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

CONFIGURATIONAL AND CONFORMATIONAL STUDIES WITH METHYL SUBSTITUTED PERHYDRODIPYRIDO [1.2-c. 2'.1'-e] IMIDAZOLES

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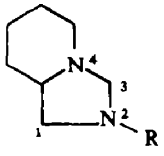
Abstract—A series of Me substituted perhydrodipyrido [1.2-c. 2'.1'-e] imidazoles have been synthesized and their configurations and preferred conformations assigned on the basis of their IR and PMR spectra.

IN THE preceding paper[1] in this series the variation of the geminal coupling constant (J_{gem}*) between the N—CH_2—N protons in octahydro-imidazo [1.5-a] pyridines (I) with the *cis* or *trans* nature of the ring fusion was described. However, this study was complicated by the presence of the 2-alkyl substituent which rendered information regarding the dihedral angle between the 2N lone pair of electrons and the C3 methylene unobtainable. Since one of the ultimate aims of our work is to establish some



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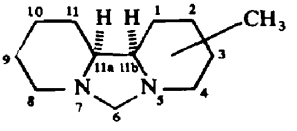

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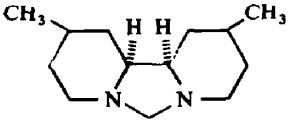

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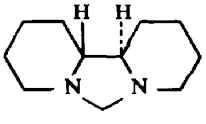

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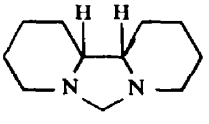


V

empirical relationship between J_{gem} and the dihedral angle between the CH_2 group and the lone pair orbitals on adjacent heteroatoms it seemed of interest to study the PMR spectra of methyl perhydrodipyrido [1.2-c. 2'.1'-e] imidazoles (II) which are free of the complicating factors discussed in connection with work on I.

* Throughout this paper J_{gem} is assumed to be negative.

Synthesis of the methyl substituted perhydrodipyrido[1.2-c.2′.1′-e] *imidazoles.* The monomethylperhydrodipyrido [1.2-c. 2′.1′-e] imidazoles were synthesized by the route shown in Fig. 1. The 2-amino-methylpyridines were converted to the corresponding bromides,[2] and then to the cyanides[3] by well known methods. The 5-ethoxy-1-(methyl-2-pyridyl)1-pentanones were prepared from the 2-cyano-methylpyridines

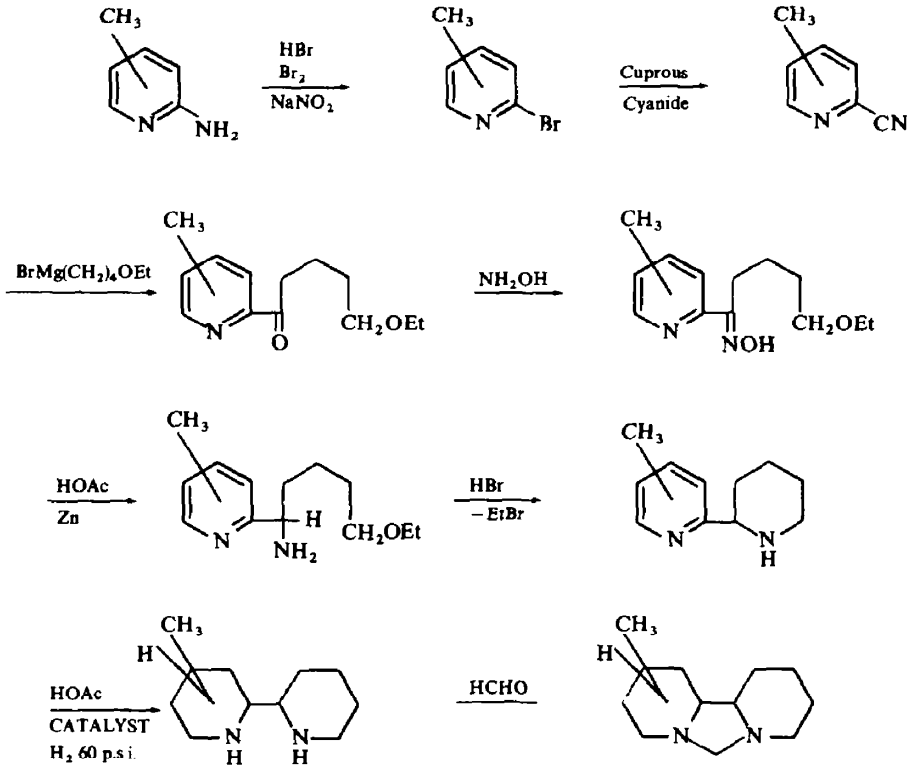


FIG. 1 Synthesis of monomethylperhydrodipyrido [1.2-c. 2′.1′-e] imidazoles.

and the Grignard reagent of 4-ethoxy-1-bromobutane in good yields. The ketones were converted to the corresponding oximes by refluxing with hydroxylamine hydrochloride in absolute alcohol and the crude oximes were readily reduced by zinc dust and glacial acetic acid to give the 1-amino-5-ethoxy-1-(methyl-2-pyridyl) pentanes in good yields. The cyclization of these amines with hydrobromic acid gave the methyl-2-(2-piperidyl) pyridines which were converted to the monomethyl-2,2′-dipiperidyls by catalytic hydrogenation. Attempts to reduce methyl-2-(2-piperidyl) pyridine with sodium and ethanol resulted in tarry products. Catalytic reduction gave all possible isomers of the 3- and 5-methyl substituted 2,2′-dipiperidyls but only two of the 6-methyl-2,2′-dipiperidyls. The addition of aqueous formaldehyde to the dipiperidyl mixtures resulted in the formation of isomeric mixtures of *anti* and *syn*-monomethylperhydrodipyrido [1.2-c. 2′.1′-e] imidazoles II. The mixtures of

isomers were separated by preparative GLC and the percentage of each isomer obtained is shown in Table 1.

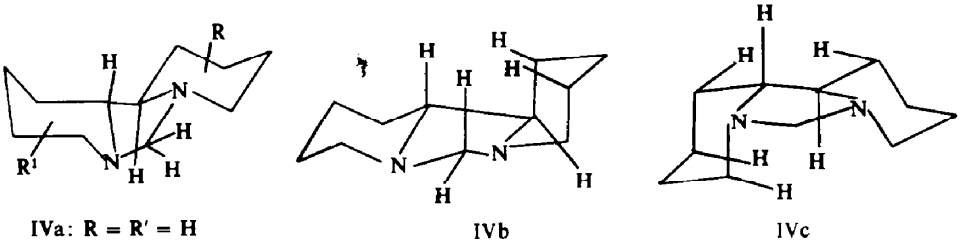
TABLE 1. PERCENTAGE ISOMERS OF THE MONOMETHYLPERHYDRODIPYRIDO [1.2-c. 2'.1'-e] IMIDAZOLES OBTAINED BY ROUTE SHOWN IN FIG. 1

Compound	% Isomers obtained			
1-Methylperhydrodipyrido [1.2-c. 2'.1'-e] imidazoles	10	10	75	5
3-Methylperhydrodipyrido [1.2-c. 2'.1'-e] imidazoles	20	30	45	5
4-Methylperhydrodipyrido [1.2-c. 2'.1'-e] imidazoles	50		50	

The coupling of γ-picoline in the presence of degassed Raney Ni[4] gave 4,4'-dimethyl-2,2'-dipyridyl which on hydrogenation and condensation of the resultant dipiperidyl mixture with formaldehyde gave a mixture of the 2,10-dimethyl-perhydrodipyrido [1.2-c. 2'.1'-e] imidazoles (III) shown by analytical GLC to contain three isomers* in the ratios 50:45:5. The minor isomer was only available in very small quantities and could not be obtained in a pure state.

DISCUSSION

The perhydrodipyrido [1.2-c. 2'.1'-e] imidazoles can exist in a variety of either *cis* or *trans* ring fused conformations because of the presence of the conformationally mobile bridgehead N atoms. Three of the possible conformations of *anti* and *syn* perhydrodipyrido [1.2-c. 2'.1'-e] imidazoles (IV and V) are shown in Figs. 2 and 3



IVa: R = R' = H
VI: R = 2-Me (eq.), R' = 10-Me (eq.)
IX: R = 4-Me (eq.), R' = H
XI: R = 3-Me (eq.), R' = H
XII: R = 3-Me (ax.), R' = H
XV: R = 1-Me (eq.), R' = H
XVI: R = 1-Me (ax.), R' = H

IVb IVc

FIG. 2 Three possible conformations of *anti* perhydrodipyrido [1.2-c. 2'.1'-e] imidazole.

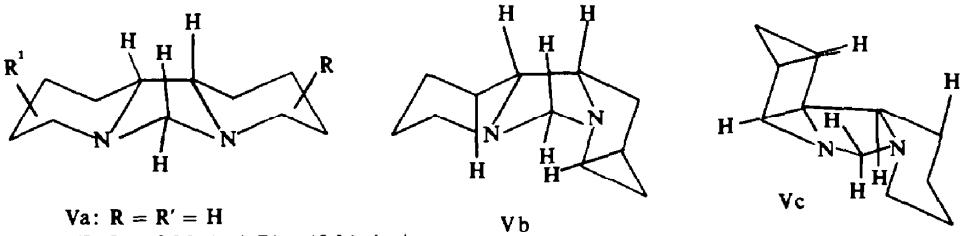
respectively, (assuming chair conformations for the 6-membered rings) and examination of Dreiding models suggests IVa and Va as being the preferred conformation for these isomers.

To assign configurations and preferred conformations to the methyl perhydrodipyrido [1.2-c. 2'.1'-e] imidazoles the following criteria are available:

(a) *Bohlmann's criterion in the IR.* It has been found that in quinolizidines in which

* All the perhydrodipyridoimidazoles exist either as racemates or in certain cases optically inactive forms.

the lone pair of electrons on nitrogen is *trans* to at least two axial hydrogens on adjacent C atoms a set of strong bands appear in the 2800–2600 cm^{-1} region of the IR.[5] Thus the appearance of these bands in the IR spectrum of a perhydrodipyrido [1.2-c. 2′.1′-e] imidazole is evidence for the presence of a *trans* ring fused conformation



Va

Vb

Vc

Va: R = R′ = H
VII: R = 2-Me (eq.), R′ = 10-Me (eq.)
VIII: R = 2-Me (ax.), R′ = 10-Me (eq.)
X: R = 4-Me (eq.), R′ = H
XIII: R = 3-Me (eq.), R′ = H
XIV: R = 3-Me (ax.), R′ = H
XVIII: R = 1-Me (ax.), R′ = H

FIG. 3 Three possible conformations of *syn* perhydrodipyrido [1.2-c. 2′.1′-e] imidazole.

and, for example, a compound existing in the *trans anti trans* conformation IVa should exhibit stronger Bohlmann bands than one in the *trans anti cis* conformation IVb.

(b) *The geminal coupling constants of the* N—CH_2—N *methylene group.* Studies of J_{gem} for methylene groups adjacent to nitrogen has proved a reliable guide to conformation[6] the most positive values being observed when one of the C—H bonds of the methylene group is parallel to the nitrogen lone pair orbital.[7] The variation of J_{gem} with the dihedral angle between the nitrogen lone pair of electrons and the C6—H bond should therefore provide conformational information regarding these compounds, since as can be seen from Figs 2 and 3 there are differences in the N—CH_2—N geometry in the conformations shown.

(c) *Chemical shift data for protons adjacent to nitrogen.* Hamlow *et al.*[8] have shown that in quinolizidine the axial protons adjacent to nitrogen give rise to signals at higher field than the corresponding equatorial protons and it has been fairly generally accepted[9, 6] that this selective shielding is due to the presence of the lone pair of electrons on the N atom.

The validity of this assumption has recently been questioned by Robinson,[10] but whatever the cause* of the pronounced shielding of an axial proton *anti*-coplanar to the lone pair in *trans*-fused systems with nitrogen at a bridgehead the chemical shifts of such protons are still of great use in conformational studies with these systems, as has been demonstrated in previous papers.[6]

(d) C-*Methyl proton resonance doublet in the PMR.* It has been shown by Schofield, Katritzky *et al.*[3] that the position of the centre of the methyl doublet in methylquinolizidines is at lower field for axial Me groups than for the corresponding equatorial groups. This is at variance with some observations on the absorption of axial

* In a previous study[11] of 6-substituted perhydrodipyrido [1.2-c. 2′.1′-e] imidazoles use was made of the Hamlow theory for configurational assignments but the same conclusions would have been reached using Robinson's argument.

and equatorial Me groups in different systems and the subject has been discussed and leading references given by these authors.[3,12] The apparent coupling constant J_{CH-Me} was also used in studying the stereochemistry of the methylquinolizidines and it was found that this apparent coupling constant was less for equatorial than for axial Me groups. This criterion has been discussed thoroughly elsewhere.[3] Although caution must be exercised in applying these criteria one feels intuitively that the same type of variation in the position of the methyl doublet with the axial or equatorial orientation of the Me group in methylquinolizidines should be observed in the methylperhydro dipyrido [1.2-c. 2'.1'-e] imidazoles.

RESULTS

syn *and* anti *Perhydrodipyrido* [1.2-c. 2'.1'-e] *imidazoles and the* 2.10-*dimethyl substituted compounds.* The evidence for the assignment of the *anti* and *syn* configurations to the two racemic perhydrodipyrido [1.2-c. 2'.1'-e] imidazoles (IV and V) was described in a previous paper[11] and the preferred conformations IVa and Va respectively were assumed for these isomers. However, the possibility of the presence of conformations with *cis* ring fusions (Figs 2 and 3) in equilibrium with the *trans anti trans* and *trans syn trans* conformations cannot be dismissed solely on the basis of the IR and PMR spectra of compounds IV and V.

In view, therefore, of the possible existence of equilibrium mixtures for IV and V it was decided to study the spectra of the 2,10-dimethylperhydrodipyrido [1.2-c. 2'.1'-e] imidazoles (III) since the position of conformational equilibrium in these dimethyl substituted compounds would be quite different from that in the unsubstituted compounds. Both major isomers, the first off the gas chromatography column being a liquid and the second a solid, showed intense Bohlmann's bands, indicating predominantly *trans*-fused ring systems, the intensity and shape of the bands being almost identical to those shown by *anti* and *syn* perhydrodipyrido [1.2'-c. 2'.1'-e] imidazoles respectively. The 100 Mc/s spectrum of the liquid isomer was almost identical to that of *anti* perhydrodipyrido [1.2-c. 2'.1'-e] imidazole (IV) with a singlet at 6·38 τ due to the protons of the N—CH_2—N methylene group, a two proton "doublet" at 7·1 τ ($J_{4a4e} = -10{\cdot}5$ c/s, $J_{4e3a} = 4$ c/s and $J_{4e3e} = 2$ c/s) due to the C4 and C8 equatorial protons adjacent to nitrogen, a four proton multiplet between 7·54 and 7·96 τ for the axial protons adjacent to nitrogen, a broad complex multiplet between 8·1 and 8·9 τ due to the ring protons, and a single methyl doublet at 9·05 τ ($J = 5{\cdot}8$ c/s). This isomer was therefore assigned the *trans anti trans* stereochemistry VI as this provides a symmetrical environment for the C6 methylene protons.

The solid isomer also showed remarkable similarity to its parent analogue in its 100 Mc/s PMR spectrum. The PMR spectrum showed an AB quartet ($J = -3{\cdot}6$ c/s) arising from the N—CH_2—N methylene protons with chemical shifts 6·2 and 6·58 τ, which can be assigned to the C6 pseudo equatorial and pseudo axial protons respectively. A six proton complex multiplet was observed between 6·95 and 7·68 τ and a two proton "doublet" at 7·06 τ was distinguishable. This doublet is characteristic of N—CH equatorial protons and first order analysis gave $J_{4a4e} = J_{8a8e} = -13$ c/s, $J_{4e3a} = 4$ c/s and $J_{4e3e} = 2$ c/s, these values being fairly typical of a piperidine ring in a chair conformation. The remaining ring protons appeared as a multiplet between 8·4–9·0 τ which converged to a sharp peak at 8·63 τ and a single Me doublet was observed at 9·1 τ ($J = 5{\cdot}8$ c/s). The solid isomer was therefore assigned the *syn*

configuration and conformation VII. An alternative structure consistent with these observations has a *trans syn trans* stereochemistry with both Me groups axial, however this can be ruled out after a consideration of the method of preparation of these compounds. Since the classical paper of Linstead *et al.*[13] it has been generally assumed that catalytic hydrogenation proceeds by *cis* addition of hydrogen to the least hindered side of the molecule and so one would expect the reduction of 4,4′-dimethyl-2,2′-dipyridyl followed by reaction of the resultant dipiperidyl with formaldehyde to give VI and VII as the predominant products.

Apart from the presence of the methyl doublet, the PMR spectra of V and VII were practically identical. In addition isomer VII showed less intense Bohlmann's bands than VI similar to the decrease in intensity observed in the case of the corresponding perhydrodipyrido [1.2-c. 2′.1′-e] imidazoles. This greater intensity of the 2800 cm^{-1} band in the two compounds having *trans anti trans* stereochemistry and the general shape of the Bohlmann's bands can therefore be used as an aid in making stereochemical assignments in this series. The near identity in PMR spectra and in the appearance of Bohlmann's bands in the two pairs of isomers is therefore strong evidence against the existence of appreciable amounts of *cis* fused ring conformations in equilibrium with conformations IVa and Va. In addition PMR spectra were observed not to vary between 33° and −60°. This supports the conclusions reached that the four perhydrodipyrido [1.2-c. 2′.1′-e] imidazoles so far discussed exist in predominantly *trans* fused ring conformations IVa, Va, VI and VII.

It was observed that the two compounds with *trans anti trans* stereochemistry showed in their PMR spectra a broadened multiplet for the ring protons whereas the two *syn* compounds showed a multiplet converging to a sharp peak at approximately

TABLE 2. COMPARISON OF MAIN FEATURES OF PMR AND IR SPECTRA OF *anti* AND *syn* PERHYDRODIPYRIDO [1.2-c. 2′.1′-e] IMIDAZOLES (IV AND V) AND THE 2.10 DIMETHYL SUBSTITUTED DERIVATIVES (VI AND VII)

Compound	PMR spectra				IR spectra Bohlmann region†
	C6 Methylene protons			Shape of signal due to ring protons	
	Chemical shift (τ)		Coupling constant		
IV	6·38		—	Broad multiplet	2800 cm^{-1} (ε* 218)
VI	6·39		—	Broad multiplet	2800 cm^{-1} (ε* 214)
V	6·14	6·59	−3·6 c/s	Multiplet converging to sharp peak	2800 cm^{-1} (ε* 147)
VII	6·2	6·58	−3·6 c/s	Multiplet converging to sharp peak	2800 cm^{-1} (ε* 148)

* Apparent extinction coefficient.
† For other peaks, see Fig. 5.

8·6 τ, and regularities such as these were utilised in making the stereochemical assignments to the compounds discussed in the rest of this paper. A summary of these important features are given in Table 2. (See also Figs. 4 and 5 and Table 4).

A third 2,10-dimethylperhydrodipyrido [1.2-c. 2'.1'-e] imidazole was obtained in only small amounts, but from the general appearance of its PMR (Table 3) and IR spectra it has been tentatively assigned the configuration and preferred conformation VIII.

Monomethylperhydrodipyrido (1.2-c. 2'.1'-e] *imidazoles*. Having established some empirical correlations between stereochemistry and IR and PMR spectra for IV, V and two of the isomers of III, the monomethyl compounds II were then examined.

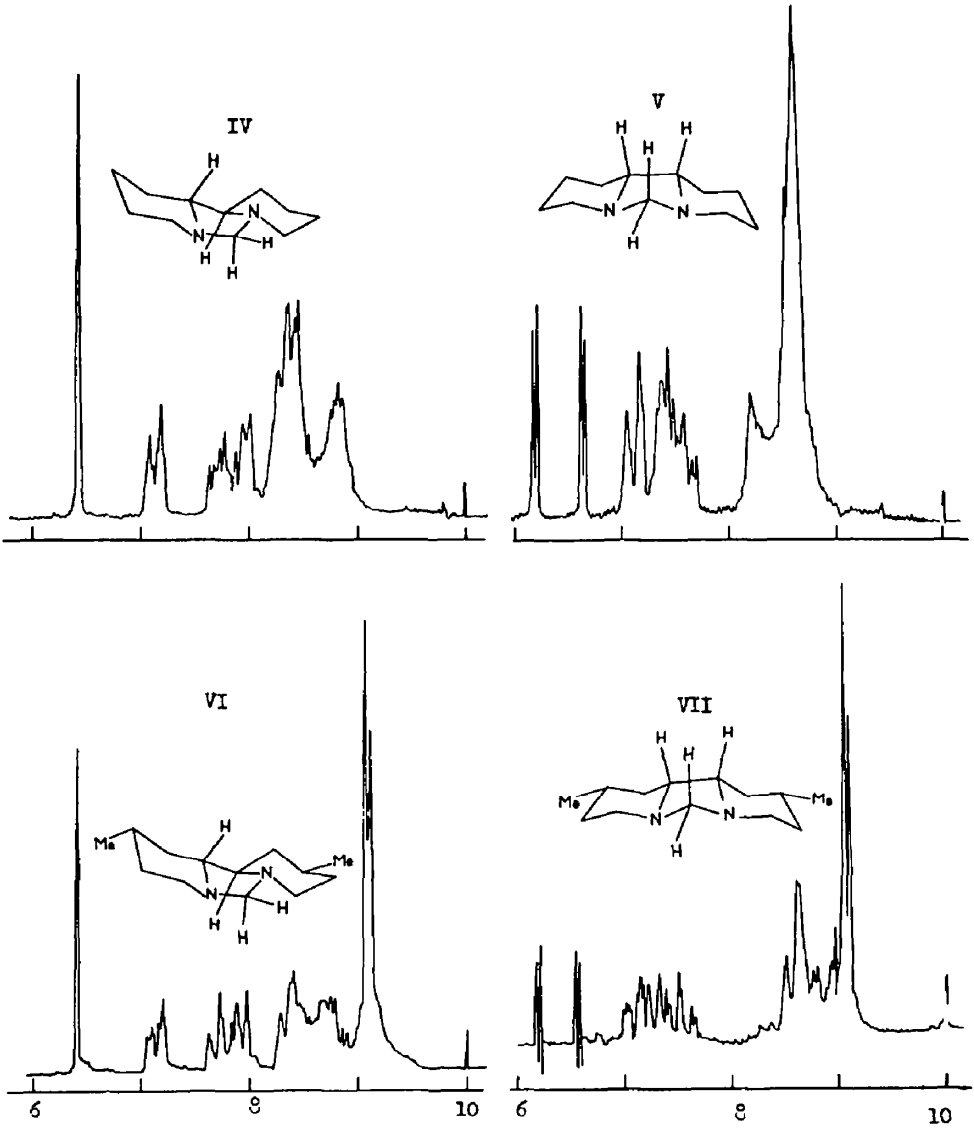


FIG. 4 PMR spectra of the perhydrodipyrido [1.2-c. 2'.1'-e] imidazoles (IV, V, VI, VII).

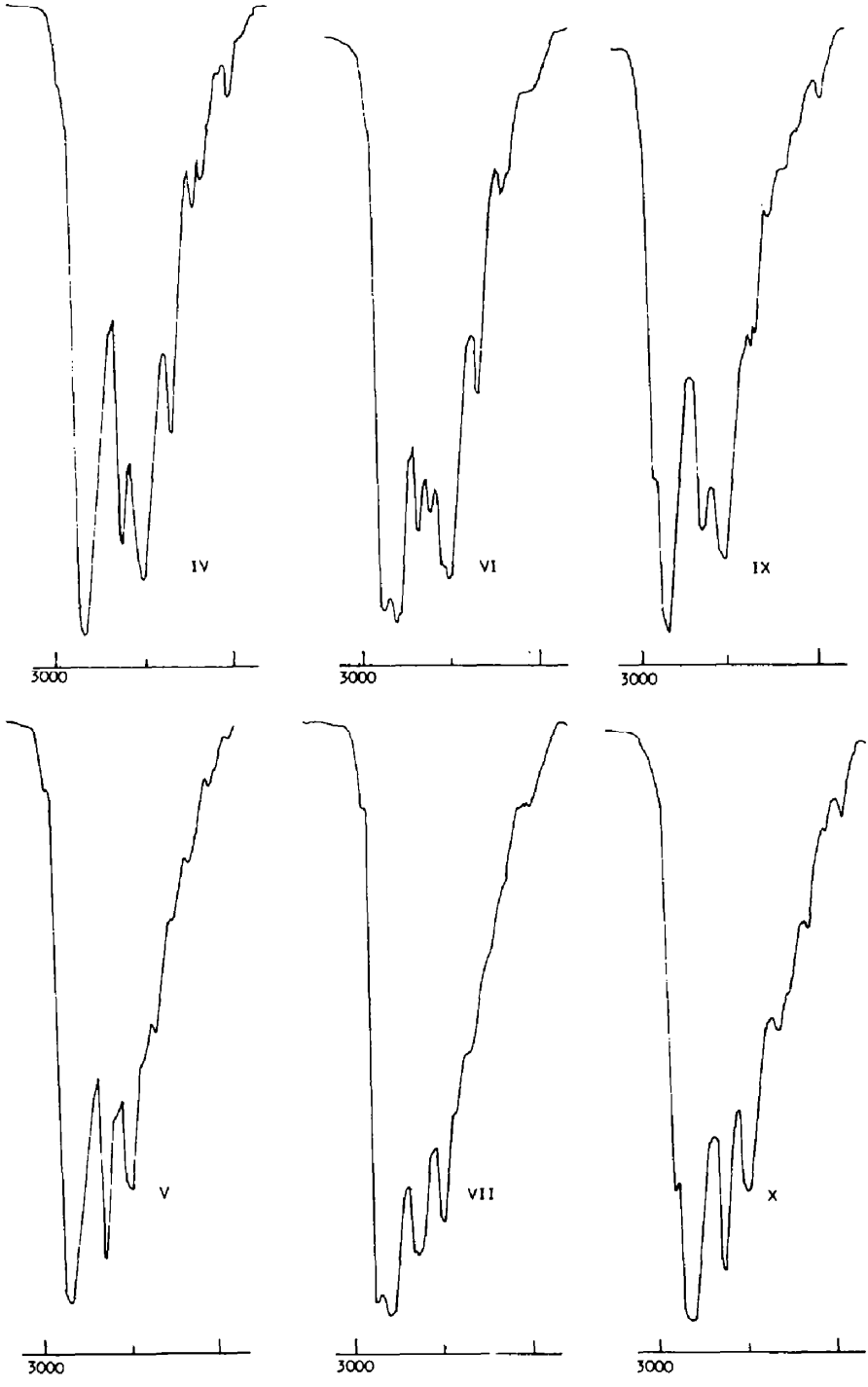


FIG. 5 The 3000–2800 cm^{-1} region of the IR spectra of some *anti* (IV, VI, IX) and *syn* (V, VII, X) perhydrodipyrido [1.2-c. 2'1'-e] imidazoles.

TABLE 3. PMR SPECTRA OF PERHYDRODIPYRIDO[1.2-c. 2′.1′-e]IMIDAZOLES

Compound	C6 Methylene protons			Protons adjacent to nitrogen		Centre of methyl doublet and apparent J				Chemical shift (τ) of ring Protons	Shape of the signal due to Ring Protons
						Equatorial Me		Axial Me			
	J (c/s)	C6 Pseudo Equatorial τ	C6 Pseudo Axial τ	C4, C8 Equatorial	C4, C8, C11a, C11b Axial	τ	J (c/s)	τ	J (c/s)		
IV[a]		6·38	6·38	7·06	7·46–8·05					8·1–9·0	B.M.
V[a]	−3·6	6·14	6·59		6·86–7·75					8·0–8·9	M.C.P.8·55 τ
VI[a]		6·38	6·38	7·10	7·54–7·96	9·05	5·8			8·1–8·9	B.M.
VII[a]	−3·6	6·20	6·58		6·95–7·68	9·10	5·8			8·4–9·0	M.C.P.8·63 τ
VIII[b]*	−4·0	6·08	6·45		6·7–7·6	9·30	6·0	8·93	6·0	8·1–8·8	M.C.P.8.6. τ
IX[a]	−3·8	6·27	6·37	7·08	7·46–7·96	8·98	6·0			8·1–8·9	B.M.
X[a]	−4·0	6·10	6·69	7·06	7·2–7·8	9·00	6·3			8·1–8·84	M.C.P.8·6. τ
XI[b]		6·35	6·35	7·10		9·10	6·0			7·4–8·8	B.M.
XII[b]	−4·0	6·3	6·50	7·05	7·3–8·0			8·95	6·6	8·0–8·8	B.M.
XIII[b]*	−3·5	6·12	6·56		6·9–7·8	9·20	5·6			8·0–8·9	M.C.P.8·55 τ
XIV[b]	−4·5	6·23	6·70		6·9–7·9			8·96	6·5	8·0–8·8	M.C.P.8·5 τ
XV[b]		6·38	6·38	7·09	7·35–8·0	9·05	5·3			8·0–8·8	B.M.
XVI[b]		6·40	6·40	7·08	7·4–8·0			9·01	6·8	8·0–8·8	B.M.
XVII[a]	−8·0	6·18	7·18	6·96				8·95	6·6	7·8–8·8	B.M.
XVIII[a]	−3·4	6·20	7·16	7·00	7·4–7·95			8·9	6·0	8·0–8·8	M.C.P.8·5 τ

B.M. = Broad multiplet. M.C.P. = Multiplet converging to peak at ...

* Spectrum of slightly impure isomer.

[a] 100 Mc/s spectrum. [b] 60 Mc/s spectrum.

TABLE 4. 2800–2500 cm^{-1} REGION OF THE IR OF PERHYDRODIPYRIDO [1.2-c. 2'.1'-e] IMIDAZOLES AND METHYL DERIVATIVES

Compound	*Anti* isomers			*Syn* isomers		
		cm^{-1}	ε^*		cm^{-1}	ε^*
Perhydrodipyrido [1.2-c.2'.1'-e] imidazoles	IV	2800	218	V	2800	147
		2742	103		2745	70
		2685	38		2707	42
		2617	17		2680	29
					2628	14
2,10-Dimethylperhydrodipyrido [1.2-c. 2'.1'-e] imidazoles	VI	2800	214	VII	2800	148
		2740	83		2747	72
		2680	32		2710	46
		2612	13		2617	15
4-Methylperhydrodipyrido [1.2-c. 2'.1'-e] imidazoles	IX	2800	186	X	2800	129
		2743	69		2731	63
		2705	38		2668	35
		2687	29		2590	16
		2646	16			
3-Methylperhydrodipyrido [1.2-c. 2'.1'-e] imidazoles	XI	2800	181	XIII	2800	149
		2749	92		2743	78
		2677	29		2680	31
		2616	16		2617	11
	XII	2800	183	XIV	2800	152
		2740	87		2755	73
		2675	31		2683	33
		2611	18		2615	16
1-Methylperhydrodipyrido [1.2-c. 2'.1'-e] imidazoles	XVI	2800	189	XVII	2780	123
		2740	84		2740	62
		2682	40		2680	30
		2607	23			
	XV	2800	192	XVIII	2800	160
		2740	83		2713	103
		2682	41		2616	36
		2607	20		2530	10

* In Table 4, apparent extinction coefficients are given. These figures are only given to provide a clearer picture of the IR spectra than is given by the description "small, medium and weak" and no more significance is intended to be attached to these numbers.

4-Methylperhydrodipyrido [1.2-c. 2'.1'-e] *imidazoles* (IX *and* X). As can be seen from Table 1, only two isomers of this compound were obtained but from a consideration of their method of preparation and studying Dreiding models it would seem reasonable to assume that these possess the *trans anti trans* and the *trans syn trans* stereochemistry with equatorially situated Me groups (IX and X). The presence of equatorial Me groups in both isomers seems certain since the PMR spectra (Table 3) showed only one proton multiplet at ca 7·1 τ, this being the usual chemical shift for equatorial protons adjacent to nitrogen.[14]

The first isomer off the gas chromatograph column showed in its 100 Mc/s PMR spectrum an AB quartet for the N—CH_2—N protons having $J_{gem} = -3{\cdot}8$ c/s and

chemical shifts of 6·27 and 6·37 τ. A complex four proton multiplet between 7·46 and 7·96 τ was assigned to the four axial protons adjacent to nitrogen while the other ring protons gave rise to a broad multiplet between 8·1 and 8·9 τ. The Me group resonance is centred at 8·98 τ (J = 6 c/s). The IR spectrum (Fig. 5) showed Bohlmann's bands of intensities (Table 4) corresponding to an isomer of the *trans anti trans* stereochemistry (IX).

The 100 Mc/s PMR spectra of the second isomer showed a quartet (J = −4 c/s) with chemical shifts of 6·10 and 6·69 τ for the N—CH_2—N protons and the five proton complex multiplet between 6·9 and 7·8 τ was assigned to the protons adjacent to nitrogen. The ring protons absorbing between 8·1–8·84 τ converged to a sharp peak at 8·6 τ and the methyl doublet was centred at 9·0 τ (J = 6·3 c/s). The 2800–2600 cm^{-1} region of the IR spectrum (Fig. 5, Table 4) was indicative of the *trans syn trans* stereochemistry (X) and the shape of the ring proton multiplet in the PMR spectrum supports this. The N—CH_2—N protons are in a much more nearly equivalent environment in IX than in X and this is reflected in the much smaller difference in chemical shift between these protons in the first isomer (0·1 ppm) than in the second (0·59 ppm), (cf. VI and VII).

3-*Methylperhydrodipyrido* [1.2-c. 2′.1′-e] *imidazoles* (XI, XII, XIII, *and* XIV). The mixture of the four possible isomers was separated into two fractions by PGLC. Column chromatography of the first fraction gave two pure isomers and both of these were assigned the *trans anti trans* stereochemistry on the basis of their PMR spectra (Table 3) and IR spectra (Table 4). Both isomers showed the more intense 2800 cm^{-1} band in the IR together with the broad ring proton multiplet in their PMR spectra, features characteristic of the *trans anti trans* stereochemistry. The first isomer off the alumina column showed a singlet for the N—CH_2—N protons and the Me resonance appeared as a doublet centred at 9·1 τ (J = 6 c/s) whereas the second isomer gave a N—CH_2—N quartet (J = −4 c/s, chemical shifts 6·3 and 6·5 τ) and the Me resonance at lower field, 8·95 τ (J = 6·6 c/s). Since the N—CH_2—N protons are in a slightly more asymmetrical environment in XII than in XI one would expect XII to correspond to the isomer showing the AB quartet for the C6 methylene protons and this observation together with the Me resonance data lead to the assignment of the structure XI (equatorial Me) to the first isomer and XII (axial Me) to the second isomer off the column.

A study of the PMR spectrum of the first fraction from PGLC (by comparison of respective intensities of the Me resonance) showed the presence of approximately equal amounts of XI and XII. Analytical GLC of the second fraction showed a 9:1 mixture of the other two isomers which were separated by column chromatography. The minor isomer could not be obtained pure and was contaminated with approximately 20% of the major isomer.

The PMR spectrum of the major isomer showed an AB quartet (J_{gem} = −4·5 c/s) with chemical shifts of 6·23 and 6·7 τ arising from the C6-methylene protons. The six proton complex multiplet between 6·9 and 7·9 τ was assigned to the protons adjacent to nitrogen with the C4 and C8 equatorial protons appearing as a "doublet" at 7·05 τ. The ring protons appeared as a multiplet between 8·0 and 8·8 τ converging to a sharp peak at 8·5 τ forming the characteristic pattern of compounds with the *syn* configuration. The Me doublet centred at 8·95 τ (J = 6·5 c/s) shows similar PMR parameters to those observed for the axial Me in XII and this together with the IR

data leads one to propose XIV with an axial methyl group as being the preferred conformation of the major isomer.

The PMR spectrum (Table 3) of the minor isomer showed an AB quartet for the N—CH_2—N protons ($J_{gem} = -3{\cdot}5$ c/s, chemical shift 6·12 and 6·56 τ). The signals for the protons next to nitrogen appeared as a six proton multiplet between 6·9 and 8·0 τ and the ring protons gave rise to a multiplet between 8·0 and 8·9 τ characteristic of isomers with the *syn* configuration. Additional evidence for the *syn* configuration is provided by the appearance of the 2800–2600 cm^{-1} region of the IR (Table 4) and the very similar chemical shifts of the C6 methylene protons in this isomer and in V. This indicates XIII to be the preferred conformation for the minor isomer, with the Me group in an equatorial position confirmed by the high field position of the centre of the doublet (9·2 τ) and its small apparent coupling constant ($J = 5{\cdot}6$ c/s).

1-*Methylperhydrodipyrido* [1.2-c. 2'.1'-e] *imidazoles* (XV, XVI, XVII *and* XVIII). Condensation of the 3-methyl-2,2'-dipiperidyls with formaldehyde gave an unexpected 10:10:75:5 distribution of the four possible isomers (arranged in order of increasing retention times) which were separated by PGLC. The two isomers of shortest retention times gave almost identical PMR spectra. Both showed singlets for the C6-methylene protons indicating rather similar environments for these two protons, broad multiplets for the ring protons, and intense bands at 2800 cm^{-1} in the IR, all features suggestive of the *trans anti trans* stereochemistry. The first isomer showed a larger apparent coupling constant ($J_{CH—Me} = 6{\cdot}8$ c/s) than did the second isomer (5·3 c/s) and on these grounds the stereochemistry XVI (axial Me) and XV (equatorial Me) were assigned to these isomers respectively.

The PMR spectrum of the third and major isomer showed a quartet ($J = -3{\cdot}4$ c/s) for the C6 methylene protons, a "doublet" at 7·0 τ for the C4 and C8 equatorial

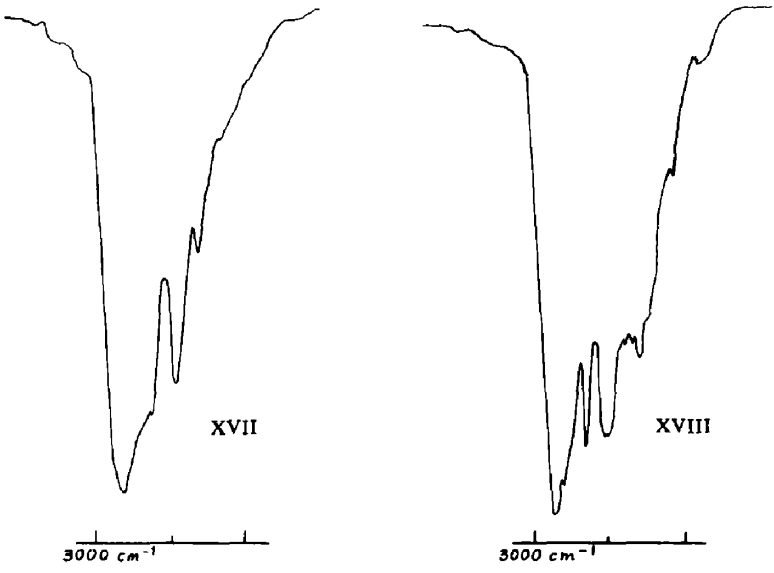
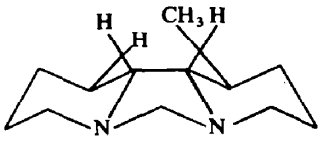


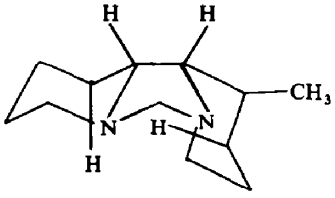
FIG. 6 The 3000–2800 cm^{-1} region of the IR spectra of the perhydrodipyrido [1.2-c. 2'.1'-e] imidazoles (XVIII and XVII).

protons, and a complex four proton multiplet between 7·4 and 7·95 τ for the axial protons adjacent to N. The ring protons multiplet converged to a sharp peak at 8·5 τ (*syn* configuration) and the Me resonance parameters are consistent with an axially situated Me group. The *trans syn trans* stereochemistry with an axial Me group (XVIII) was assigned to this isomer on the spectral evidence and also since this isomer should be one of the major ones produced[13] by the reaction scheme shown in Fig. 1. It is interesting to note that this isomer showed unusually broad Bohlmann's bands in the IR (Fig.6).

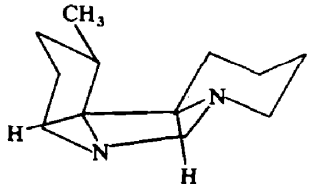
The PMR spectrum of the fourth isomer, which could only be obtained in small quantities, showed a strikingly different AB quartet for the C6 methylene protons



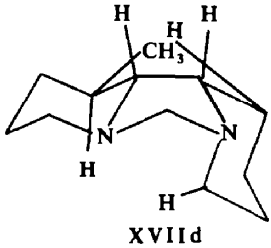
XVIIa



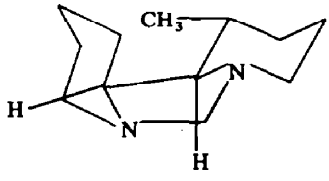
XVIIb



XVIIc



XVIId



XVIIe

FIG. 7 Conformations of *trans*, 1H, 11b*H*-1-methyl-*syn* perhydrodipyrido [1.2-c. 2'.1'-e] imidazole.

with the unusually negative J_{gem} of −8 c/s. A two proton "doublet" was observed at 6·96 τ and the remaining ring protons appeared as a broad multiplet between 7·8 and 8·8 τ. The Me resonance was centred at 8·95 τ (J = 6·6 c/s). The IR spectrum of this minor isomer which must, *per exclusionem*, possess the *syn* configuration and a *trans* arrangement of the C1 and C11b hydrogens, showed a marked reduction in the area of Bohlmann's bands (Fig. 6) consistent with a conformation possessing one *cis*-fused and one *trans*-fused ring junction. The rest of the IR spectrum was quite

different to that of all the preceeding isomers. Fig. 7 shows all the possible conformations of *trans*-1H,11bH-1-methyl-*syn*-perhydrodipyrido [1.2-c. 2′.1′-e] imidazole (assuming only chair conformations for the 6-membered rings), possessing one *trans* and one *cis* ring fusion. The Dreiding model of conformation XVII shows a severe non-bonded interaction between the Cl Me group and the C11 equatorial hydrogen and conformation XVIId can also be ruled out since the severe interaction between the C1 equatorial Me and C11 equatorial hydrogen is still present.

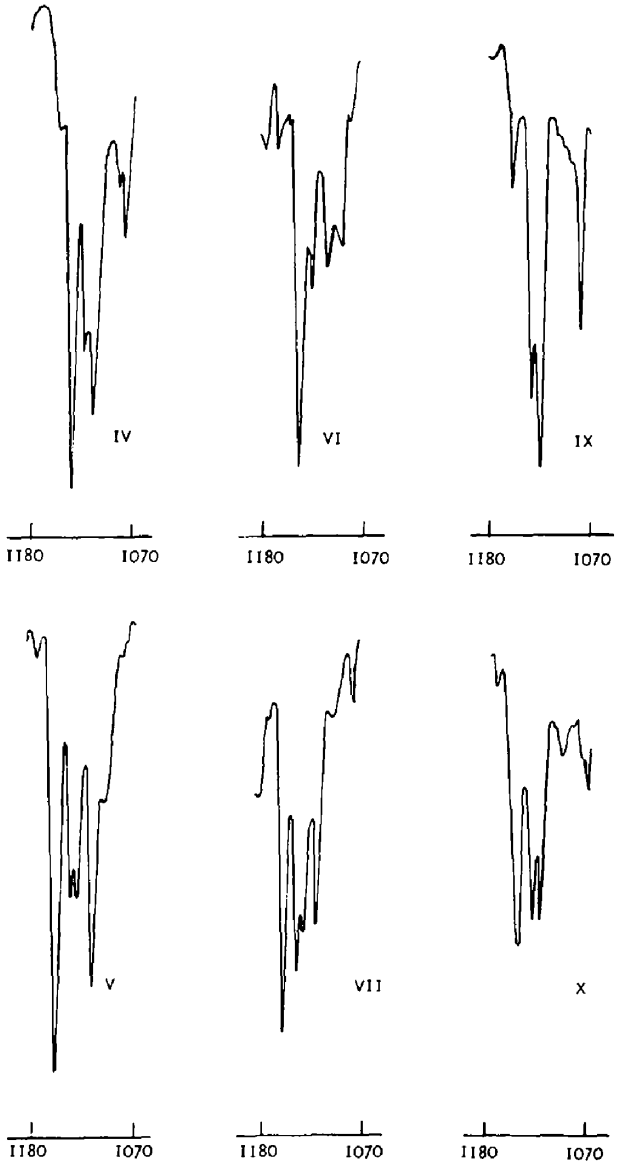


FIG. 8 The 1070–1180 cm^{-1} region of the IR spectra of some *anti* (IV, VI, IX) and *syn* (V, VII, X) perhydrodipyrido [1.2-c. 2′.1′-e] imidazoles.

A comparison of the N—CH_2—N geometry in XVIIc and XVIIe with that in the *trans anti trans* compounds previously discussed would lead one to expect a similar J_{gem} (i.e. ca. −4 c/s) to be observed for this isomer if it existed in these conformations. However, in conformation XVIIb the lone pair of electrons on the N5 atom bisects the C6 methylene group and should therefore not contribute[7,15] to the value of J_{gem} thus giving rise to a more negative J_{gem} as is observed. On the basis therefore of the reduced intensity of Bohlmann's bands and of the value of −8 c/s for the J_{gem} of the C6 methylene group, conformation XVIIb is assigned to the fourth isomer.

Having made configurational and conformational assignments to fifteen of the perhydrodipyrido [1.2-c. 2'.1'-e] imidazoles the fingerprint region of the IR was examined for features which may be characteristic of the *syn* and *anti* compounds. Distinct differences were observed in the 1180–1080 cm^{-1} region with compounds assigned the *trans anti trans* stereochemistry having a smaller number of absorbances than the corresponding *trans syn trans* isomers. This criterion fitted the assignments previously made without exception and a selection of the infrared spectra of this region for some pairs of isomers is shown in Fig. 8. It is also interesting to note that gas chromatography of all the compounds examined showed that the *anti* isomers in the mixtures always had shorter retention times than the *syn* isomers.

EXPERIMENTAL

The PMR spectra were recorded as solns in $CDCl_3$ on a Perkin–Elmer R10 60 MHz spectrometer using TMS as internal standard or where indicated on a Varian HA-100 MHz spectrometer at Imperial College of Science and Technology. IR spectra were measured as 0·2M solns in $CDCl_3$ on a Perkin–Elmer 457 spectrophotometer. Mixtures of isomers were separated by preparative GLC using an Aerograph Autoprep gas chromatograph. Elemental analysis were carried out by Dr. F. Pascher and E. Pascher, Microanalytical Laboratory, Bonn, Germany and by Reading University. M.ps are uncorrected.

Perhydrodipyrido [1.2-c. 2'.1'-e] *imidazoles* IV *and* V. These were prepared as previously described.[11]

Synthesis of monomethylperhydrodipyrido[1.2-c. 2'.1'-e] *imidazoles.* These were prepared by the route shown in Fig. 1. The 2-bromo-methylpyridines were prepared from the 2-amino-methylpyridines by the method of Leonard and Ryder[2a] for the 3- and 5-methyl-2-amino-pyridines and Adams and Miyano[2b] for the 2-amino-6-methylpyridine. The 2-cyano-methylpyridines were prepared from the 2-bromo-methyl-pyridines by the method of Katritzky *et al.*[3]

Preparation of the 5-ethoxy-1-(methyl-2-pyridyl)1-pentanones

General procedure. A soln of the Grignard reagent, prepared from 1-bromo-4-ethoxy-butane (75 g) and Mg (14 g), in dry ether (400 ml) was allowed to drop slowly into a vigorously stirred soln of a 2-cyano-methylpyridine (54 g, 0·45 mole) in dry ether (400 ml). The reaction mixture was stirred overnight, and the addition product so formed was destroyed with concentrated HCl (70 ml) and water (50 ml). The soln was basified with NH_4OH, the ether layer separated, and the basic layer extracted twice more with ether (200 ml). The combined ether extracts were dried, the ether evaporated, and the residual oil was distilled under reduced press.

5-Ethoxy-1-(3-methyl-2-pyridyl)1-pentanone (50 g, 51%) was prepared from 2-cyano-3-methyl-pyridine (54 g, 0·45 mole) as a yellow oil, b.p. 120–122°/0·8 mm, n_D^{15} 1·5061 (Found: C, 70·84; H, 8·71. $C_{13}H_{19}NO_2$ requires: C, 70·55; H, 8·65%).

5-Ethoxy-1-(5-methyl-2-pyridyl)1-pentanone (50 g, 51%) was obtained from 2-cyano-5-methyl-pyridine (54 g, 0·45 mole) as a yellow oil, b.p. 124–126°/0·55 mm, n_D^{15} 1·5044 (Found: C, 70·71; H, 8·64. $C_{13}H_{19}NO_2$ requires: C, 70·55; H, 8·65%).

5-Ethoxy-1-(6-methyl-2-pyridyl)1-pentanone (54 g, 53%) was prepared from 2-cyano-6-methyl-pyridine (54 g, 0·45 mole) as a yellow oil, b.p. 116–117°/0·1 mm, n_D^{15} 1·5027 (Found: C, 70·63; H, 8·71. $C_{13}H_{19}NO_2$ requires: C, 70·55; H, 8·65%).

1-Amino-5-ethoxy-1-(methyl-2-pyridyl)pentanes

General procedure. A soln of 90% alcohol (500 ml), hydroxylamine hydrochloride (35 g) and a 5-ethoxy-1-(methyl-2-pyridyl)1-pentanone (50 g) was refluxed overnight and the alcohol was removed *in vacuo* to leave a thick syrup. Water (50 ml) and enough K_2CO_3 to neutralize the soln were added and the oxime extracted with ether (150 ml). The ether extract was dried and the ether evaporated. The crude oxime could not be crystallized or distilled and was used without further purification.

The crude oxime (50 g) was dissolved in 95% alcohol (500 ml), Zn dust (250 g) and glacial AcOH (250 ml) were added alternately in small amounts over a period of 2 hr. During the addition, the temp of the reaction was kept below 50°. After 3 hr the excess Zn and zinc acetate was filtered off and washed with cold EtOH. The EtOH was evaporated, the residual oil basified with 30% NaOH aq and the oily amine liberated was extracted with ether (3 × 100 ml). The combined ether extracts were dried and evaporated and the residual oil was distilled.

1-*Amino-5-ethoxy-1-(3-methyl-2-pyridyl)pentane* (33 g, 68%) was obtained from 5-ethoxy-1-(3-methyl-2-pyridyl)1-pentanone (48 g, 0·215 mole) as a colourless oil, b.p. 84–85°/0·1 mm, n_D^{15} 1·5083 (Found: C, 70·45; H, 10·21; N, 12·48. $C_{13}H_{22}N_2O$ requires: C, 70·23; H, 9·97; N, 12·60%).

1-*Amino-5-ethoxy-1-(5-methyl-2-pyridyl)pentane* (35 g, 71%) was prepared from 5-ethoxy-1-(5-methyl-2-pyridyl)1-pentanone (50 g, 0·22 mole) as a colourless oil, b.p. 68°/0·2 mm, n_D^{15} 1·5070 (Found: C, 70·34; H, 10·13; N, 12·31. $C_{13}H_{22}N_2O$ requires: C, 70·23; H, 9·97; N, 12·60%).

1-*Amino-5-ethoxy-1-(6-methyl-2-pyridyl)pentane* (34 g, 67%) was obtained from 5-ethoxy-1-(6-methyl-2-2-pyridyl)1-pentanone (50 g, 0·22 mole) as a colourless oil, b.p. 90°/0·1 mm, n_D^{15} 1·5067 (Found: C, 71·66; H, 10·16; N, 11·87. $C_{13}H_{22}N_2O$ requires: C, 70·23; H, 9·97; N, 12·60%).

Methyl-2-(2-piperidyl)pyridines

General procedure. A soln of a 1-amino-5-ethoxy-1-(methyl-2-pyridyl)pentane (45 g) and 48% HBr (300 ml) in a flask fitted with a vertical 50 cm air condenser, the upper end of which was fitted to a downward pointing coil condenser, was heated until the EtBr formed during the cyclization just distilled over and the heating continued until the theoretical amount of EtBr had been collected. The reaction mixture was evaporated to ¼ bulk and then basified with 30% NaOH aq. The oily layer was extracted with ether (3 × 100 ml), and the extracts were combined, dried and evaporated and the residual oil distilled under reduced press.

3-*Methyl-2-(2-piperidyl)pyridine* (24 g, 66%) was prepared from 1-amino-5-ethoxy-1-(3-methyl-2-pyridyl)pentane (45 g, 0·25 mole) as a colourless oil, b.p. 90–91°/0·35 mm, n_D^{15} 1·5386 (Found: C, 74·68; H, 9·48; N, 16·27. $C_{11}H_{16}N_2$ requires: C, 74·95; H, 9·15; N, 15·90%).

5-*Methyl-2-(2-piperidyl) pyridine* (20 g, 56%) was obtained from 1-amino-5-ethoxy-1-(5-methyl-2-pyridyl)pentane (42 g, 0·24 mole) as colourless oil b.p. 97–98°/0·9 mm, n_D^{15} 1·5386 (Found: C, 74·88; H, 9·30; N, 16·18. $C_{11}H_{16}N_2$ requires: C, 74·95; H, 9·15; N, 15·90%).

6-*Methyl-2-(2-piperidyl)pyridine* (23 g, 64%) was obtained from 1-amino-5-ethoxy-1-(6-methyl-2-pyridyl) pentane (45 g, 0·25 mole) as a colourless oil, b.p. 60°/0·1 mm, n_D^{15} 1·5376 (Found: C, 74·71; H, 9·18; N, 15·72. $C_{11}H_{16}N_2$ requires: C, 74·95; H, 9·15; N, 15·90%).

Methyl-2,2'-dipiperidyls

General procedure. A soln of a methyl-2-(2-piperidyl)pyridine (22 g, 0·125 mole) in glacial AcOH (250 ml) was hydrogenated at 60 p.s.i. using Adams Pt catalyst (2·2 g). After the theoretical volume of H_2 had been taken up, the soln was filtered and evaporated under vacuum to 60 ml. The soln was then basified with 30% NaOH aq, the oily amine layer extracted with ether (3 × 100 ml) and the ethereal extracts combined, dried and the ether evaporated. The residual oil was distilled under vacuum.

3-*Methyl-2,2'-dipiperidyl* (17 g, 73%) was prepared from 3-methyl-2-(2-piperidyl)pyridine (22 g, 0·125 mole) as a colourless oil, b.p. 84–88°/0·55 mm, n_D^{15} 1·5104 (Found: C, 72·08; H, 12·53; N, 14·98. $C_{11}H_{22}N_2$ requires: C, 72·47; H, 12·16; N, 15·37%).

5-*Methyl-2,2'-dipiperidyl* (15 g, 64%) was obtained from 5-methyl-2-(2-piperidyl)pyridine (22 g, 0·125 mole) as a colourless oil, b.p. 93–96°/0·6 mm, n_D^{15} 1·5119 (Found: C, 72·75; H, 12·35; N, 15·51. $C_{11}H_{22}N_2$ requires: C, 72·47; H, 12·16; N, 15·36%).

6-*Methyl-2,2'-dipiperidyl* (19 g, 77%) was prepared from 6-methyl-2-(2-piperidyl)pyridine (22 g, 0·125 mole) as a colourless oil, b.p. 56–58°/0·15 mm, n_D^{15} 1·1113. (Found: C, 72·75; H, 12·35; N, 15·51. $C_{11}H_{22}N_2$ requires: C, 72·47; H, 12·16; N, 15·37%).

Monomethylperhydrodipyrido [1.2-c. 2'.1'-e] *imidazoles*

General procedure. A methyl-2,2'-dipiperidyl (16 g) was shaken with 36% formaldehyde (12 ml) at room temp for 5 min and an ice cold soln of 30% NaOH aq added. The oily monomethylperhydrodipyrido [1.2-c. 2'.1'-e] imidazole was extracted with ether (3 × 100 ml) and the ethereal extracts were combined, dried and evaporated. The residual oil was distilled under reduced press.

1-*Methylperhydrodipyrido* [1.2-c. 2'.1'-e] *imidazoles* XV, XVI, XVII *and* XVIII. The residual oil obtained from 3-methyl-2,2'-dipiperidyl and formaldehyde was distilled and the fraction b.p. 86–89°/0·5 mm was collected. Analytical GLC and PMR showed that the fraction contained 4 isomers in the approximate proportions 10:10:75:5. The isomers were separated by PGLC using a 22 ft × $\frac{3}{8}$ in aluminium column packed with 20% Carbowax 1540 on 60–80 mesh chromosorb W. The conditions for the separation were: column temp 160°, injection temp 200°, the carrier gas at 30 psi and a flow rate of 200 ml/min, injection size 0·1 ml. The isomers obtained in order of increasing retention time were: XV 0·75 g, b.p. 79°/0·5 mm, n_D^{15} 1·4993 (Found: C, 73·93; H, 11·60; N, 14·24. $C_{12}H_{22}N_2$ requires: C, 74·17; H, 11·41; N, 14·42%); XVI 0·78 g, b.p. 81–82°/0·5 mm, n_D^{15} 1·5004 (Found: C, 73·83; H, 11·47; N, 14·41. $C_{12}H_{22}N_2$ requires: C, 74·17; H, 11·41; N, 14·42%); XVIII 4 g, b.p. 84°/0·5 mm, n_D^{15} 1·5072 (Found: C, 73·73; H, 11·49; N, 14·28. $C_{12}H_{22}N_2$ requires: C, 74·17; H, 11·41; N, 14·42%). Only 0·2 g of XVII was available and this was used directly for IR and PMR spectra.

3-*Methylperhydrodipyrido* [1.2-c. 2',1'-e] *imidazoles* XI, XII, XIII and XIV. The residual oil obtained from the reaction of 5-methyl-2,2'-dipiperidyl (15 g) with formaldehyde was distilled and the fraction boiling at 80–86° at 0·55 mm (10 g) collected. The fraction was shown by PMR to contain 4 isomers though GLC on a number of columns showed only two distinct sharp peaks. Two fractions were collected by PGLC on a 22 ft × $\frac{3}{8}$ in coiled aluminium column packed with 20% carbowax on 60–80 mesh chromosorb W. The column temp was maintained at 160° and the injector at 200°, H_2 was used as carrier gas at 30 psi pressure and a flow rate of 200 ml/min, the injection size was 0·4 ml. The first fraction b.p. 60–62°/0·1 mm (3 g) was shown by PMR to contain two isomers in approximately 1:1 proportions and this mixture was separated by column chromatography on a Woelm alumina using petroleum ether (40–60°) an eluant to yield XI (0·75 g) b.p. 58°/0·1 mm, n_D^{15} 1·4990. (Found: C, 74·30; H, 11·15; N, 14·64. $C_{12}H_{22}N_2$ requires: C, 74·17; H, 11·41; N, 14·42%); and XII (1 g) b.p. 59–60°/0·1 mm, n_D^{15} 1·4996 (Found: C, 73·92; H, 11·37; N, 14·44. $C_{12}H_{22}N_2$ requires: C, 74·17; H, 11·41; N, 14·42%).

The second fraction, b.p. 56°/0·1 mm, was shown by PMR to contain two more isomers and analytical GLC on a 1,4-butandiol succinate packed column showed one isomer to be present in less than 10%. This separation could not be reproduced on a preparative scale and column chromatography using the same conditions as above gave one isomer pure XIV and the other as a 4:1 mixture of XIII and XIV. XIV (yield 1·5 g) had b.p. 66°/0·25 mm, n_D^{15} 1·5063 (Found: C, 73·67; H, 11·60; N, 14·24. $C_{12}H_{22}N_2$ requires: C, 74·17; H, 11·41; N, 14·42%). Since XIII could not be obtained pure no analytical data is reported.

4-*Methylperhydrodipyrido* [1.2-c. 2'.1'-e] *imidazoles* IX *and* X. The residual oil obtained from the reaction of 6-methyl-2,2'-dipiperidyl (16 g) with formaldehyde was distilled and the fraction b.p. 74–77°/0·2 mm (11 g) was collected. This fraction was shown by GLC and PMR to contain 2 isomers in approximately equal proportions. The isomers were separated using a 22 ft × $\frac{3}{8}$ in aluminium column packed with 20% Carbowax 1540 on 60–80 mesh chromosorb W; separation conditions were: column 155°, injector 200°, H_2 carrier gas at 30 p.s.i. pressure, flow rate 200 ml/min, injection size 0·3 ml. The first isomer IX had b.p. 61°/0·2 mm, n_D^{15} 1·4916 (Found: C, 74·40; H, 11·53; N, 14·21. $C_{12}H_{22}N_2$ requires: C, 74·17; H, 11·41; N, 14·42%) and the second, X, had b.p. 52°/0·1 mm, n_D^{15} 1·5051 (Found: C, 73·83; H, 11·47; N, 14·47. $C_{12}H_{22}N_2$ requires: C, 74·17; H, 11·41; N, 14·42%).

Synthesis of 2,10-*dimethylperhydrodipyrido* [1.2-c. 2'.1'-e] *imidazoles* VI, VII *and* VIII. 4,4'-Dimethyl-2,2'-dipyridyl was prepared by the method of Sasse and Whittle[4] from 4-methylpyridine. The 4,4'-dimethyl-2,2'-dipyridyl (23 g, 0·125 mole) was reduced in glacial AcOH over Adams PT catalyst at 60 psi, H_2 press to give 4,4'-dimethyl-2,2'-dipiperidyl (15 g), 63% b.p. 72–75°/0·45 mm, n_D^{15} 1·5206 (Found: C, 72·98; H, 12·39; N, 14·30. $C_{12}H_{24}N_2$ requires: C, 73·41; H, 12·32; N, 14·27%). A mixture of 4,4'-dimethyl-2,2'-dipiperidyl (15 g, 0·075 mole) and 36% formaldehyde soln (12 ml, 0·1 mole) was shaken for 5 min at room temp, and any excess formaldehyde destroyed by the addition of 30% NaOH aq. The mixture was extracted with ether (3 × 100 ml) and the ethereal extracts dried and the ether evaporated. The residual oil was distilled and the fraction 65–69°/0·5 mm (11 g) was collected. The fraction was shown to contain three isomers by analytical GLC in the approximate proportions 50:45:5. The isomers were separated by preparative GLC using a 22 ft × $\frac{3}{8}$ in aluminium column packed with 20% Apiezon L on 60–80 chromosorb W. The separation conditions were: column temperature 200°, injector temp 240°, and H_2 at 30 psi press as carrier gas at a flow

rate of 200 ml/min, injection size was 0·2 ml. The isomers in order of increasing retention time were: VI (2 g) b.p. 56–57°/0·45 mm, n_D^{15} 1·4941 (Found: C, 74·98; H, 11·54; N, 13·78. $C_{13}H_{24}N_2$ requires: C, 74·94; H, 11·61; N, 13·45%); XIV (1·5 g) m.p. 62–64° as white plates from 60–80° petroleum ether (Found: C, 74·98; H, 11·54; N, 13·78. $C_{13}H_{24}N_2$ requires: C, 74·94; H, 11·61; N, 13·45%). The third isomer VIII could not be obtained pure.

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