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

CONFIGURATIONAL STUDIES ON DERIVATIVES OF 2,2′-DIPIPERIDYL

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Abstract—A series of racemic 6-substituted perhydrodipyrido [1.2-c, 2′.1′-e] imidazoles have been prepared and their configurations and preferred conformations assigned on the basis of NMR and IR spectroscopy. The two racemic isomers of perhydrodipyrido [1.2-a, 2′.1′-c] pyrazine and their 6-oxo derivatives have also been studied.

TREATMENT of the mixture of dipiperidyls I and II, obtained by catalytic reduction of 2,2′-dipyridyl, with aldehydes would be expected to give a mixture of the three possible 6-substituted perhydrodipyrido [1.2-c, 2′.1′-e] imidazoles III, IV and V. The mixture of 2,2′-dipiperidyls I and II was reacted with formaldehyde, acetaldehyde, isobutyraldehyde and *p*-nitrobenzaldehyde, and the respective isomeric mixtures so formed were separated either by preparative GLC or by fractional crystallization. All the isomers isolated showed intense Bohlmann's bands[2] in the 2800–2600 cm^{-1} region of their IR spectrum and this fact together with features of their NMR spectra (Table 1) indicate them to exist in predominantly *trans*-fused ring conformations

TABLE 1. NMR SPECTRA OF 6-SUBSTITUTED-PERHYDRODIPYRIDO [1.2-c, 2′. 1′-c] IMIDAZOLES[a]

	H6 eq.	H6 ax.	H4H8 eq.	H4, 8, 11a, 11b axial	Other ring protons	Alkyl substituent
III (R = H)	6·33[b] (s)	6·33 (s)	7·06 (m)	7·46–8·05 (m)	8·1–9·0 (m)	
IV (R = H)	6·14 (d)	6·59 (d)	6·86–7·75 (m)		8·0–8·8 (m)	
	(J = −3·6 Hz.)					
III (R = Me)		6·4 (q)	6·9–8·0 (m)		8·0–8·75 (m)	8·95 (d)
IV (R = Me)		7·05 (q)	7·7–7·4 (m)	7·4–7·9 (m)	8·0–8·6 (m)	8·87 (d)
V (R = Me)	5·9 (q)		6·7–7·5 (m)		8·0–8·8 (m)	8·97 (d)
III (R = Pr^i)		6·77 (d)	7·0–7·9 (m)		8·0–8·9 (m)	9·1 (d)
		(J = 3 Hz.)				
IV (R = Pr^i)		6·15 (d)	6·7–7·4 (m)		8·0–8·8 (m)	9·0 (d)
		(J = 2 Hz.)				9·06 (d)
III (R = p $NO_2C_6H_4$)		5·84 (s)	7·0–7·8 (m)		7·9–9·0 (m)	
IV (R = p $NO_2C_6H_4$)		5·23 (s)	7·0–7·9 (m)		7·9–8·8 (m)	

[a] Measured at 60 MHz in $CDCl_3$ abbreviations used: s, singlet, d, doublet, q, quartet, m, multiplet.
[b] Chemical shifts in τ units

IIIa and IVa. A considerable variation in the appearance of the Bohlmann bands are exhibited by these compounds and some examples are shown in Fig. 1. A detailed discussion of the influence of substituents and structure on the infrared absorptions in this region must be deferred until more observations have been made.

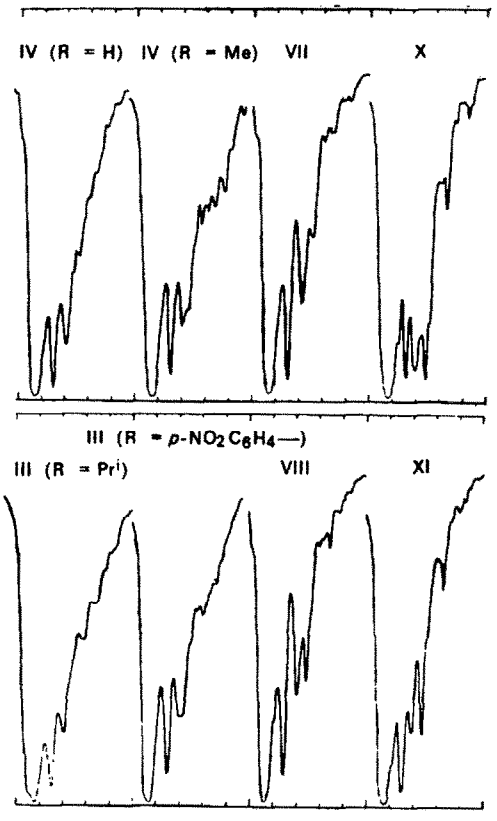
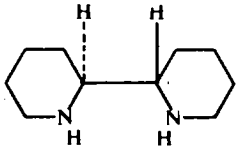
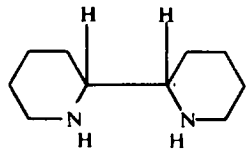


FIG. 1 IR spectra (3000–2500 cm^{-1} region) of some 6-substituted perhydrodipyrido [1.2-c, 2'.1'-e] imidazoles and perhydrodipyrido [1.2-a, 2'.1'-c] pyrazines.

Condensation of the dipiperidyls I and II with formaldehyde gave an approximately 1:1 mixture of isomers which were separated by preparative GLC. The NMR spectrum of one of the isomers showed a singlet at 6·33 τ due to the N—CH_2—N protons and hence this isomer has the configuration III (R = H) and the preferred conformation IIIa (R = H) since in this case the C-6 methylene protons are in an identical environment. The second isomer showed an AB quartet ($J = -3{\cdot}6$ Hz) for the N—CH_2—N methylene protons with chemical shifts of 6·14 τ and 6·59 τ *which is consistent with the unsymmetrical configuration IV = V (R = H).*

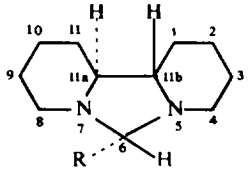


I

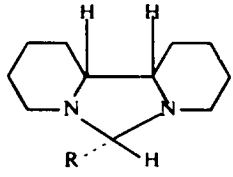


II

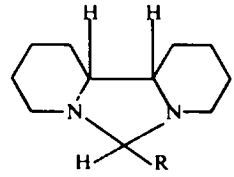
Studies of J_{gem} for methylene groups adjacent to nitrogen has proved a reliable guide to conformation[1,3,4b] since the most positive values are observed when one of the C—H bonds of the methylene group is parallel to the nitrogen lone pair orbital.[4] In *trans* fused ring compounds of the type VI where there is a degree of conformational



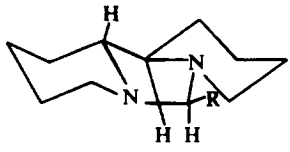
III



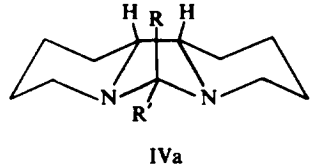
IV



V



IIIa

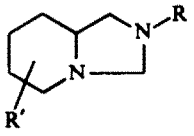


IVa

uncertainty regarding the N-alkyl group, J_{gem} is in the region of $-4{\cdot}5$ Hz.[5] Thus the more positive J_{gem} of $-3{\cdot}6$ Hz observed for IV (R = H) is a strong indication of the preferred conformation IVa (R = R′ = H) in which one of the C6—H bonds is in a near axial arrangement and parallel to the two nitrogen lone pair orbitals. The chemical shift data also favours this conformation since this C6-H proton should absorb at much higher field[6] than the C6 pseudo-equatorial proton. The signals at 6·59 τ and 6·14 τ may thus be assigned to the C6 axial and C6 equatorial protons respectively. The broadened doublet centred at 7·06 τ which appeared in the spectrum of the *trans* isomer III (R = H) corresponds to the identical C4 and C8 equatorial protons ($J_{4a4e} = J_{8a8e} = -10{\cdot}0$ Hz) while the complex four proton multiplet occurring between 7·46 and 8·05 τ may be assigned to the remaining axial protons adjacent to N atoms. The spectrum of the other isomer IV = V (R = H) showed a complex six proton multiplet between 6·86 and 7·75 τ corresponding to the protons adjacent to N atoms but the characteristic pattern observed for the C4 and C8 equatorial protons in the spectrum of III (R = H) was again apparent giving ($J_{4a4e} = J_{8a8e} \simeq -11{\cdot}5$ Hz.

Reaction of the dipiperidyl mixture I and II with acetaldehyde gave a mixture of the expected three isomers in the relative proportions 10:9:1 which were each obtained pure by preparative GLC. Examination of the Dreiding models of the *trans* fused ring

conformations of the three possible isomers shows that the C6 proton in each case is in different situations with respect to the adjacent N atoms and this proton would be expected to show quite different chemical shifts. In IVa (R′ = Me, R = H) the C6 proton is axial and *trans* orientated to both nitrogen lone pairs and so should be very highly shielded[6] whereas in IVa (R′ = H, R = Me) this proton has an equatorial-



VI

axial relationship with the nitrogen lone pairs which should cause considerable deshielding.[7] In IIIa (R = Me), however, the C6 proton is *trans* to one nitrogen lone pair and *cis* to the other and hence should have a chemical shift approximately midway between the two extremes predicted for IV and V (R = Me). The NMR spectra of the isomers (Table 1) confirm these proposals. The minor isomer has a quartet centred at 5·9 τ corresponding to a highly deshielded N—CH—N proton which must be equatorial with respect to the axial nitrogen lone pairs and this isomer may be assigned the configuration V (R = Me). One of the other isomers has a highly shielded C6 proton absorbing at 7·05 τ which corresponds to the value expected for the axial proton present in the configuration IV (R = Me), and the structure of the major isomer, which has a quartet centred at 6·4 τ for this proton, corresponds to III (R = Me). The chemical shifts for the C6 Me protons in these isomers is also of note as they show an opposite shielding effect to their corresponding C6 protons (Table 1).

The poor yield of V (R = Me) is predicted from examination of its Dreiding model which shows that in the most probable conformation, IVa (R = Me, R′ = H), the pseudoaxial C6 Me group has severe 1,3 interactions with four axial protons and the transition state for its formation should be energetically unfavourable compared to that of its epimer, IV (R = Me) in which these 1,3-axial interactions are absent. The narrow multiplet centred at 7·17 τ equivalent to six protons, which is present in the NMR of the minor isomer, corresponds to the remaining six protons adjacent to nitrogen and the low chemical shift value for the four axial protons provides additional evidence that configuration V (R = Me) is correct as in conformation IVa (R = Me, R′ = H) the pseudoaxial C6 methyl group can strongly deshield[8] the axial protons at C4, 8, 11a and 11b.

In IV (R = Me), the broadened doublet centred at about 6·95 τ ($J_{4\text{-}4a}$ = −10 Hz) may be assigned to the equatorial protons situated at positions C4 and C8. The four axial protons adjacent to nitrogen are now no longer deshielded by the equatorial C6 Me group [cf. the epimer V (R = Me)] and correspond to the complex four proton absorption between 7·4 and 7·9 τ.

p-Nitrobenzaldehyde readily condensed with the dipiperidyl mixture I and II to give a mixture which was separated by fractional crystallization into approximately equal amounts of two isomers melting at 98° and 123°. There was no evidence for the existence of a third isomer and the formation of this isomer V (R = *p*-$NO_2C_6H_4$—) can probably be ruled out on steric grounds (cf. V, R = Me). Both isomers had

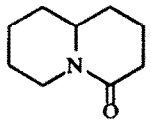
singlets in their NMR spectrum corresponding to the N—CH—N proton with chemical shifts of 5·23 τ and 5·84 τ for the low melting and high melting isomers respectively. By similar arguments to those already presented we assign configuration III (R = *p*-$NO_2C_6H_4$—) to the low melting isomer and IV (R = *p*-$NO_2C_6H_4$—) to the other isomer. The lower values of the chemical shifts observed for these C6 protons compared to the corresponding absorptions for the Me substituted isomers are due to deshielding by the aromatic ring. In IV (R = *p*-$NO_2C_6H_4$—) the six protons adjacent to N atoms occur as a narrow multiplet centred at 7·45 τ. The C4 and C8 equatorial protons are at a higher field than normally observed probably due to shielding by the aromatic ring. This isomer presumably exists in a preferred conformation in which the aromatic ring bisects the molecule in a perpendicular plane. In III (R = *p*-$NO_2C_6H_4$—) similar shielding of the C4 and C8 equatorial protons probably exists and these and the remaining four axial protons appear as a multiplet between 7·0 and 7·8 τ. It is interesting to note that in this isomer a symmetrical quartet with the additional inside lines expected for an AA'BB' system is observed for the aromatic protons whereas in IV (R = *p*-$NO_2C_6H_4$—), however, we see considerable broadening of the high field half of the "quartet" and this would support the idea of the preferred conformation of the aromatic ring postulated above.

Separate hydrolysis of the pure isomers III and IV (R = *p*-$NO_2C_6H_4$—) with mineral acid regenerated the parent dipiperidyls as white crystalline solids and which must therefore be assigned the configurations I and II respectively. Condensation of the dipiperidyl I with formaldehyde and acetaldehyde gave the expected products III (R = H) and III (R = Me) respectively, thus confirming our configurational assignments. Similarly, the dipiperidyl II gave the formal IV = V (R = H) with formaldehyde and with acetaldehyde it gave a two component mixture of the epimers IV and V (R = Me) in the expected proportions.

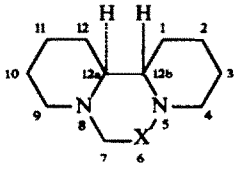
The dipiperidyl mixture and isobutyraldehyde gave a 1:1 mixture of two isomers which were separated by preparative GLC. One of the isomers was identical with that obtained by treatment of the dipiperidyl I with isobutyraldehyde and must therefore have the structure III (R = Pr^i) and the other corresponded to the single product obtained from the aldehyde and the dipiperidyl II which on steric grounds we assign the configuration IV (R = Pr^i). Assignment of the configuration of these isomers solely on the basis of chemical shifts of the C6 protons as previously described for III and IV (R = Me) gives misleading results and with these isomers their configurations can only be assigned with certainty from their method of preparation. In IV (R = Pr^i) the C6 proton appears as a doublet at 6·15 τ (J = 2·1 Hz) and examination of Dreiding models and application of the Karplus equation[9] leads one to postulate a conformation with one of the isopropyl Me groups eclipsing the C6—H bond. In such an arrangement this eclipsing methyl group may be responsible for the deshielding of this C6 proton compared with the C6 proton in IV (R = Me). However, the known influences of adjacent lone pairs on vicinal coupling constants[10] precludes a detailed analysis of the conformational preferences of the isopropyl group. The suggested existence of the isopropyl group in a preferred conformation accounts for the presence in the NMR spectrum of two Me doublets both with J = 7 Hz.

The isomer III (R = Pr^i) has a doublet centred at 6·77 τ (J = 3 Hz) which must be assigned to the N—CH—N proton although the chemical shift is at much higher field

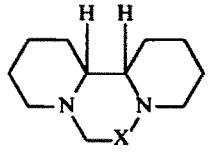
than that expected for a proton in this type of environment (cf. III R = H and R = Me). As stated earlier, the IR spectrum (Fig. 1) of this isomer, like the spectra of the other compounds, shows the presence of strong Bohlmann's bands and we must accept a predominantly *trans* fused ring conformation. Dreiding models of IIIa (R = Pr^i) in this conformation indicate a degree of mobility available to the isopropyl group and a seemingly satisfactory arrangement for this group is one in which one of the Me groups is gauche to the C6 proton. This spatial arrangement has a formal similarity to the steric relationship between an equatorial Me group and a vicinal axial proton in cyclohexanes and this proton is known to be shielded by the equatorial Me group.[8] Thus the unexpected shielding of the C6 proton in this isomer may be due to the isopropyl group having the preferred conformation postulated above. In addition, the presence of the large substituent at C6 might force the C6—H bond to be more nearly *trans* diaxial to one of the nitrogen lone pairs and thus be more shielded than it was in III (R = H or Me). The isopropyl group in this isomer III (R = Pr^i) is situated in an asymmetric environment but the pair of doublets which might have been expected[11] for the methyl protons of this group was not observed in its NMR spectrum either in deuterochloroform or benzene.



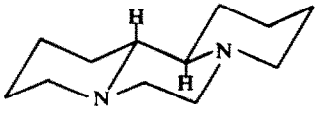
IX



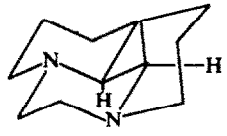
VII X = >C=O
X X = >CH_2
XII X = >CD_2



VIII X = >C=O
XI X = >CH_2
XIII X = >CD_2



Xa



XIa

Reaction of the 2,2'-dipiperidyl mixture I and II with ethyl chloroacetate gave a 1:1 mixture of isomers which were separated by column chromatography and identified as VII and VIII by comparison with the compounds obtained individually from the pure dipiperidyls. The 100 MHz. NMR spectra of these (Fig. 2a and b) showed striking resemblances to that of the lactam IX (R = H) studied by Bohlmann.[12]

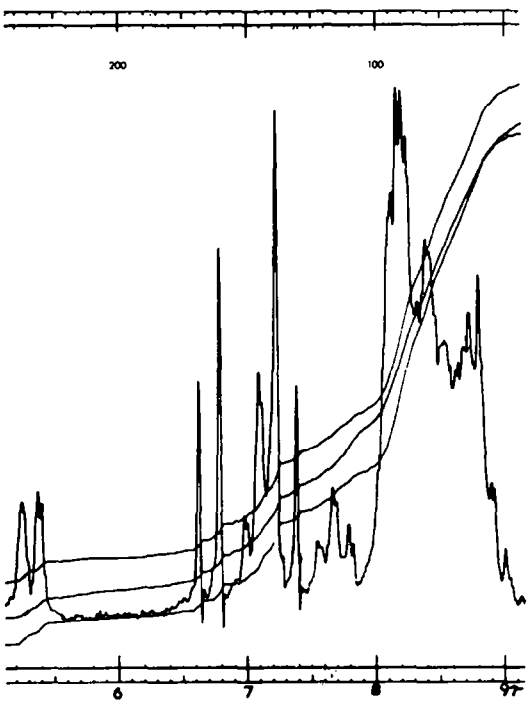


FIG. 2a 100 MHz NMR spectrum of VII

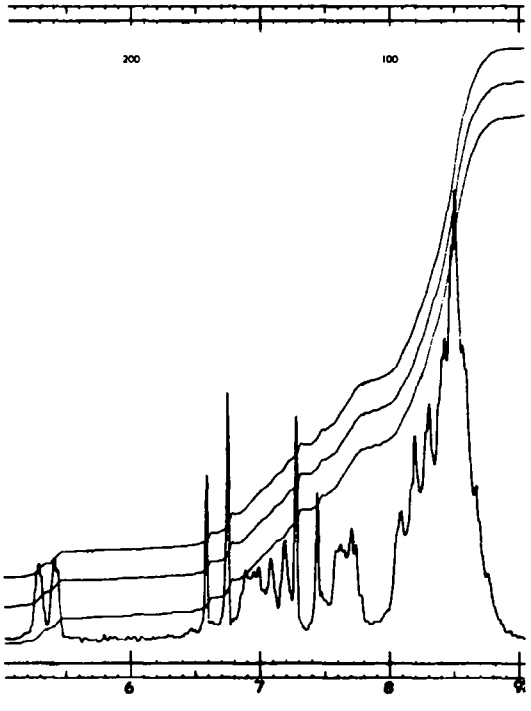


FIG. 2b 100 MHz NMR spectrum of VIII

The NMR spectrum of VII showed a one proton broadened doublet centred at 5·32 τ and this was assigned unambiguously to the C4 equatorial proton which is strongly deshielded by the amide carbonyl group. A similar signal centred at 5·35 τ is observed for the C4 equatorial proton in VIII. In addition to coupling with the C3 protons the signals for these equatorial protons in both isomers also showed evidence of long range coupling probably to the proton at $C2_e$. VII showed a multiplet centred at 7·69 τ identical in appearance to the pattern observed by Bohlmann in IX and this was assigned to the C4 axial proton. First order analysis of this multiplet (100 MHz spectrum) gave $J_{4a4e} = -13$ Hz, $J_{4a3a} = 12$ Hz and $J_{4a3e} = 3$ Hz. Both VII and VIII showed an AB quartet for the C7 methylene protons with a geminal coupling constant of −16 Hz. J_{gem} is normally about −12·5 Hz for a methylene group adjacent to nitrogen in 6-membered rings[13] but a more negative J_{gem} is to be expected in these compounds since the amide carbonyl should withdraw electrons from the anti-symmetric —CH_2— molecular orbital[14] in the same way as a normal carbonyl group. If a Barfield-Grant J^{π}-ϕ type of relationship[15] holds, the J_{gem} of −16 Hz corresponds to a conformation in which the π bond of the amide CO makes a dihedral angle of about 40° with an adjacent C—H bond. The observed value of J_{gem} is surprisingly negative since the electron withdrawing power of the CO group should be partially satisfied by donation of the lone pair of electrons from the amide N atom. Since both isomers showed strong Bohlmann's bands (Fig. 1, VII and VIII) in the IR and no such bands are observed in amides of the type IX the piperidine ring in each compound must be in a chair conformation with a *trans* ring fusion to the lactam ring. LAH reduction of VII and VIII gave the perhydrodipyridopyrazines X and XI respectively which had been previously prepared by Brian[16] by a different route but with no indication regarding the stereochemistry of the product. These compounds have an analogous ring system to the perhydrophenanthrenes whose stereochemistry has been extensively studied and the relative stabilities of the six geometrical isomers assigned.[17] However, in the nitrogen analogues, the two N atoms introduce conformational mobility at the ring junctions and now only two geometrical isomers are possible with the two piperidine rings either *syn* or *anti* to each other. From their method of preparation X and XI have the configurations shown and therefore by analogy with the perhydrophenanthrenes, X should exist in the *trans anti trans* conformation Xa which corresponds to the most stable configuration of all the perhydrophenanthrenes. Similarly XI should have the preferred *cis syn trans* conformation XIa which corresponds to the most stable isomer of the three *syn* perhydrophenanthrenes. Additional support for the stereochemical assignments of these compounds is provided by their infrared spectra in the 2800–2600 cm^{-1} region. Both isomers showed strong Bohlmann's bands but they were considerably more intense in X (Fig. 1). Examination of the proposed conformation Xa of this isomer shows that there are six C—H bonds *trans* and axial with respect to the nitrogen lone pairs, whereas in the other isomer XIa there are three such C—H bonds adjacent to one N atom but only one adjacent to the other. Hence the intensity of the absorptions in this latter isomer should be considerably reduced and this is found experimentally to be the case. Furthermore, the intensity of the bands in XI is similar to those found in the lactams VII and VIII in which there is only one *trans* fused piperidine ring. The presence of intense Bohlmann's bands also rules out substantial amounts of the *cis-anti-cis* and *cis-syn-cis* conformations for X and XI respectively. LAD reduction of

the lactams VII and VIII gave the expected 6-dideuteroperhydrodipyridopyrazines XII and XIII respectively. The NMR spectra of these isomers were somewhat simpler than the complex features observed for their hydrogen substituted analogues but they still had no significantly revealing features. The deuterated isomers showed a reduction in the intensities of Bohlmann's bands with the expected greater reduction in the case of XII than in XIII.

EXPERIMENTAL

The NMR spectra were recorded as solns in $CDCl_3$ on a Perkin–Elmer R.10 60 MHz spectrometer using TMS as internal reference 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 Unicam S.P. 100 spectrophotometer. Elemental analysis were carried out by Dr. F. Pascher and E. Pascher, Microanalytical Laboratory, Bonn, Germany, or at the Organic Chemistry Department of Reading University. M.ps are uncorrected.

2,2'-Dipiperidyls I *and* II. The epimeric mixture of 2,2'-dipiperidyls was prepared by catalytic reduction of 2,2'-dipyridyl.[18] The fraction b.p. 63–65° at 0·8 mm was collected and shown by the GLC using a 20% Carbowax on 60–80 mesh chromosorb W packed column to be a 1:1 mixture of I and II. This mixture, unless otherwise stated, was used for all the cyclization experiments.

Perhydrodipyrido [1.2-c, 2'.1'-e] *imidazoles* III *and* IV (R = H). The dipiperidyl mixture (21 g, 0·125 mole) was shaken with 36% formaldehyde soln (11 g, 0·125 mole) for 5 min and the resulting soln was saturated with NaOH. The organic layer was extracted with ether (3 × 150 ml) and the ethereal soln was dried and evaporated. The residual oil was distilled and the fraction b.p. 85–88° at 0·8 mm collected, yield 16 g, 71%. The product was shown by GLC and NMR analysis to be a 1:1 mixture of III and IV (R = H). The two isomers were separated by preparative GLC on a Varian Autoprep gas chromatograph using a 12 ft column packed with 20% Apiezon L on 60–80 mesh chromosorb W at 200° and H_2 carrier gas at 30 psi with a flow rate of 200 ml/min. The isomer of shorter retention time was identified as IV (R = H) by its NMR spectrum. It was obtained as a colourless oil b.p. 85–86°/1 mm, n_D^{25} 1·5058, ν 2790 (s), 2740 (m), 2685 (w), 2660 (w) cm^{-1}. (Found: C, 73·31; H, 11·1; N, 15·57. $C_{11}H_{20}N_2$ requires: C, 73·28; H, 11·8; N, 15·54%). The isomer III (R = H) was obtained as a colourless oil b.p. 79–80°/1 mm; n_D^{25} 1·5010, ν 2800 (s), 2735 (m), 2690 (w), 2660 (w) cm^{-1}. (Found: C, 73·3; H, 11·1; N, 15·6. $C_{11}H_{20}N_2$ requires: C, 73·28; H, 11·8; N, 15·54%).

6-Methylperhydrodipyrido [1.2-c, 2'.1'-e] *imidazoles* III, IV and V (R = Me). A soln of the dipiperidyl mixture (21 g, 0·125 mole) and acetaldehyde (5 g, 0·13 mole) in benzene (200 ml) was refluxed for 10 min and then the water formed in the condensation was removed by azeotropic distillation and collected in a Dean and Stark water separator. After removal of water (2·2 ml), the benzene was evaporated under vacuum and the residual oil distilled b.p. 58–61°/0·1 mm, yield 16 g (73%). The product was shown by analytical GLC to be a mixture of three isomers, III, IV and V (R = Me) of approximate composition 50:45:5 respectively. The mixture (10 g) was separated into its pure components by preparative GLC as described in the previous experiment. The isomers which came off the column in the order III, IV, V (R = Me), were identified by their NMR spectra; III (R = Me), b.p. 61–62°/0·1 mm, yield 2·5 g; n_D^{25} 1·4989, ν 2790 (s), 2735 (m), 2710 (w) cm^{-1}. (Found: C, 74·18; H, 11·51; N, 14·44. $C_{12}H_{22}N_2$ requires: C, 74·17; H, 11·41; N, 14·42%). IV (R = Me), b.p. 62–63°/0·1 mm, yield 2·5 g; n_D^{25} 1·5038, ν 2800 (s); 2770 (s); 2725 (m); 2690 (m); 2620 (m); 2545 (w); 2515 (w) cm^{-1}. (Found: C, 74·20; H, 11·61; N, 14·34. $C_{12}H_{22}N_2$ requires: C, 74·17; H, 11·41; N, 14·42%). V (R = Me) b.p. 60–61°/0·1 mm, yield 0·25 g; n_D^{25} 1·5004, ν 2800 (s), 2720 (w), 2700 (w), 2670 (w) cm^{-1}.

6-Isopropylperhydrodipyrido [1.2-c, 2'.1'-e] *imidazoles* III *and* IV (R = Pr^i). 2,2'-Dipiperidyl (21 g, 0·125 mole) in dry benzene (200 ml) was reacted with isobutyraldehyde (9 g, 0·13 mole) as described in the previous experiment. After work up, the residual oil was distilled and the fraction b.p. 82–84°/0·5 mm collected (15 g, 71%). The product was shown by analytical GLC and NMR to be a mixture of two isomers which were separated by preparative GLC using a 12 ft 20% Carbowax 1500 on 60–80 mesh chromosorb W column maintained at 170° using H_2 carrier gas at 30 psi at a flow rate of 200 ml/min. The pure isomers were identified as III (R = Pr^i), a colourless oil (5 g) b.p. 80–81°/0·5 mm; n_D^{25} 1·4960, ν 2800 (s), 2730 (m), 2670 (w) cm^{-1}. (Found: C, 75·69; H, 11·81; N, 12·43. $C_{14}H_{26}N_2$ requires: C, 75·61; H, 11·79; N, 12·60%), and IV (R = Pr^i) b.p. 82–83°/0·5 mm, yield 5 g, n_D^{25} 1·4990, ν 2795 (s), 2770 (s), 2725 (m), 2660 (w), 2620 (w)

cm^{-1}. (Found: C, 76·64; H, 11·90; N, 12·51. $C_{14}H_{26}N_2$ requires: C, 75·41; H, 11·79; N, 12·60%), by their NMR spectra.

6-p-*nitrophenylperhydrodipyrido* [1.2-c, 2'.1'-e] *imidazoles* III *and* IV (R = p-*nitrophenyl*). 2,2'-Dipiperidyl (21 g, 0·125 mole) and *p*-nitrobenzaldehyde (19 g, 0·13 mole) was dissolved in benzene (200 ml) and the mixture treated as previously described. After removal of the benzene the residual syrup solidified on stirring with EtOH at −40°. Careful fractional crystallization of the solid product from EtOH gave two isomers IV (R = *p*-nitrophenyl-) as pale yellow needles m.p. 122–123°, yield 10·5 g (26%), ν 2790 (s), 2735 (m), 2700 (m) cm^{-1}. (Found: C, 67·71; H, 7·70; N, 14·03. $C_{17}H_{24}N_3O_2$ requires: C, 67·75; H, 7·69; N, 13·94%) and III (R = *p*-nitrophenyl) as pale yellow prisms, m.p. 98–99°, yield 9 g, (24%), ν 2790 (s), 2720 (m), 2695 (m), 2640 (w) cm^{-1}. (Found: C, 67·65; H, 7·74; N, 14·03. $C_{17}H_{24}N_3O_2$ requires: C, 67·75; H, 7·79; N, 13·94%), which were identified by their NMR spectra.

2,2'-*Diperidyl* II. 6-*p*-Nitrophenylperhydrodipyrido [1.2-c, 2'.1'-e] imidazole IV (R = *p*-$NO_2C_6H_4$—; 6 g, 0·02 mole) was hydrolysed by stirring with 10% HCl aq (20 ml) and after 1 hr the *p*-nitrobenzaldehyde formed was filtered off. The filtrate was basified with 30% NaOH aq and the oily amine layer extracted with ether (3 × 50 ml). The ether extracts were dried and evaporated and the residual semi-solid was purified by vacuum sublimation to give a white solid which was recrystallized from light petroleum (b.p. 40–60°) as colourless prisms m.p. 55–56°, yield 3·8 g (67%), ν 2795 (s), 2730 (m), 2650 (w) cm^{-1}; NMR spectrum: doublet centred at τ 6·8, N–CH eq. (2 protons), $J = -12$ Hz; 4 N–CH ax. protons τ 7–7·7; singlet at τ 8·4 for N–H (2 protons); 12-CH_2— protons between 7·9–8·9 τ. (Found: C, 70·98; H, 12·00; N, 16·51. $C_{10}H_{20}N_2$ requires: C, 71·37; H, 11·98; N, 16·65%).

2,2'-*Dipiperidyl* I 6-*p*-Nitrophenylperhydrodipyrido [1.2-c, 2'.1'-e] imidazole II (R = *p*-$NO_2C_6H_4$—; 6 g, 0·02 mole) was treated as described above to yield the amine I as colourless needles from light petroleum (b.p. 40–60°) m.p. 48–49°, yield 3·5 g (62%), ν 2790 (m), 2720 (w), 2660 (w) cm^{-1}; NMR spectrum: doublet centred τ 6·9, N—CH eq. (2 protons), $J = -12$ Hz; 4 N—CH ax. protons, multiplet τ 7·1–8; two proton singlet for N—H τ 8·5; and 12 —CH_2— protons between 8–9 τ. (Found: C, 71·04; H, 11·71; N, 16·34. $C_{10}H_{20}N_2$ requires: C, 71·37; H, 11·98; N, 16·65%).

The pure dipiperidyls I and II were each reacted with formaldehyde, acetaldehyde and isobutyraldehyde as described for the dipiperidyl mixture. In each experiment the dipiperidyls gave the expected product(s) which were identical in all respects to those obtained from the mixture of dipiperidyls. Thus I, with formaldehyde, acetaldehyde and isobutyraldehyde gave III, R = H, Me and Pr^i respectively while the dipiperidyl II gave IV = V (R = H) with formaldehyde, IV (R = Pr^i) with isobutyraldehyde and a mixture of IV and V (R = Me) with acetaldehyde. The ratio of the isomers in this latter mixture was the same as that previously obtained. These experiments therefore prove the configurational assignments made for these products.

6-*Oxoperhydrodipyrido* [1.2-a, 2'.1'-c] *pyrazines* VII *and* VIII. The 2,2'-diperidyl mixture (21 g, 0·125 mole) and ethyl chloroacetate (16 g, 0·125 mole) were carefully mixed and then heated for ½ hr at 100°. The crude solid formed on cooling was treated with excess K_2CO_3 aq, extracted with ether (3 × 150 ml) and the ethereal extracts were dried and evaporated to yield a white solid m.p. 79–83°, which was shown by analytical GLC and NMR to be a 1:1 mixture of isomers. The mixture was separated into its pure components by column chromatography on activity II Woelm neutral alumina using light petroleum (b.p. 40–60°) as eluant. The crude isomers were recrystallized from ether–light petroleum (b.p. 60–80°) one isomer, m.p. 85–86° obtained as white needles yield 7 g; (28%), ν 2790 (m), 2755 (m), 2700 (w), 2680 (w), 2650 (w) cm^{-1}. (Found: C, 69·83; H, 9·60; N, 13·68, $C_{12}H_{20}N_2O$ requires: C, 69·90; H, 9·68; N, 13·60%) was identified as VIII by comparison of its NMR and IR spectra with those of the compound VIII formed on treating the 2,2'-dipiperidyl epimer II with ethyl chloroacetate as described above. Similarly the other isomer was obtained as white star shaped crystals, m.p. 92–93°, yield 6·4 g, (24%), ν 2770 (m), 2750 (m), 2700 (w), 2670 (w), 2595 (w) cm^{-1}. (Found: C, 69·61; H, 9·61; N, 13·68. $C_{12}H_{20}N_2O$ requires: C, 69·90; H, 9·68; N, 13·60%) was shown to be VII by comparison with an authentic sample prepared directly from the 2,2'-dipiperidyl epimer I.

Perhydrodipyrido [1.2-a, 2'.1'-c] *pyrazine* XI. To a stirred soln of VIII (4 g, 0·02 mole) in abs ether (100 ml) was added a soln of LAH (0·6 g) in dry ether (20 ml) at a rate sufficient to maintain reflux. After the addition the mixture was heated for a further ½ hr, and then water added dropwise until reaction ceased. The ethereal soln was dried and evaporated leaving a residual oil which distilled at 95–96°/0·2 mm, yield 2·5 g (67%); n_D^{25} 1·5148, ν 2805 (s), 2763 (m), 2673 (w), 2610 (w) cm^{-1}. (Found: C, 73·63; H, 11·88; N, 14·72. $C_{12}H_{22}N_2$ requires: C, 74·17; H, 11·41; N, 14·42%).

Perhydrodipyrido [1.2-a, 2'.1'-c] *pyrazine* X. The lactam VII (4 g, 0·02 mole) was reduced as described in

the previous experiment to give X b.p. 86–87°/0·2 mm, yield 2·55 g (69%), n_D^{25} 1·5904, ν 2804 (s), 2760 (s), 2745 (m), 2700 (w), 2670 (w), 2595 (w) cm^{-1}. (Found: C, 73·35; H, 11·98; N, 14·74. $C_{12}H_{22}N_2$ requires: C, 74·17; H, 11·41; N, 14·42%).

6,6'-*Dideuteroperhydrodipyrido* [1.2-a, 2'.1'-c] *pyrazine* XIII. The lactam VIII (2 g, 0·01 mole) in dry ether (50 ml) was reduced with LAD (0·4 g) in dry ether (50 ml) as described above. The dideutero pyrazine XIII yield 0·75 g (41%), n_D^{25} 1·5153 showed ν 2800 (m), 2760 (m), 2670 (w), 2600 (w) cm^{-1}.

6,6'-*Dideuteroperhydrodipyrido* [1.2-a, 2'.1'-c] *pyrazine* XII. The lactam VII (2 g, 0·01 mole) was deuterated as described in the previous experiment to give XII yield 0·74 g, (40%), n_D^{25} 1·5102, ν 2800 (s), 2760 (m), 2670 (w) and 2580 (w) cm^{-1}.

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