (ε_a 92) 2720 cm^{-1} (ε_a 73)
	XXVIII	6·0	6·04	6·96	0·92	9·05	6·7	
	XXIX	6·8	6·05	6·77	0·72	9·05	5·8	
	XXX	6·2	6·05	6·88	0·83	9·04	6·0	
	XXXI	7·0	5·85	6·75	0·90	9·05	6·0	

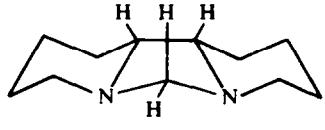
apparent in the PMR and IR spectra of the parents when compared with the Me substituted compounds as the presence of the Me groups would significantly change the positions of conformational equilibrium. Additional evidence is provided by variable temperature PMR of both III and IV which showed no changes down to −80° (acetone solution).

To make a firm decision regarding the *syn* and *anti* configurations of isomers 1 and 2 from a study of their PMR spectra, in isolation from the data presented in the rest of this paper, would be open to objection and was, in fact, not done. However, it is convenient to assign configurations to these two isomers at this point and justify the reasoning involved when the configurations of the Me substituted perhydropyrido [1.2-*c*]pyrrolo[2.1-*e*] imidazoles are discussed.

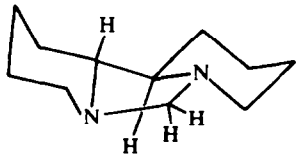
The relative dispositions of the N5 lone pair, the C6 methylene C—H bonds, and and the N7 lone pair for the conformations of *syn* and *anti* perhydropyrido [1.2-*c*]-pyrrolo[2.1-*e*] imidazole shown in Fig. 1 and of conformations IX, X, XI of *syn* and *anti* perhydrodipyrido [1.2-*c*, 2′.1′-*e*] imidazoles are indicated in Fig. 4. This figure is a schematic representation of the two sets of dihedral angles combined in one drawing. The angles were estimated from Dreiding models and Fig. 4 illustrates only relative dispositions of the N lone pairs and the C—H bonds in the various conformations: the figure must not be taken to mean that we believe the conformations in solution bear an exact resemblance to the drawings or to the Dreiding models. Since a relationship must exist between these dihedral angles and J_{gem} one would expect conformation III of *syn* perhydropyrido [1.2-*c*]pyrrolo[2.1-*e*] imidazole to possess a J_{gem} of similar magnitude to that in *trans*, 1*H*, 11b*H*-1-methyl-*syn*-perhydro [1.2-*c*, 2′.1′-*e*] imidazole (XII) which was shown[2] to exist in the *trans syn cis* conformation IX. J_{gem} for XII was found to be = −8 Hz. The closest model we have for the *trans* A:B conformation of the *anti* isomer of II (IV) is *syn*-perhydrodipyrido [1.2-*c*, 2′1′-*e*] imidazole[2] which exists in conformation X and shows a J_{gem} of −3·6 Hz.



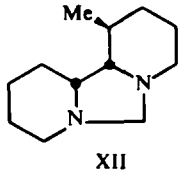
IX



X



XI

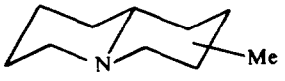


XII

As stated above, isomer 1 of the perhydropyrido [1.2-*c*]pyrrolo[2.1-*e*] imidazole shows a J_{gem} of −7·2 Hz and isomer 2 a value of −4·0 Hz. Both of these coupling constants correspond closely to the values observed for compounds existing in conformations IX (J_{gem} = −8 Hz) and X (J_{gem} = −3·6 Hz) and on these grounds the *syn* configuration (*trans* A:B ring junction) (III) may be assigned to isomer 1 and the *anti* configuration (*trans* A:B ring junction) (IV) to isomer 2.

Methyl substituted perhydropyrido [1.2-c]*pyrrolo*[2.1-e] *imidazoles*

From previous discussion on the importance of dipole interactions in influencing the position of conformational equilibria in 1,3-heterosystems one would expect methyl substituted derivatives of II possessing the *syn* configuration to exist in the *trans* A:B conformation III even with an axial Me group present since this conformation is relatively free of non-bonded interactions and possesses a *trans* arrangement of the N lone pairs of electrons. As previously discussed, derivatives of II possessing the configuration and conformation implied in III showed a similar IR spectrum in Bohlmann's region and similar PMR parameters for the C6 methylene protons to those shown by *syn*-perhydropyrido [1.2-*c*]pyrrolo[2.1-*e*] imidazole. Six isomers (XIII–XVIII) did in fact resemble closely this compound in spectral features (Table 1). All showed a single strong band at 2800 cm^{-1} in the IR and values of J_{gem} ranging between −6·8 to −7·3 Hz and of ΔH6H6′ between 0·50 to 0·73 ppm in their PMR spectra. The actual chemical shifts of the C6 methylene protons varied only very slightly from one isomer to the other. ΔH6H6′ was greatest for the 4-Me substituted compound (XVIII) and this must be due to the direct effect of the Me group on the C6 methylene protons. A similar effect has been noted in V (X = O, R = Me)[6]. It seems reasonable therefore to assign to all these six compounds the *syn* configuration and the preferred conformation (III). The remaining feature to be discussed is the axial or equatorial nature of the Me group. The criteria to be used here are (a) a study of the percentage of isomers formed (discussed later) and (b) the centre of the Me doublet and the apparent $J_{CH—Me}$. The PMR parameters are subject to many influences but in the methylquinolizidines[10] (XIX), derivatives of sedridine[11] (XX), trimethylcyclohexanes,[12] and in the Me substituted perhydrodipyrido [1.2-c, 2′1′-*e*] imidazoles I (R = Me)[2], axial Me protons are found to be deshielded relative to the equatorial Me protons and "$J_{CH—Me}$" is somewhat larger for axial Me groups than for equatorial Me groups. As can be seen from Table 1, particularly in the case of the two 3-Me isomers (XVI and XVII) and the two 1-Me isomers (XIII and XIV), equatorial and axial Me groups have been assigned assuming the validity of this criterion.



XIX

XX

All the isomers listed in Table 2 have been assigned the *anti*-configuration and since a number of these compounds (XXIV–XXVII) showed no Bohlmann's bands in the IR they must therefore possess *cis* A:B ring fusions. A *cis* A:B junction is, of course, evidence for the *anti* configuration since the near parallel arrangement of the N lone

pairs in the *trans* A:B *anti* stereochemistry (IV) disfavours the *trans* A:B conformations relative to the *cis*. Before discussing the special features of the compounds in Table 2 it is necessary to consider the conformations of the *anti* isomers in more detail.

The possible conformational equilibria for *trans* 3*H*,10b*H*-3-methyl-*anti*-perhydropyrido [1.2-*c*]pyrrolo[2.1-*e*] imidazole (XXII) and the *cis* 3*H*,10b*H* isomer (XXVI) are shown in Fig. 5. In our studies on the oxa-aza V (X = O),[6] thia-aza (V, X = S),[5] and diazabicyclo [4.3.0] nonanes[13] it was found that the preferred conformation of, for example, the *trans* 6*H*,3*H*-3-Me substituted derivatives was that with the *trans* ring fusion (VI, X = O, S, NR) and an equatorial Me group: the corresponding *cis* 6*H*,3*H*-3-Me substituted compounds adopted the *cis* fused ring conformation (VII, X = O, S, NR) with an equatorial Me group rather than the *trans* conformation (VI) with an axial Me group. By analogy one might expect XXII to adopt the preferred conformation XXIIa with an equatorial Me and a *trans* A:B junction and XXVI to exist as XXVIa with an equatorial Me and a *cis* A:B junction.

Mixtures of the 2,3 and 4-Me substituted compounds, when separated by chromatography each gave an isomer XXI, XXII, XXIII, (Table 2) that showed close IR and PMR parallels with *anti* perhydropyrido [1.2-*c*]pyrrolo[2.1-*e*] imidazole (IV). All three showed the characteristic two peak pattern at 2800 cm^{-1} and 2740 cm^{-1} in the IR, and in their PMR spectra a J_{gem} of −4 Hz and a ΔH6H6′ of 1·35 to 1·59 ppm. The large value of 1·59 ppm in XXIII may be explained by the proximity of the 4-Me to the C6 methylene; a similar effect was observed in the corresponding *syn* isomer XVIII. On this basis these three compounds were assigned the *anti* configuration and the *trans* A:B conformation (IV) and must therefore possess equatorially orientated substituents.

In addition, the mixtures of the 2, 3 and 4-Me substituted compounds each gave an isomer XXV, XXVI, XXVII (Table 2) which showed little or no absorption in

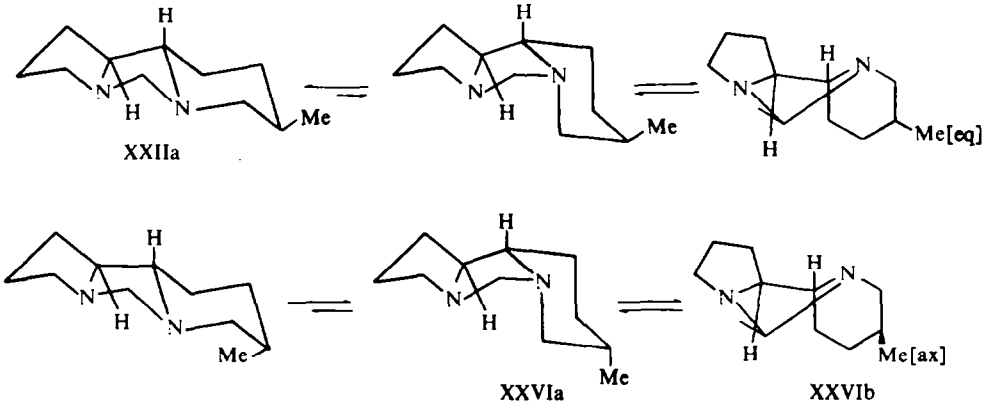
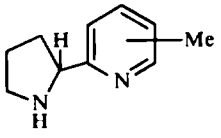


FIG. 5 Conformations of *trans* 3*H*,10b*H*-3 methyl-*anti*-perhydropyrido [1.2-c]pyrrolo[2.1-*e*] imidazole (XXII) and corresponding *cis* 3*H*,10b*H*—3 methyl isomer.

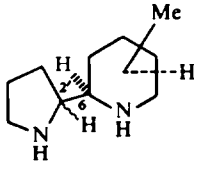
the 2800–2700 cm^{-1} region of the IR. One isomer (XXIV) isolated from the 1-Me substituted mixture also had little absorption in this Bohlmann region. This provides strong evidence that the A:B ring fusion in these isomers is *cis*. They must, therefore, possess the *anti* configuration and the Me group must be orientated so that it is axial

when the A:B ring fusion is *trans* i.e. the four compounds showing no Bohlmann's bands must be *cis* 1H, 10b*H*-1-Me (XXIV), *trans* 2*H*, 10b*H*-2-Me (XXV), *cis* 3*H*, 10b*H*-3-Me (XXVI) and *trans* 4*H*, 10b*H*-4-Me *anti* perhydropyrido [1.2-*c*]pyrrolo-[2.1-*e*] imidazole (XXVII).*

As is shown in Fig. 5 for the particular case of the 3-Me isomer, two *cis* A:B conformations are possible for the Me substituted compounds but XXVIa with an equatorial Me group is to be preferred over XXVIb with an axial Me group. J_{gem} values for the C6 methylene protons in the four *cis* A:B *anti* compounds were found to be between −6·0 and −7·0 Hz and ΔH6H6′ varied between 0·72 and 0·92 ppm. The N—CH_2—N geometry (Fig. 4) of IVa resembles that of III for which a J_{gem} of −7·2 Hz was observed and this confirms our conformational arguments.



XXVIII



XXIX

Having assigned the configurations and preferred conformations to the methylperhydropyrido [1.2-*c*]pyrrolo[2.1-*e*] imidazoles on spectral grounds it is worth considering the percentage isomers obtained (Table 3) to see if the generally accepted[13]

TABLE 3. PERCENTAGE ISOMERS OF METHYLPERHYDROPYRIDO [1.2-*c*]PYRROLO[2.1-*e*] IMIDAZOLES OBTAINED BY ROUTE SHOWN IN FIG. 2

Compound	% *syn* isomers		% *anti* isomers	
	cis Me 10b*H*	*trans* Me 10b*H*	*cis* Me 10b*H*	*trans* Me 10b*H*
1-Methylperhydropyrrolo [1.2-*c*]pyrido-[2.1-*e*] imidazoles	5 XIII	65 XIV		30 XXIV
2-Methylperhydropyrrolo [1.2-*c*]pyrido-[2.1-*e*] imidazoles		45 XV	5 XXV	50 XXI
3-Methylperhydropyrrolo [1.2-*c*]pyrido-[2.1-*e*] imidazoles	25 XVI	25 XVII	40 XXII	10 XXVI
4-Methylperhydropyrrolo [1.2-*c*]pyrido-[2.1-*e*] imidazoles		50 XVIII	3 XXVII	47 XXIII

cis addition of hydrogen to aromatic rings supports the conclusions reached, particularly those relating to the relative orientation of the Me group with respect to the angular 11b hydrogen atom.

Assuming no complicating factors, catalytic reduction of the pyrrolidinyl pyridine

* Another possible isomer of the 4-methyl mixture is *trans* 4*H*, 11b*H* 4 methyl *syn* perhydropyrido [1.2-*c*]pyrrolo[2.1-*e*] imidazole which would be expected to possess a *trans* A:B ring fusion and an axial Me group. Like XXVII, this compound also would not show Bohlmann's bands in the IR since there is only one αC—H bond *axial* and *trans* with respect to the N lone pair of electrons. However, this compound would be characterized by a J_{gem} of −4 Hz as well as by the absence of Bohlmann's bands. An isomer with this configuration is therefore excluded and the three 4-Me isomers obtained are XVIII, XXIII and XXVII.

(XXVIII) would be expected to give the *trans* Me, 6*H* pyrrolidinyl (XXIX) as the major product. The relative stereochemistry of the 6*H* with respect to the 2′*H* will of course be influenced by other more complicated factors. Reduction of 3 methyl 2(2′ pyrrolidinyl) pyridine followed by formaldehyde treatment gave three isomeric perhydro [1.2-*c*]pyrrolo[2.1-*e*] imidazoles obtained in the relative quantities shown in Table 3. The major isomer (65%) possessed the *syn* configuration and a *trans* relationship between the 1Me and the 10b*H* corresponding to *cis* addition of hydrogen to the pyridine (XXVIII). The isomer obtained as 30% of the mixture possessed the *anti* configuration and a Me group orientated such that it must have arisen by *cis* addition of hydrogen. The third isomer (corresponding to *trans* addition of hydrogen) was obtained in only 5% yield and possessed the *syn* configuration. The two major isomers of 2-methyl perhydropyrido [1.2-*c*]pyrrolo[2.1-*e*] imidazole obtained possessed the *cis* 2*H*, 10b*H*, stereochemistry in accord with predominant *cis* addition of hydrogen.

All four isomers of the 3-Me substituted derivatives of II were obtained but the results were not consistent with simple *cis* addition of hydrogen. Both *syn* compounds were obtained in equal amounts and the two *anti* isomers could not be separated by preparative gas chromatography. The *anti* isomers were finally obtained pure by column chromatography over Woelm alumina, the *cis* 3*H*, 10b*H* compound coming off the column first and the *trans* 3*H*, 10b*H* compound having to be removed from the column by elution with methanol. The three isomers of 4-Me substituted perhydropyrido [1.2-*c*]pyrrolo[2.1-*e*] imidazole obtained were separated by PGLC and the two major isomers possessed the 4*H*, 10b*H* stereochemistry consistent with *cis* addition of hydrogen. The chemical evidence therefore, with the exception of that concerning the 3-Me compounds, is in accord with the stereochemical assignments made on spectral grounds. In all separations including that of the two parent compounds *syn* isomers were found to possess shorter retention times than the *anti* isomers.

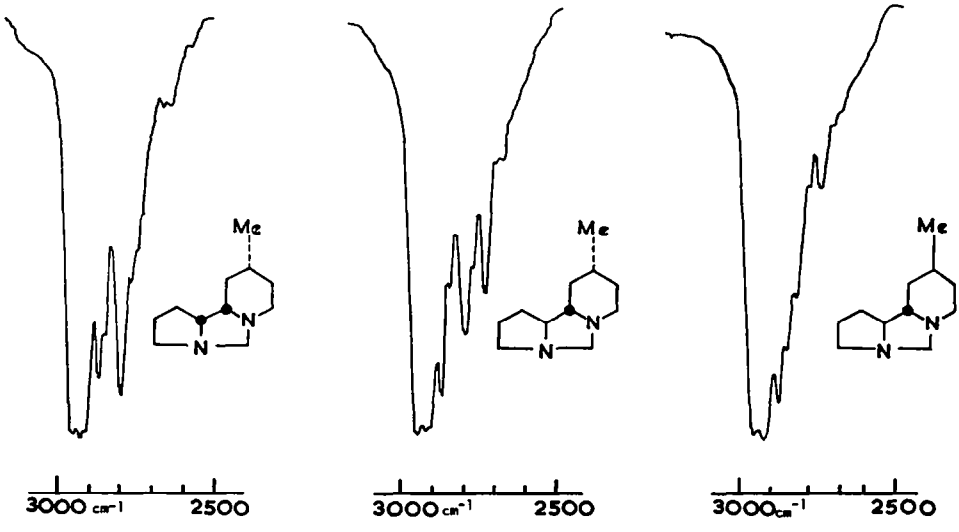


FIG. 6 IR spectra of isomeric 2 methyl perhydropyrido [1.2-*c*]pyrrolo[2.1-*e*] imidazoles (XV, XXI, XXV).

EXPERIMENTAL

Elemental analyses were carried out by Dr. F. Pascher and E. Pascher, Micro-analytical Laboratory, Bonn, or at the Organic Chemistry Department of Reading University. The NMR spectra were recorded as solns in $CDCl_3$ on a Perkin–Elmer R.10 60 MHz spectrometer using TMS as internal reference, the low temp NMR were recorded in acetone on a Varian HA-100 MHz spectrometer. IR spectra were measured as 0·1 M solns in $CDCl_3$ on a Perkin–Elmer 457 Grating IR Spectrophotometer. Isomeric mixtures were separated on a Varian Aerograph A700 or on a Pye 105 instrument.

Synthesis of perhydropyrido [1.2-c]*pyrrolo*[2.1-e] *imidazole.* The compounds were prepared by the route shown in Fig. 1. α-Nornicotine was synthesized from α-cyanopyridine by the method of Craig.[8]

2-(2-*Pyrrolidinyl*) *piperidine.* A soln of 2-(2-pyrrolidinyl) pyridine (20 g) in glacial AcOH (250 ml) was hydrogenated at 50° and 60 psi using Adams catalyst (2 g). After theoretical uptake of H_2, the soln was decanted and evaporated under vacuum to 60 ml. The soln was basified with 30% NaOH aq, the oily amine layer extracted with ether (3 × 150 ml) and the ethereal extracts were combined, dried and the ether was evaporated. The residual oil was distilled and the fraction b.p. 52–54°/0·1 mm was collected; n_D^{15} 1·5094. (Found: C, 69·94; H, 11·66; N, 18·10. $C_9H_{18}N_2$ requires: C, 70·07; H, 11·76; N, 18·16%).

Perhydropyrido [1.2-c]*pyrrolo*[2.1-e] *imidazoles.* 2-(2-Pyrrolidinyl) piperidine (15 g) was shaken with 36% formaldehyde soln (12 ml) at room temp for 5 min, an ice cold soln of 30% NaOH aq added, and the oily perhydropyrido [1.2-c]pyrrolo[2.1-e] imidazoles extracted with ether (3 × 100 ml) and the ethereal extracts combined, dried and evaporated. The residuel oil was distilled and the fraction b.p. 76°/0·5 mm was collected (10 g). Analytical GLC showed the fraction was a 1:1 mixture. The isomers were separated by PGLC using 22′ × $\frac{3}{8}$″ aluminium column packed with 20% Carbowax 1540 on 60–80 chromosorb W. Separation conditions were: column temp 160°, injection temp 200°, the carrier gas was H_2 at 30 psi and a flow rate of 200 ml/min, injection size 0·25 ml.

The first isomer III had b.p. 65–66°/0·6 mm, n_D^{15} 1·4960. (Found: C, 72·18; H, 10·88; N, 16·81. $C_{10}H_{18}N_2$ requires: C, 72·24; H, 10·91; N, 16·85%).

The second isomer (IV) had b.p. 71–72°/0·8 mm, n_D^{15} 1·4924 (Found: C, 72·18; H, 10·88; N, 16·81. $C_{10}H_{18}N_2$ requires: C, 72·24; H, 10·91; N, 16·85%).

Synthesis of monomethylperhydropyrido [1.2-c]*pyrrolo*[2.1-e] *imidazoles.* The compounds were prepared by the route shown in Fig. 1. The cyano methylpyridines were prepared by the method of Katritzky *et al.*[10] except 4-methyl-2-cyanopyridine which was prepared by the method of Feely and Beavers[15] from 4-methyl pyridine N-oxide.

4-*Ethoxy*-1-(*methyl-2-pyridyl*) *butanones*

General procedure. The Grignard reagent prepared from 1-ethoxy-3-bromo-propane (128 g) and Mg (24 g) in ether (600 ml) was slowly added with vigorous stirring to a soln of the 2-cyano-methylpyridine (81 g) in ether (600 ml). The reaction mixture was stirred for 10 hr and the addition product was then hydrolysed with HCl (140 ml) and water (140 ml). The soln was basified with 30% NaOH aq and the ether layer was removed, the alkaline soln was extracted once with ether (200 ml) and the extracts were combined, dried, evaporated and the residual oil was distilled.

4-*Ethoxy*-1-(3-*methyl*-2-*pyridyl*) 1-*butanone* (78 g) was obtained from 2-cyano-3-methylpyridine (81 g) as a yellow viscous liquid b.p. 120–122°/0·8 mm lit. 108–111°/0·5 mm.

4-*Ethoxy*-1-(4-*methyl*-2-*pyridyl*) 1-*butanone* (80 g) was obtained from 2-cyano-4-methylpyridine (81 g) as a yellow viscous liquid b.p. 124–125°/1·0 mm lit. 124–126°/1·0 mm.

4-*Ethoxy*-1-(5-*methyl*-2-*pyridyl*) 1-*butanone* (76 g) was obtained from 2-cyano-5-methylpyridine (81 g) as a yellow viscous oil b.p. 111–115°/0·7 mm lit. b.p. 122–125°/0·8 mm.

4-*Ethoxy*-1-(6-*methyl*-2-*pyridyl*) 1-*butanone* (80 g) was obtained from 2-cyano-6-methylpyridine (81 g) as a colourless viscous oil b.p. 108–110°/0·6 mm lit. 98–100°/0·1 mm.

1-*Amino*-4-*ethoxy*-1-(*methyl*-2-*pyridyl*) *butanes*

General procedure. A soln of a 4-ethoxy-1-(methyl-2-pyridyl)-1-butanone (75 g), hydroxylamine hydrochloride (56 g) and 90% alcohol (900 ml) was refluxed for 12 hr, the alcohol was removed by rotary evaporation and water (200 ml) was added to the residue. The aqueous soln was basified with K_2CO_3 soln and the oily oxime was extracted with ether (3 × 150 ml). The ethereal extracts were combined and evaporated and the residue of crude oxime was used without further purification. The oxime was dissolved in abs EtOH (1000 ml), Zn dust (500 g) and glacial AcOH (500 g) were added alternately in small amounts over a period of 5 hr during which time the temp was kept below 25°. The mixture was stirred in an ice bath for an additional 3 hr and allowed to stand for a further hr. The inorganic residues were filtered off and the

ethanol was removed under reduced press. The residue was basified with 30% NaOH aq and extracted with ether (3 × 200 ml); the ethereal extracts were combined, dried and evaporated, and the residual oil was distilled.

1-*Amino-4-ethoxy*-1-(3-*methyl*-2-*pyridyl*) *butane* (68 g) was obtained from 4-ethoxy-1-(3-methyl-2-pyridyl)-butanone (75 g) as a colourless oil b.p. 106–108°/1·1 mm, n_D^{15} 1·5083 (Found: C, 70·30; H, 9·96; N, 13·58. $C_{12}H_{20}N_2O$ requires: C, 69·19; H, 9·68; N, 13·45%).

1-*Amino-4-ethoxy*-1-(4-*methyl*-2-*pyridyl*) *butane* (70 g) was obtained from 4-ethoxy-1-(4-methyl-2-pyridyl) butanone (75 g) as a colourless oil b.p. 94–96°/0·6 mm, n_D^{15} 1·5044 (Found: C, 69·98; H, 9·82; N, 13·55. $C_{12}H_{20}N_2O$ requires: C, 69·19; H, 9·68; N, 13·45%).

1-*Amino-4-ethoxy*-1-(5-*methyl*-2-*pyridyl*) *butane* (63 g) was obtained from 4-ethoxy-1-(5-methyl-2-pyridyl) butanone (75 g) as a colourless oil b.p. 100–102°/0·4 mm, n_D^{15} 1·5003 (Found: C, 69·17; H, 9·71; N, 13·58. $C_{12}H_{20}N_2O$ requires: C, 69·19; H, 9·68; N, 13·45%).

1-*Amino-4-ethoxy*-1-(6-*methyl*-2-*pyridyl*) *butane* (70 g) was obtained from 4-ethoxy-1-(6-methyl-2-pyridyl) butanone (75 g) as a colourless oil b.p. 105–106°/0·5 mm, n_D^{15} 1·5050 (Found: C, 69·18; H, 10·01; N, 13·44. $C_{12}H_{20}N_2O$ requires: C, 69·19; H, 9·68; N, 13·45%).

General procedure. A soln of 45% HBr (400 g) and a 1-amino-4-ethoxy-1-(methyl-2-pyridyl) butane (60 g) was placed in a flask fitted with a vertical 50 cm air condenser, the upper end of which was fitted to a downward coil condenser. The flask was heated until the EtBr formed during the cyclization just distilled over and heating was continued at this temp until all the EtBr had been collected. The soln was reduced to $\frac{1}{6}$ volume by rotary evaporation and then basified with 30% NaOH aq and extracted with ether (3 × 150 ml). The ether extracts were combined, dried, evaporated and the residual oil was distilled under vacuum.

3-*Methyl*-2-(2-*pyrrolidinyl*) *pyridine* (24 g) was obtained from 1-amino-4-ethoxy-1-(3-methyl-2-pyridyl) butane (60 g) as a colourless oil b.p. 84–86°/0·8 mm, n_D^{15} 1·5439 (Found: C, 74·01; H, 8·72; N, 17·26. $C_{10}H_{20}N_2$ requires: C, 74·03; H, 8·70; N, 17·27%).

4-*Methyl*-2-(2-*pyrrolidinyl*) *pyridine* (26 g) was obtained from 1-amino-4-ethoxy-1-(4-methyl-2-pyridyl) butane (60 g) as a colourless oil b.p. 98–99°/0·7 mm, n_D^{15} 1·5424 (Found: C, 73·98; H, 8·78; N, 17·03. $C_{10}H_{20}N_2$ requires: C, 74·03; H, 8·70; N, 17·27%).

5-*Methyl*-2-(2-*pyrrolidinyl*) *pyridine* (26 g) was obtained from 1-amino-4-ethoxy-1-(5-methyl-2-pyridyl) butane (60 g) as a colourless oil b.p. 78–80°/0·5 mm, n_D^{15} 1·5406 (Found: C, 74·00; H, 8·70; N, 17·33. $C_{10}H_{20}N_2$ requires: C, 74·03; H, 8·70; N, 17·27%).

6-*Methyl*-2-(2-*pyrrolidinyl*) *pyridine* (28 g) was obtained from 1-amino-4-ethoxy-1-(6-methyl-2-pyridyl) butane (60 g) as a colourless oil b.p. 70–73°/0·25 mm, n_D^{15} 1·5461 (Found: C, 74·04; H, 8·70; N, 17·33. $C_{10}H_{20}N_2$ requires: C, 74·03; H, 8·70; N, 17·27%).

Methyl-2-(2-*pyrrolidinyl*) *piperidines.*

General procedure. A soln of methyl-2-(2-pyrrolidyl) piperidine (22 g) in glacial AcOH (250 ml) was hydrogenated at 60 psi over Adams catalyst (2·2 g). After the theoretical volume of H_2 had been taken up the soln was reduced under vacuum to 50 ml and basified with 30% NaOH aq. The amine layer was extracted with ether (3 × 100 ml), the extracts were combined, dried, evaporated and the residual oil was distilled under reduced press.

3-*Methyl*-2-(2-*pyrrolidinyl*) *piperidine* (18 g) was obtained from 3-methyl-2-(2-pyrrolidinyl) pyridine (22 g) as a colourless oil b.p. 50–52°/0·2 mm, n_D^{15} 1·4933 (Found: C, 71·14; H, 12·04; N, 16·52. $C_{10}H_{20}N_2$ requires: C, 71·37; H, 11·98; N, 16·65%).

4-*Methyl*-2-(2-*pyrrolidinyl*) *piperidine* (19 g) was obtained from 4-methyl-2-(2-pyrrolidinyl) pyridine (24 g) as a colourless oil b.p. 58–60°/0·08 mm, n_D^{15} 1·4936 (Found: C, 71·45; H, 11·88; N, 16·65. $C_{10}H_{20}N_2$ requires: C, 71·37; H, 11·98; N, 16·65%).

5-*Methyl*-2-(2-*pyrrolidinyl*) *piperidine* (19 g) was obtained from 5-methyl-2-(2-pyrrolidinyl) pyridine (24 g) as a colourless oil b.p. 58–60°/0·15 mm, n_D^{15} 1·4948 (Found: C, 71·38; H, 11·98; N, 16·68. $C_{10}H_{20}N_2$ requires: C, 71·37; H, 11·98; N, 16·65%).

6-*Methyl*-2-(2-*pyrrolidinyl*) *piperidine* (20 g) was obtained from 6-methyl-2-(2-pyrrolidinyl) pyridine (25 g) as a colourless oil b.p. 58–59°/0·08 mm, n_D^{15} 1·4926 (Found: C, 71·27; H, 11·97; N, 16·64. $C_{10}H_{20}N_2$ requires: C, 71·37; H, 11·98; N, 16·65%).

Monomethylperhydropyrido [1.2-c]*pyrrolo*[2.1-e] *imidazoles*

General procedure. The isomeric mixture of a methyl-2-(2-pyrrolidinyl) piperidine (17 g) was treated

with 36% formaldehyde soln (17 ml) and the mixture was shaken at room temp for 5 min. The excess formaldehyde was destroyed with 30% NaOH aq; the soln was extracted with ether (3 × 100 ml); the ethereal extracts were combined, dried, evaporated and the residual oil was distilled *in vacuo*.

1-*Methylperhydropyrido* [1.2-c]*pyrrolo*[2.1-e] *imidazoles* XIII, XIV, XXIV (14 g) was obtained from 3-methyl-2-(2-pyrrolidinyl) piperidine (17 g) as a colourless oil b.p. 80–83°/0·80 mm. The fraction was shown by a GLC to contain three isomers which were separated by PGLC on a 22′ × $\frac{3}{8}$″ aluminium column packed with 20% Carbowax 20 M on 60–80 mesh chromosorb W, the separation conditions were, injection 220°, column 160° H_2 carrier gas at 30 psi with a flow rate of 200 ml/min, injection size 0·2 ml.

XIII, b.p. 52–53°/0·2 mm, n_D^{15} 1·4944 (Found: C, 73·32; H, 11·38; N, 15·42. $C_{11}H_{20}N_2$ requires: C, 73·28; H, 11·18; N, 15·54%).

XIV, b.p. 54–55°/0·15 mm, n_D^{15} 1·4960 (Found: C, 73·32; H, 11·26; N, 15·66. $C_{11}H_{20}N_2$ requires: C, 73·28; H, 11·18; N, 15·54%).

XXIV, b.p. 55°/0·15 mm, n_D^{15} 1·4901 (Found: C, 73·26; H, 11·44; N, 15·45. $C_{11}H_{20}N_2$ requires: C, 73·28; H, 11·18; N, 15·54%).

2-*Methylperhydropyrido* [1.2-c]*pyrrolo*[2.1-e] *imidazoles* XV, XXI, XXV (16 g) was obtained from 4-methyl-2-(2-pyrrolidinyl) piperidine (18 g) as a colourless oil b.p. 65–68°/0·2 mm. The fraction was shown to contain 3 isomers by AGLC and the mixture was separated by PGLC as described in the previous mixture.

XV, b.p. 61–62°/0·2 mm, n_D^{15} 1·4940 (Found: C, 73·26; H, 11·18; N, 15·33. $C_{11}H_{20}N_2$ requires: C, 73·28; H, 11·18; N, 15·54%).

XXI, b.p. 64°/0·25 mm, n_D^{15} 1·4936 (Found: C, 73·28; H, 11·23; N, 15·45. $C_{11}H_{20}N_2$ requires: C, 73·28; H, 11·18; N, 15·54%).

XXV, b.p. 67–68°/0·3 mm, n_D^{15} 1·4912 (Found: C, 73·32; H, 11·19; N, 15·48; $C_{11}H_{20}N_2$ requires: C, 73·28; H, 11·18; N, 15·54%).

4-*Methylperhydropyrido* [1.2-c]*pyrrolo*[2.1-e] *imidazoles* XVIII, XXIII, XXVII (16 g) was obtained from 6-methyl-2-(2-pyrrolidinyl) piperidine (18 g) as a colourless oil b.p. 68–72°/0·15 mm.

The fraction was shown to contain three isomers by AGLC and the mixture was separated by PGLC on a 15′ × $\frac{3}{8}$″ glass column packed with 20% Carbowax 20M on 60–80 chromosorb W, separation conditions were: injection 220 column 160° N_2 carrier gas at 70 psi flow rate 200 ml/min injection 0·4 ml automatically.

XVIII, b.p. 65–66°/0·1 mm, n_D^{15} 1·4959 (Found: C, 73·25; H, 11·26; N, 15·32. $C_{11}H_{20}N_2$ requires: C, 73·28; H, 11·18; N, 15·54%).

XXIII, b.p. 69°/0·15 mm, n_D^{15} 1·4972 (Found: C, 73·29; H, 11·19; N, 15·51. $C_{11}H_{20}N_2$ requires: C, 73·28; H, 11·18; N, 15·54%).

The third isomer (XXVII) which was present in approx 2% of the mixture had the same retention time as a high boiling impurity and it could not be obtained in a pure condition. No constants are quoted.

3-*Methylperhydropyrido* [1.2-c]*pyrrolo*[2.1-e] *imidazoles* XVI, XVII, XXII, XXVI (14 g) was obtained from 5-methyl-2-(2-pyrrolidinyl) piperidine (18 g) as a colourless oil b.p. 58–61°/0·15 mm. The fraction was shown to contain three compounds by AGLC which were separated by PGLC as described in the previous case. The third fraction was seen by NMR to contain two isomers (by observing the Me resonance) which were separated by column chromatography on Woelm alumina using petroleum ether 40–60° as eluant for one isomer and methanol for the other.

XVI, b.p. 50–51°/0·06 mm, n_D^{15} 1·5001 (Found: C, 73·31; H, 11·06; N, 15·51. $C_{11}H_{20}N_2$ requires: C, 73·28; H, 11·18; N, 15·54%).

XVII, b.p. 54°/0·08 mm, n_D^{15} 1·4905 (Found: C, 73·17; H, 11·26; N, 15·41. $C_{11}H_{20}N_2$ requires: C, 73·28; H, 11·18; N, 15·54%).

XXII, b.p. 61–62°/0·08 mm, n_D^{15} 1·4947 (Found: C, 73·30; H, 11·37; N, 15·42. $C_{11}H_{20}N_2$ requires: C, 73·28; H, 11·18; N, 15·54%).

XXVI, b.p. 61–62°/0·08 mm, n_D^{15} 1·4928 (Found: C, 73·19; H, 11·17; N, 15·44. $C_{11}H_{20}N_2$ requires: C, 73·28; H, 11·18; N, 15·54%).

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