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

CONFIGURATIONAL AND CONFORMATIONAL STUDIES WITH PERHYDROCYCLOALKANO [*e*] PYRIDO [1.2-*c*] [1.3] OXAZINES

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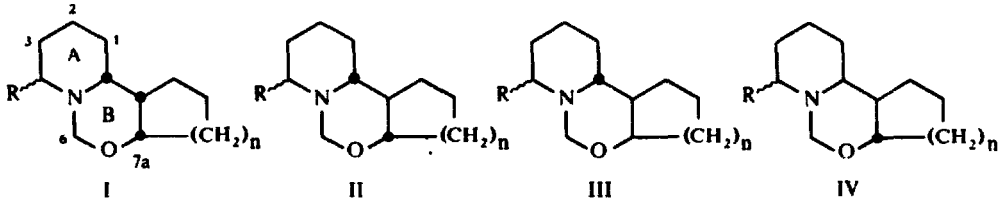
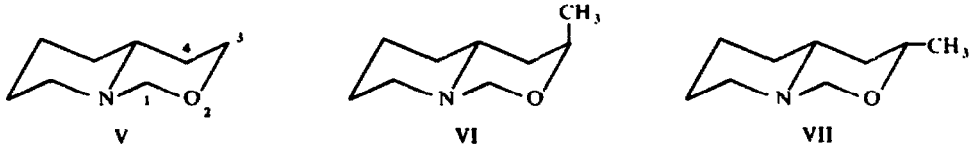
Abstract—The four possible racemic isomers of perhydrobenzo [*e*] pyrido [1.2-*c*] [1.3] oxazine, three isomers of perhydrocyclopentano [*e*] and three isomers of perhydrocycloheptano [*e*] pyrido [1.2-*c*] [1.3] oxazine together with some of their 4-methyl derivatives have been synthesized. Their configurations and preferred conformations have been assigned from a study of their NMR spectra and from an examination of their IR spectra in the 2700–2800 cm^{-1} region.

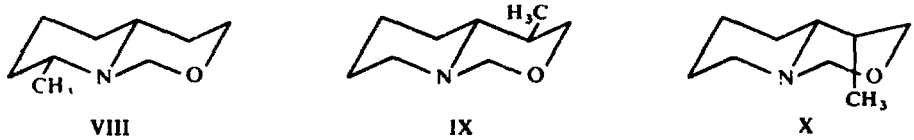
IN STUDYING conformational preferences of saturated 1,3-heterocyclic systems the value of the geminal coupling constant (J)[2] and the chemical shifts of protons adjacent to the heteroatoms[2, 3] have proved to be of considerable use since both these NMR parameters are sensitive to the orientation of lone pairs of electrons on the heteroatoms. Chemical shifts are, in addition, influenced by substituents but some of these correlations[4] between position and orientation of alkyl substituents and the chemical shifts of ring protons in cyclohexanes do not apply without exception to heterocyclic systems.[5] Large variations in J with changes in molecular environment are readily explicable in terms of current theory[6, 7] but small differences in J, observed



I II III IV



V VI VII



VIII IX X

for similarly situated methylene groups in different types of compounds, are naturally difficult to rationalise. It seemed desirable therefore to study the NMR spectra of a set of closely related compounds to gather information regarding variations in spectral parameters brought about by relatively small structural changes and for this purpose the perhydrocycloalkano [*e*] pyrido [1.2-*c*] [1.3] oxazines were chosen since the stereochemistry of the related perhydrophenanthrenes[8] has been described in detail.

The influence of the orientation of the C ring on the C6 and C7a chemical shifts and coupling constants in the isomers I–IV (n = 2) should be paralleled by the effect of axial and equatorial C4 Me groups on the NMR parameters of the analogous protons in octahydropyrido [1.2-*c*] [1.3] oxazines. Accordingly compounds V–X were chosen to act as reference compounds with which to compare the NMR spectra of the isomers under discussion and the relevant spectra data is summarized in Table 1. Compounds

TABLE 1. 60 MHz NMR SPECTRA OF SUBSTITUTED OCTAHYDROPYRIDO [1.2-c] [1.3] OXAZINES

Compound	Solvent	Chemical shifts (τ) H_{1eq}	H_{1ax}	H_{3eq}	H_{3ax}	Me[a]	J_{1eq1ax} (Hz)
V	CCl_4	5·82	6·48	6·05	6·64	—	−8·0
VI	CCl_4	6·13	6·13	5·98	—	8·78	—
VI	C_6H_6	5·95	6·15	5·80	—	—	−8·0
VII	CCl_4	5·75	6·36	—	6·60	8·87	−8·0
VII	C_6H_6	5·71	6·45	—	6·60	—	−8·0
VIII	CCl_4	5·42	6·73	6·10	6·67	8·97	−8·0
IX	CCl_4	5·86	6·45	6·10	6·95	9·30	−7·8
X	CCl_4	5·86	6·73	6·40	6·40	8·93	−7·8

[a] Centre of Me doublet.

V–VIII have been described previously[2] when they were shown to exist in predominantly *trans*-fused ring conformations. To complete the series IX and X were prepared by the reaction of formaldehyde with 2-ethylpyridine to give β-(2-pyridyl) propanol.[9] Catalytic reduction followed by treatment with formaldehyde produced the mixture of IX and X which were separated by preparative GLC. Since both isomers showed Bohlmann bands[10] in their IR spectra they were assigned predominantly *trans*-fused ring conformations. The decision regarding the axial or equatorial nature of the Me group in the two isomers was made initially on the basis of the position of the centre of the C-Me doublet which was 0·37 ppm to higher field in one isomer (assigned configuration IX) than in the other (X), since in a variety of Me substituted saturated heterocyclic compounds axial Me groups are found[11, 12] to absorb at lower field than equatorial Me groups. The correctness of these stereochemical assignments is confirmed by comparing the chemical shifts of the C3 protons in IX and X with those in V (Table 1). Existing chemical shift correlations[4] suggest that an equatorial Me group should shield a vicinal axial proton by up to 0·47 ppm. The chemical shift of 6·95 τ for the C3 axial proton in IX compared to the value of 6·64 τ in the unsubstituted compound V is therefore consistent with the presence of an equatorial Me group at C4. An axial Me group deshields an adjacent axial proton by ca. 0·2 τ and shields the corresponding equatorial proton by ca. 0·4 τ.[4] Application of

this rule to the change V–X leads one to expect chemical shifts of ca. 6·4 τ for both C3 protons in X which is in fact observed.

The reaction between aromatic N-oxides and the morpholine enamine of cyclohexanone in the presence of acylating agents has been studied in detail by Hamana and Noda[13, 14] and in the case of pyridine N-oxide and 2-picoline N-oxide the corresponding 2-(2-pyridyl)-cyclohexanones are produced. This synthetic method proved to be perfectly adaptable to the enamines of cyclopentanone and cycloheptanone and the 2-(2-pyridyl)-cyclopentanones and heptanones were readily

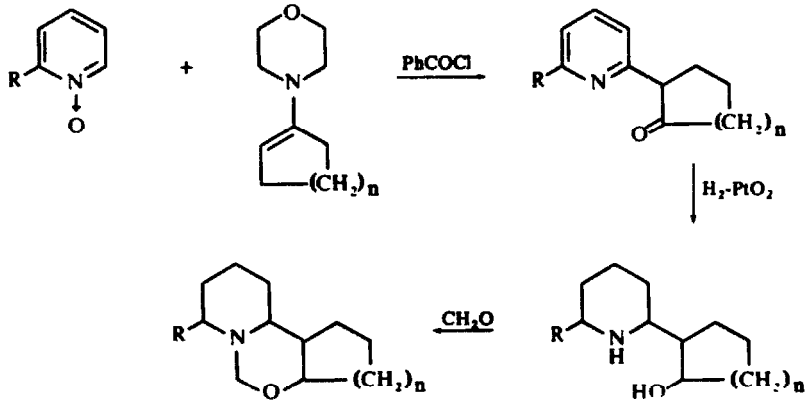


FIG. 1. Synthesis of perhydrocycloalkano [*e*] pyrido [1.2-*c*] [1.3] oxazine

obtained. Catalytic hydrogenation of these pyridyl ketones in glacial acetic acid using Adams platinum oxide catalyst gave mixtures of isomeric 2-(2-piperidyl)-cycloalkanols which were not separated but converted directly to mixtures of the required tricyclic compounds by treatment with aqueous formaldehyde (Fig. 1). The mixtures of isomers were separated by preparative GLC on a carbowax column and the percentages of isomers obtained are shown in Table 2 together with the stereochemical assignments made on the basis of the spectral evidence described below.

Stereochemistry of perhydrobenzo [e] *pyrido* [1.2-c] [1.3] *oxazines**

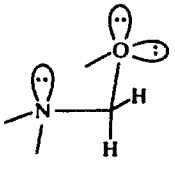
There are four possible diastereoisomers of perhydrocyclobenzo [*e*] pyrido [1.2-*c*] [1.3] oxazine I–IV (R = H, n = 2) and the stereochemistry of these differs from the superficially related perhydrophenanthrenes by the presence of the conformationally mobile N atom which permits each isomer to exist as an equilibrium mixture of *cis* A:B and *trans* A:B conformations. Differences between the systems might also be expected to arise from, for example, the shorter C—O as compared to C—C bond length and from dipole-dipole interactions involving the heteroatoms. Before discussing the stereochemistry and spectra of the individual isomers in detail it is convenient to describe a spectral feature common to all the isomers—the *J* of the C6 methylene protons. All four isomers of perhydrobenzo [*e*] pyrido [1.2-*c*] [1.3] oxazine

* All the perhydrocycloalkano [*e*] pyrido [1.2-*c*] [1.3] oxazines described in this paper are racemic mixtures.

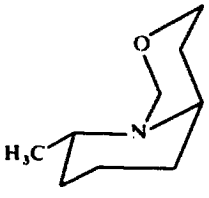
TABLE 2. PERCENTAGE ISOMERS OF PERHYDROCYCLOALKANO [e] PYRIDO [1.2-c] [1.3] OXAZINES OBTAINED BY SYNTHETIC ROUTE SHOWN IN FIG. 1

Compound	% Isomer obtained	Order of collection from carbowax column
I (R = H, n = 1)	17	1
II (R = H, n = 1)	60	2
III (R = H, n = 1)	23	3
I (R = H, n = 2)	59	1
II (R = H, n = 2)	18	2
III (R = H, n = 2)	17	3
IV (R = H, n = 2)	6	4
I (R = H, n = 3)	73	1
II (R = H, n = 3)	9	2
III (R = H, n = 3)	17	3
I (R = Me, n = 1)	43	1
III (R = Me, n = 1)	25	2
II (R = Me, n = 1)	32	3
I (R = Me, n = 2)	59	1
II (R = Me, n = 2)	41	2
III (R = Me, n = 2)		
I (R = Me, n = 3)	75	1
III (R = Me, n = 3)	25	2

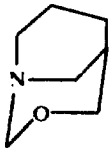
showed a J^* for the C6 methylene protons of between $-7{\cdot}2$ and $-8{\cdot}0$ Hz (Table 3) indicating a similar spatial relationship between the lone pairs of electrons on the N and O atoms and the C6—H bonds in each of the isomers. This value of J is typical of N—CH_2—O protons orientated with respect to the heteroatom lone pairs as show in XI, e.g. J is $-7{\cdot}7$ Hz[15] for 5-nitro, 5-methyl, 3-t-butyl-tetrahydro-1,3-oxazine, which exists in a chair conformation with an equatorial N-t-Bu substituent, and J is $-7{\cdot}8$ to $-8{\cdot}0$ Hz for the bicyclic oxazines V–X (Table 1). Conformations with the N lone pairs bisecting the C6 methylene H-H internuclear axis cannot be considered to be present to an appreciable extent in the possible equilibrium mixture of compounds, I–IV (R = H, n = 2) since J for such lone pair —CH orientations has been found to be ca. -10 Hz; J being -10 Hz for XII[2] and $-10{\cdot}6$ Hz for XIII.[3]



XI



XII



XIII

*J is assumed to be negative.

One surprising feature of the NMR spectrum of X which was of use in assigning configurations to the tricyclic compounds I–IV is the high field absorption (τ = 6·73) of the Cl axial proton (cf 6·48 τ in V), representing an apparent shielding of this proton by the axial C4 Me group of 0·25 ppm. The origin of this shielding which may in part be due to differences in the shape of the oxazine ring in X as compared to V is under investigation. The chemical shift of the equatorial Cl proton is practically identical in V, IX and X.

TABLE 3. NMR SPECTRA OF PERHYDROCYCLOALKANO [*e*] PYRIDO [1.2-*c*] [1.3] OXAZINES

Compound	Solvent	Chemical shifts						J_{CH-Me} (Hz)[b]
		H_{4eq}	H_{6eq}	H_{6ax}	H_{7a}	J_{6eq6ax} (Hz)	Me[a]	
I (R = H, n = 1)[c]	CCl_4	7·41	5·98	6·67	6·29	−7·5		
I (R = H, n = 2)	CCl_4	7·50	5·80	6·63	6·60	−7·2		
I (R = H, n = 2)	C_6H_6	7·58	5·64	6·60	6·55	−7·2		
I (R = H, n = 3)	CCl_4	7·45	5·82	6·65	6·45	−7·4		
II (R = H, n = 1)[c]	CCl_4	7·30	5·79	6·28	6·98	−8·5		
II (R = H, n = 2)[c]	CCl_4	7·40	5·86	6·38	7·20	−8·0		
II (R = H, n = 3)[c]	CCl_4	7·40	5·88	6·42	7·20	−8·0		
III (R = H, n = 1)[c]	CCl_4	7·30	6·10	6·26	5·86	−8·4		
III (R = H, n = 2)	CCl_4	7·25	6·04	6·04	6·25	—		
III (R = H, n = 2)[c]	C_6H_6	7·45	5·87	5·99	6·18	−8·0		
III (R = H, n = 3)	CCl_4	7·30	6·12	6·30	6·45	−8·2		
IV (R = H, n = 2)[c]	CCl_4	7·20	5·51	6·06	6·95	−7·4		
I (R = Me, n = 1)	CCl_4		5·45	6·71	6·22	−8·0	8·95	5·4
I (R = Me, n = 2)	CCl_4		5·34	6·69	6·58	−7·4	8·99	5·8
I (R = Me, n = 3)	CCl_4		5·37	6·72	6·50	−7·2	8·98	5·7
II (R = Me, n = 1)	CCl_4		5·25	6·44	6·94	−7·8	8·94	5·3
II (R = Me, n = 2)	CCl_4		5·36	6·55	7·18	−7·5	8·96	5·4
III (R = Me, n = 1)	CCl_4		5·58	6·17	6·00	−7·5	8·95	5·7
III (R = Me, n = 2)[d]	CCl_4		5·68	6·10	6·30	−7·5	8·95	—
III (R = Me, n = 3)	CCl_4		5·68	6·47	6·25	−7·5	8·98	5·8

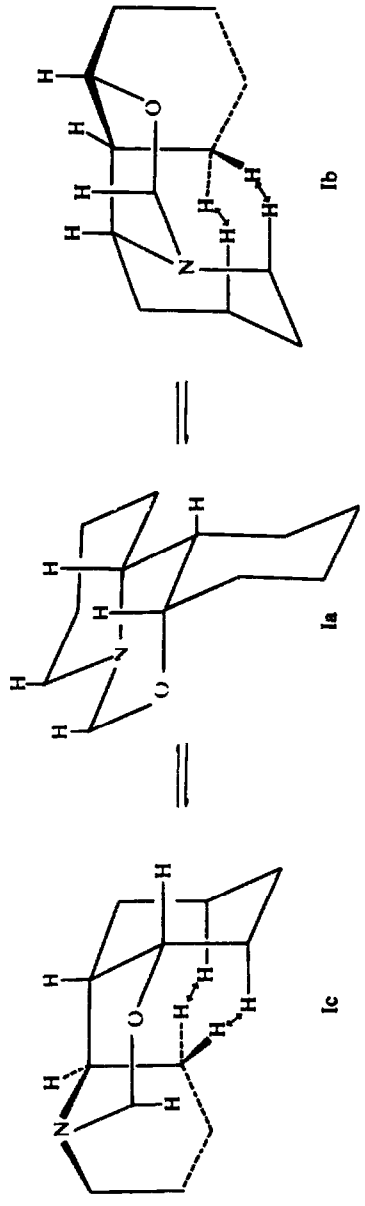
[a] Centre of Me doublet. [b] Apparent coupling constant.

[c] Denotes spectrum run on Varian H.A.100 spectrometer, all other spectra run on Perkin–Elmer R.10 spectrometer.

[d] NMR parameters extracted from spectrum of this isomer contaminated with II (R = Me, n = 2).

trans syn cis-*Perhydrobenzo* [e] *pyrido* [1.2-c] [1.3] *oxazine* (I; R = H, n = 2)

The first isomer off the preparative GLC column was assigned the *trans syn cis* stereochemistry Ia (R = H, n = 2). The *J* of −7·2 Hz and the presence of Bohlmann bands[10, 2] in the IR spectrum is in accord with Ia but not with the alternative *cis syn cis* conformation Ib (no Bohlmann bands, *J* ca-10 Hz) or the *cis syn cis* conformation Ic


Ib
Ia
Ic

(J ca-8 Hz, no Bohlmann bands). Also by analogy with the perhydrophenanthrenes, the latter two conformations can be neglected. The data so far presented is, of course, equally consistent with *trans* A:B conformations of II and III.

The real lead to the stereochemistry of this isomer was the chemical shift (6·63 τ) of the C6 axial proton which was the highest field absorption for this proton to be observed in the four isomers. This suggested the presence of an axial ring methylene at C11a(cf. X). The chemical shift of the axial C7a proton of 6·60 τ is the same as that of the C3 ax proton in VII. Deshieldings by 0·20 ppm of an axial proton by a vicinal axial Me group have been reported.[4] If Ia is the correct structure for this isomer then the signals arising from the C7a proton might be expected to have a band width of ca. 12 Hz arising from three approximately equal Jax-eq of ca. 4 Hz. The C7a proton signals were in fact partially overlapped by the C6Hax doublet so that the splitting pattern could not be seen but the line width of the signals was in accord with the predicted value.

trans, anti, trans-*Perhydrobenzo* [e] *pyrido* [1.2-c] [1.3] *oxazine II* (R = H, n = 2)

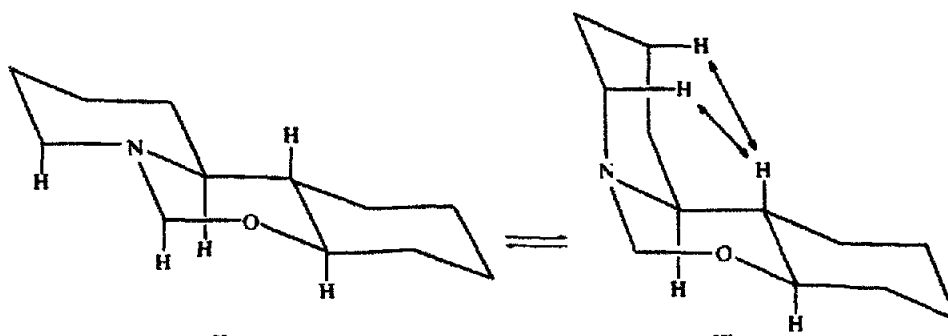
The *trans anti trans* stereochemistry IIa was assigned to the second isomer off the column. The alternative *cis anti trans* conformation IIb is inconsistent with the

TABLE 4. IR SPECTRA OF PERHYDROCYCLOALKANO [*e*] PYRIDO [1.2-*c*] [1.3] OXAZINES

Compound	2800–2650 cm^{-1}	1200–1000 cm^{-1}
I (R = H, n = 1)	2765(m) 2710(mw) 2680(mw)	1185(mw) 1160(m) 1150(m) 1140(m) 1125(s) 1100(s) 1065(ms) 1030(mw)
I (R = H, n = 2)	2765(m) 2730(mw) 2710(mw) 2690(mw) 2680(mw)	1185(mw) 1160(m) 1145(s) 1130(s) 1120(s) 1110(s) 1095(s) 1075(s) 1055(mw) 1040(mw)
I (R = H, n = 3)	2770(m) 2740(mw) 2720(mw) 2700(mw) 2680(mw)	1200(mw) 1170(mw) 1150(m) 1135(s) 1120(s) 1110(s) 1080(ms) 1035(mw)
II (R = H, n = 1)	2765(m) 2740(mw) 2710(mw) 2690(mw)	1185(m) 1175(mw) 1150(m) 1135(s) 1125(s) 1110(m) 1100(s) 1085(m) 1060(s) 1050(m) 1020(m) 1000(mw)
II (R = H, n = 2)	2765(m) 2740(mw) 2715(mw) 2690(mw)	1165(ms) 1150(s) 1140(s) 1125(s) 1110(ms) 1100(s) 1090(s) 1075(ms) 1050(s) 1020(mw)
II (R = H, n = 3)	2770(m) 2740(mw) 2695(mw)	1180(m) 1155(mw) 1140(s) 1120(s) 1095(mw) 1090(m) 1070(mw) 1050(mw) 1035(mw) 1030(mw)
III (R = H, n = 1)	2770(m) 2740(mw) 2690(mw)	1180(m) 1155(s) 1150(ms) 1140(s) 1135(s) 1120(s) 1090(s) 1065(m) 1060(m) 1045(mw) 1025(mw) 995(mw)
III (R = H, n = 2)	2770(m) 2730(mw) 2710(mw) 2700(mw)	1195(m) 1160(m) 1150(s) 1140(ms) 1125(s) 1110(mw) 1090(s) 1080(s) 1160(s) 1025(m) 1005(mw)
III (R = H, n = 3)	2770(m) 2720(mw) 2700(mw)	1200(m) 1185(mw) 1160(m) 1150(mw) 1140(s) 1130(s) 1125(s) 1100(ms) 1087(m) 1077(ms) 1070(ms) 1050(mw) 1040(m)
IV (R = H, n = 2)	2760(w) 2750(w) 2730(w)	1185(mw) 1165(mw) 1150(s) 1130(ms) 1120(ms) 1110(ms) 1090(s) 1080(s) 1050(m) 1035(m) 1020(mw) 995(mw)

observed value (−7·8 Hz) of *J* (C6 methylene) and with the presence of Bohlmann bands in the IR (Table 4). This compound showed the highest chemical shift (7·20 τ) for the C7a proton of all four isomers. A comparison with the chemical shift of the C3-Hax in octahydropyrido [1.2-*c*] [1.3] oxazine, shows that this represents a shielding of ca. 0·50 ppm by the C ring.

Segre and Musher[16] have reported the marked shielding effect of an equatorial Me substituent on axial protons which are on adjacent C atoms in cyclohexane ring systems. The axial proton vicinal to two equatorial Me groups in *cis,cis*-1,3,5-trimethylcyclohexane and in *cis,trans*-1,3,5-trimethylcyclohexane absorbs at 9·53 τ;



IIa IIb

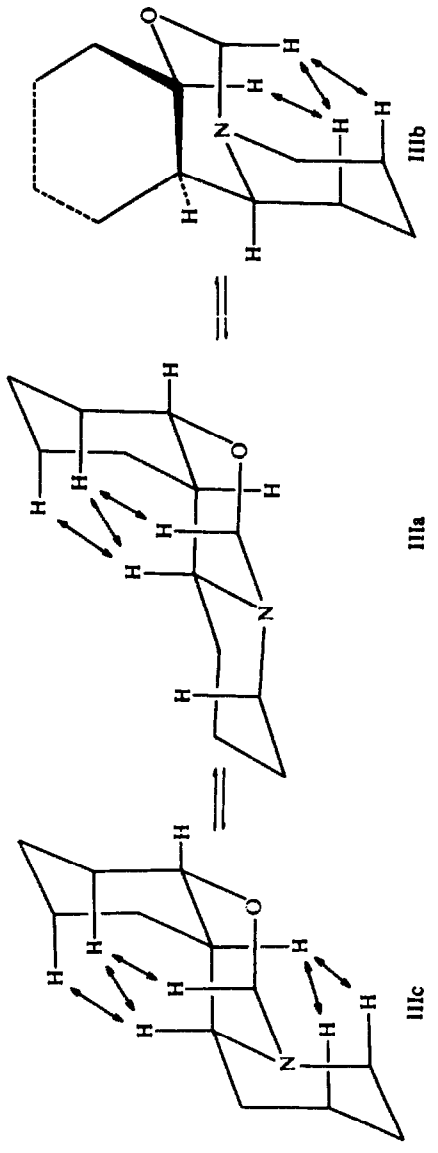
0·73 ppm to higher field as compared with the axial protons in cyclohexane which absorb at 8·80 τ. Therefore in cyclohexane ring systems the effect of one equatorial Me substituent is to shield the axial proton on the adjacent C atom by 0·37 ppm. A shielding of 0·47 ppm has been reported[17] for the axial C1 hydrogen in cyclohexanol which has been equatorially substituted at C2 by a Me group. It is reasonable to assume that this shielding effect will still operate in heterocyclic analogues especially in view of the observation by Delmau[18] of a shielding of the C5-Hax in 4-methyl-1,3-dioxan, by the equatorial Me group of 0·4 ppm.

One would therefore expect the chemical shift of the axial C7a proton in IIa to be ca. 0·4 ppm to higher field than in VII (6·60 τ) i.e. 7·0 τ which is lower than the observed value of 7·2 τ. However such a high chemical shift can only be attributed to an axial proton shielded by a vicinal methylene group and the influence of the remaining ring methylenes cannot be overlooked.

The C7a proton signal has a line width of 25–30 Hz. Although the pattern cannot be analyzed due to its overlap with the signals arising from the C4Heq proton, the wide line width is consistent with two axial–axial proton interactions (*J* ax–ax = 10 Hz) and one axial–equatorial interaction (*J* ax–eq = 4 Hz). These compounds show very slight long range coupling of the C6Heq proton, presumably with the C7a proton, such couplings having been observed[19] between H2eq and H4ax in 1,3-dioxans.

trans anti cis-*Perhydrobenzo* [e] *pyrido* [1.2-c] [1.3] *oxazine* III (R = H, n = 2)

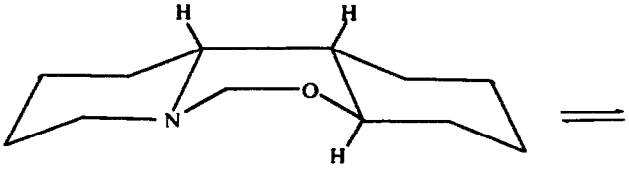
The spectral data obtained from the third isomer off the column is in complete


IIIb
IIIa
IIIc

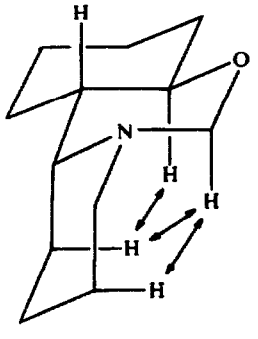
accord with this being the *trans anti cis* isomer. By analogy with the perhydrophenanthrenes,[8] IIIa is expected to be the preferred conformation for this compound. The presence of Bohlmann bands in the IR and the J(C6 methylene) of $-8{\cdot}0$ Hz agree with the presence of the *trans*-fused octahydropyrido [1.2-*c*] [1.3] oxazine moiety in the molecule but not with IIIb (no Bohlmann bands, $J = -8{\cdot}0$ Hz) or IIIc (no Bohlmann bands, $J = -10$ Hz). The chemical shifts of the C6 protons in III should resemble those in VI. In carbon tetrachloride solution the C6 methylene protons of III appeared as a singlet at 6·04 τ and the corresponding protons in VI also gave rise to a singlet (CCl_4 soln) at 6·13 τ. This deshielding of the axial proton by 0·44 and by 0·35 ppm (compared with that in V) is a result of the presence of the *syn* axial C8 methylene in IIIa or of the axial Me group in VI. The equatorial N—CH—O proton in both compounds (compared to V) is shielded by this axial substituent by 0·22 (in IIIa) and by 0·31 ppm (in VI) whereas in cyclohexanes[4] an axial C3 Me deshields an equatorial C1 proton by 0·08 ppm. Shielding rules for carbocyclic compounds are not expected to be exactly applicable to heterocyclic systems but since so many analogies exist it is important to note the apparent exceptions. Delmau[5] has observed a shielding of similar magnitude of the C3 equatorial proton in 1,3-dioxans by the axial C4 Me group to that observed in IIIa which supports the stereochemical assignment made.

The chemical shift (6·25 τ) of the equatorial C7a proton in III represents a shielding of 0·27 ppm by the C11 methylene group (cf τ = 5·98 for the C3Heq proton in VI). This is in agreement with the known[4] shieldings of equatorial CH protons by vicinal equatorial Me groups. First order analysis of the signals arising from the C7a proton in this isomer gives $J_{7a8ax} = 10$ Hz and $J_{7a11a} = 4$ Hz in agreement with stereochemistry IIIa.

This group of compounds show no significant long range coupling of the C6Heq proton even though the extended W stereochemistry is present. A study[5] of long range coupling in Me substituted 1,3-dioxans has shown that the introduction of an axial Me at C4 reduces the long range coupling of H2e with H6e and H6a, the latter coupling becoming unobservable. The axial substitution at position 7a would therefore greatly contribute to the reduction of the long range coupling between the C7a-H proton and the C6-Heq proton.



IVb



IVa

cis syn trans-*Perhydrobenzo* [e] *pyride* [1.2-c] [1.3] *oxazine* IV (R = H, n = 2)

The *cis syn trans* isomer is expected to exist in the most favourable all chair conformation IVa the less favourable conformation IVb involving a boat B ring. The *cis* A:B ring junction in conformation IVa is consistent with this being the structure for the isomer (fourth off the column) showing only weak Bohlmann bands (Table 4). In addition IVa has the correct N—CH_2—O geometry for the observed J of −7·6 Hz.

The chemical shifts of the C6 and C7a protons are in accord with the stereochemistry IVa. Thus compared with the corresponding signals in the spectrum of V the C6 axial proton absorbs at 0·42 ppm to lower field consistent with it being deshielded by the *syn* axial C1 methylene group. This is comparable to the deshielding by 0·45 ppm of the α-proton in going from *trans* 2-t-butylcyclohexanol to iso-t-butylmenthol. Somewhat surprising is the low field absorption of the C6 equatorial proton of 5·51 τ (cf 5·82 τ in V). The C1 methylene would be expected to deshield this proton by only ca. 0·08 ppm if analogies can be drawn with carbocyclic systems.[4] The chemical shift of 6·95 τ for the axial C7a proton is 0·35 ppm to higher field than in VII consistent with the known shieldings[4] of axial protons by vicinal equatorial alkyl substituents (in this case the C11 methylene group). First order analysis of the C7a proton signals gave $J_{7a8ax} = J_{7a11a} = 9{\cdot}4$ Hz, $J_{7a8eq} = 4$ Hz in agreement with IVa. The three proton multiplet at 7·2 τ must be due to the three N—CH protons skew to the N lone pair.

Rates of methylation of the isomeric perhydrobenzo [e] *pyrido* [1.2-c] [1.3] *oxazines*

Stereochemical assignments to certain saturated heterocyclic compounds, for example the isomeric julolidines[20, 21] and the perhydronaphthoquinolizidines[22] have been assisted by studies on the rate of reaction of these bases with methyl iodide. To provide independent evidence in support of the stereochemical assignments made on spectral grounds the rates of methylation of the isomeric perhydrobenzo [*e*] pyrido [1.2-c] [1.3] oxazines and of the two isomeric 4-methyloctahydropyrido [1.2-*c*] [1.3] oxazines (IX and X) were determined. The results (Table 5) indicate a much slower rate for the *trans syn cis* isomer I (R = H, n = 2) and for X than for the remaining compounds. This is in accord with the proposed structures for these compounds since the axially situated C11 methylene in I (R = H, n = 2) and the axial Me in X is expected to shield the nitrogen atom from attack by methyl iodide.

Stereochemistry of perhydrocyclopentano [e] *and perhydrocycloheptano* [e] *pyrido* [1.2-c] [1.3] *oxazines*

Three isomeric perhydrocyclopentano and three isomeric perhydrocycloheptano

TABLE 5. RATES OF QUATERNISATION OF PERHYDROBENZO [*e*] PYRIDO [1.2-*c*] [1.3] OXAZINES AND 4-METHYL SUBSTITUTED OCTAHYDROPYRIDO [1.2-c] [1.3] OXAZINES WITH METHYL IODIDE IN ACETONITRILE AT 29·4°

Compound	K (l mole^{-1} min^{-1})
I (R = H, n = 2)	0·022 ± 0·004
II (R = H, n = 2)	0·321 ± 0·004
III (R = H, n = 2)	0·419 ± 0·002
IX	0·255 ± 0·001
X	0·073 ± 0·002

[*e*] pyrido [1.2-*c*] [1.3] oxazines were obtained by the route shown in Fig. 1 and configurations and preferred conformations Ia–IIIa (R = H, n = 1 and n = 3) assigned to these compounds by comparing the order of collection of the isomers off the carbowax column (Table 2), NMR spectral parameters (Table 3) and the appearance of the 2800–2600 cm^{-1} and 1200–1000 cm^{-1} region of the IR spectrum (Table 4) with the corresponding data for compounds I–III (R = H, n = 2). As can be seen from the Tables, the stereochemically related isomers resembled each other closely in relative retention times and in spectral data and only compounds showing values differing significantly from the other isomers in a set require comment. We were unable to obtain any of the *cis syn trans* isomers IV (R = H, n = 1 and n = 3).

In the case of the *trans syn cis* cyclopentano isomer (I, R = H, n = 1) the chemical shift of the C6 equatorial proton is 0·18 ppm to higher field and that of the C7a proton 0·31 ppm to lower field compared with the corresponding chemical shifts observed for the 6-membered ring analogue (I, R = H, n = 2). This lower field absorption of the C7a proton in the cyclopentano isomer is also observed in the *trans anti trans* and *trans anti cis* series. A contributing factor to this deshielding might be a distortion of ring B caused by the fusion to the 5-membered ring. This would result, among other things, in slightly different lone pair —CH bond orientations and in support of this, *J* (C6 methylene) in the three sets of isomers is observed to be always slightly more negative for the cyclopentano isomers. In the *trans anti cis* compounds the C7a proton absorbs at increasingly higher field as the ring size increases.

The values of *J* (C6 methylene) were observed to be rather similar for the 6 and 7-membered ring compounds and in each set the chemical shifts of these protons tended to be slightly to higher field for the cycloheptano compounds. *J* (C6 methylene) was found to be ca. 0·1 Hz more positive for the *trans syn cis* isomers (I, R = H) than for II and III (R = H). In all the isomers I–III (R = H) a broadened one proton doublet was observed at ca. 7·4 τ characteristic of an equatorial C—H proton adjacent to a N atom with its lone pair of electrons axially orientated and the coupling constant of ca. −11 Hz is in the expected range for *J* 4eq4ax in the environment shown in Ia, IIa and IIIa.

As stated above the IR spectra of all the isomers possessing the same stereochemistry show similarities in the appearance of Bohlmann bands and in the 1200–1000 cm^{-1} region. The *trans syn cis* isomers (I) show one prominent band at 2765 cm^{-1} with a number of moderate to weak absorptions on its low wave number side. The *trans anti trans* isomers (II) show Bohlmann bands of similar appearance to those shown by I whereas the *trans anti cis* isomers (III) show a prominent band at ca. 2770 cm^{-1} with a set of descending maxima on the low wave number side. In the 1200–1000 cm^{-1} region, isomers I show a fairly symmetrical absorption pattern with a marked doublet in the central region, quite distinctive from the more complex absorption observed for II and III.

4-Methylperhydrocycloalkano [e] *pyrido* [1.2-c] [1.3] *oxazines*

Having established the configurations and preferred conformations of the unsubstituted tricyclic compounds it was considered of importance to study some Me substituted derivatives since if significant variations in NMR parameters (other than the direct effect of the Me on chemical shifts) between these compounds and their unsubstituted analogues were to be observed, the presence of appreciable quantities of alternative conformations in equilibrium with Ia, IIa and IIIa would be indicated.

Eight racemic isomers are possible for a monomethylperhydrocycloalkano [*e*] pyrido [1.2-*c*] [1.3] oxazine and because separation problems with such a mixture might be anticipated to prove difficult it was decided to prepare the 4 Me compounds. In this case only four isomers, i.e. those with the C4 hydrogen possessing a *cis* relationship to the A:B bridgehead hydrogen, were expected to be produced by the synthetic route shown in Fig. 1 since catalytic reduction of 6-methyl-2-pyridyl carbinol[23] and of 6-methyl-2-pyridyl ethanol[2] has been found to give exclusively the *cis*-2,6-*H*-piperidine derivatives. Less than four isomers for each set were in fact obtained and these were assigned the configurations and preferred conformations shown in the Tables for reasons to be discussed below.

As was the case with the unsubstituted compounds the *trans syn cis* isomer (I, R = Me) came off the GLC column first (Table 2) but the *trans anti trans* isomer (II, R = Me, n = 2) and the *trans anti cis* isomer (III, R = Me, n = 2) came off the column together and were then separated by column chromatography over Woelm alumina. Unlike the unsubstituted analogues, III (R = Me, n = 1) possessed a shorter retention time than II (R = Me, n = 1).

The presence of Bohlmann bands in the IR spectra (Table 6) and absence from the NMR spectra of the doublet at ca. 7·4 τ observed in I–III (R = H) corresponding to the C4 equatorial proton is in accord with all the Me isomers existing in a *trans* A:B conformation with the C4 Me group equatorially orientated. In agreement with this the centre of the Me doublet in the 4-Me isomers varied only from 8·94 to 8·99 τ (Table 3) this being close to the value of 8·97 τ observed for the closely related *cis*-9,5-*H*-9-methyloctahydropyrido [1.2-*c*] [1.3] oxazine which has been shown[2] to exist in the *trans*-fused ring conformation VIII with an equatorial Me group. The geminal couplings between the C6 methylene protons also agrees with a *trans* A:B ring junction.

TABLE 6. IR SPECTRA OF 4-METHYL PERHYDROCYCLOALKANO [*e*] PYRIDO [1.2-*c*] [1.3] OXAZINES

Compound	2800–2650 cm^{-1}	1200–1000 cm^{-1}
I (R = Me, n = 1)	2815(mw) 2765(m) 2740(m) 2720(m) 2680(mw)	1203(mw) 1180(mw) 1160(m) 1140(m) 1120(m) 1103(vs) 1080(m) 1060(m)
I (R = Me, n = 2)	2820(m) 2780(m) 2760(m) 2720(m) 2690(mw) 2660(mw)	1195(mw) 1165(m) 1150(vs) 1125(vs) 1115(s) 1105(s) 1085(m) 1055(m)
I (R = Me, n = 3)	2780(m) 2760(m) 2740(m) 2730(m) 2720(m) 2690(m) 2660(m)	1205(m) 1200(m) 1180(mw) 1170(mw) 1148(s) 1135(vs) 1115(vs) 1093(s) 1070(mw) 1055(m)
II (R = Me, n = 1)	2820(m) 2785(m) 2750(m) 2740(m) 2720(m) 2690(mw)	1190(mw) 1180(mw) 1152(s) 1140(m) 1125(s) 1110(m) 1090(m) 1080(m) 1060(s) 1040(mw) 1020(mw)
II (R = Me, n = 2)	2820(m) 2780(m) 2760(m) 2740(m) 2730(m) 2720(m) 2690(mw) 2660(mw)	1298(m) 1165(m) 1155(vs) 1135(m) 1120(mw) 1105(vs) 1095(vs) 1065(m) 1055(m) 1040(mw) 1030(mw)
III (R = Me, n = 1)	2820(mw) 2790(m) 2780(m) 2760(m) 2740(mw)	1203(mw) 1185(m) 1157(m) 1140(m) 1130(s) 1120(m) 1100(s) 1085(m) 1064(m) 1045(mw)
III (R = Me, n = 3)	2820(m) 2790(m) 2760(m) 2735(m) 2690(mw) 2660(mw)	1205(m) 1198(m) 1156(s) 1138(s) 1124(s) 1118(s) 1095(s) 1080(s) 1066(m) 1030(mw)

An estimation of the magnitude of changes (compared to I–III, R = H) in chemical shifts of the C6 and C7a protons in the 4-Me compounds brought about by the presence of the equatorial Me group may be obtained by studying the chemical shift differences between V and VIII. Table 1 shows that the Me group does not significantly alter the chemical shifts of the C3 protons whereas the equatorial C1H proton is deshielded by 0·40 ppm and the corresponding axial proton is shielded by 0·25 ppm. An examination of the NMR parameters of the 4-methylperhydrobenzo [*e*] pyrido [1.2-*c*] [1.3] oxazines (Table 3) shows that the chemical shifts of the C7a protons are almost identical with those of the unsubstituted analogues and the C6 equatorial proton is deshielded by the Me group by 0·46 to 0·62 ppm, and the axial C6 proton shielded by 0·06–0·17 ppm. Thus, the deshielding by the Me group of the C6 Heq is apparently greater than in VIII and the shielding of C6 Hax less. The deshielding of C6 Heq in the cyclopentano compounds is ca. 0·53 ppm and in the cycloheptano compounds ca. 0·44 ppm. The corresponding shieldings of the C6 Hax protons vary from 0·04 to 0·17 ppm with the exception of III (R = Me, n = 1) where this proton is deshielded by 0·09 ppm. From this comparative study of the NMR data the stereochemical assignments shown in the Tables were made, with all the isomers possessing a *trans* A:B ring junction (Ia, IIa, IIIa) and an equatorial Me group. The lack of an exact match between the observed chemical shift data and the values predicted by the change V → VIII may arise from small variations in the shape of the oxazine ring, presumably brought about by fusion to the various C rings.

EXPERIMENTAL

All elemental analyses were carried out by Dr. F. Pascher and E. Pascher, Microanalytical Laboratory, Bonn, W. Germany and at Reading University (m.p. are uncorrected). IR spectra were recorded on a Perkin–Elmer 457 grating instrument and measured as 0·2M solns in CCl_4 using 0·2 mm matched cells. The NMR spectra were determined on a Perkin–Elmer R-10 and a Varian HA-100 spectrometer as 10% solns in CCl_4 or benzene with TMS as internal reference. Separations were carried out on a Varian Autoprep gas chromatograph.

Preparation of 2-(2-pyridyl) cycloalkanones

General procedure. The preparation of 2-(2-pyridyl) cyclohexanone was carried out according to the method of Hamana and Noda,[13] from pyridine-1-oxide and 1-morpholino-cyclohexen-1-amine. This method was also employed in the preparation of 2-(2-pyridyl) cyclopentanone and 2-(2-pyridyl) cycloheptanone from 1-morpholino-cyclopenten-1-amine and 1-morpholino-cyclohepten-1-amine respectively.

2-(2-Pyridyl) cyclopentanone. The reaction of 1-morpholino-cyclopenten-1-amine (153 g, 1M) with pyridine-N-oxide (47·5 g, 0·5M) and benzoyl chloride (84·3 g, 0·6M) gave on distillation 2-(2-pyridyl) cyclopentanone (40 g, 40%) as an orange-yellow oil b.p. 54–56°/0·04 mm.

2-(2-Pyridyl) cycloheptanone. The reaction of 1-morpholino-cyclohepten-1-amine (50 g, 0·3M) with pyridine-1-oxide (15 g, 0·15M) and benzoyl chloride (41·6 g, 0·19M) gave on distillation 2-(2-pyridyl) cycloheptanone (26·8 g, 90%) as a yellow oil b.p. 84–88°/0·15 mm. (Found: C, 76·04; H, 7·99; N, 7·64. $C_{12}H_{15}NO$ requires: C, 76·15; H, 7·99; N, 7·40%).

Preparation of 2-(2-piperidyl) cycloalkanols

General procedure. The 2-(2-pyridyl) cycloalkanone was hydrogenated at 60 psi and at room temp using PtO_2 catalyst. The colourless soln was basified with NaOH aq and ether extracted 3 times. The ether soln was dried over Na_2SO_4 and evaporated to leave the crude 2-(2-piperidyl) cycloalkanol which was distilled.

2-(2-Piperidyl) cyclohexanol. The product of hydrogenation of 2-(2-pyridyl) cyclohexanone was sublimed at 102°/0·35 mm. The mixture of isomers was obtained as a solid, m.p. 70·5–80°. (Found: C, 72·21; H, 11·47; N, 7·65. $C_{11}H_{21}NO$ requires: C, 72·08; H, 11·55; N, 7·64%).

2-(2-Piperidyl) cyclopentanol. The product of hydrogenation of 2-(2-pyridyl) cyclopentanone was sublimed at 118°/0·4 mm to give a solid, m.p. 141·5–143°. (Found: C, 71·54; H, 11·59; N, 8·40. $C_{10}H_{19}NO$ requires: C, 70·96; H, 11·32; N, 8·28%).

2-(2-Piperidyl) cycloheptanol. The product of hydrogenation of 2-(2-pyridyl) cycloheptanone was sublimed at 44–48°/0·1 mm to give a solid, m.p. 51–53°. (Found: C, 72·95; H, 11·76; N, 7·20. $C_{12}H_{23}NO$ requires: C, 73·04; H, 11·75; N, 7·10%).

Preparation of perhydrocycloalkano [e] *pyrido* [1.2-c] [1.3] *oxazines*

General procedure. The 2-(2-piperidyl) cycloalkanol was shaken with an excess of 36% aqueous formaldehyde soln for ½ hr. The mixture was basified with NaOH aq and ether extracted 3 times. The ether soln was dried (Na_2SO_4), evaporated, and the residue distilled to give the required perhydrocycloalkano [*e*] pyrido [1.2-*c*] [1.3] oxazine.

Perhydrobenzo [e] *pyrido* [1.2-c] [1.3] *oxazine.* 2-(2-Piperidyl) cyclohexanol (40 g) gave a mixture of 4 isomers (18·5 g, 45%) as a colourless oil, b.p. 56–60°/0·01 mm. (Found: C, 73·77; H, 10·84; N, 6·94. $C_{12}H_{21}NO$ requires: C, 73·79; H, 10·84; N, 7·17%). The isomers were separated on a 15% carbowax/chromosorb W. column, oven 180°, with a sample injection of 0·2 ml and with H_2 as carrier gas (flow rate of 200 ml/min).

trans syn cis Isomer I (R = H, n = 2) n_D^{13} 1·5173, picrate m.p. 205·5–206·5° (Found: N, 13·48%).

trans anti trans Isomer II (R = H, n = 2) n_D^{13} 1·5121 m.p. 180–180·5° (Found: N, 13·32%).

trans anti cis Isomer III (R = H, n = 2) n_D^{13} 1·5160, picrate m.p. 156–157° (Found: N, 13·43%).

cis syn trans Isomer IV (R = H, n = 2) m.p. 39–40°, picrate m.p. 150·5–152·5° (Found: N, 13·41. $C_{18}H_{24}N_4O_8$ requires: N, 13·20%).

Perhydrocyclopentano [e] *pyrido* [1.2-c] [1.3] *oxazine.* 2-(2-Piperidyl) cyclopentanol (17 g) gave a mixture of three isomers (9·4 g, 56%) as a colourless oil b.p. 47–49°/0·1 mm. (Found: C, 72·85; H, 10·24; N, 7·80. $C_{11}H_{19}NO$ requires: C, 72·88; H, 10·57; N, 7·73%).

The isomers were separated on a 15% carbowax/chromosorb W. Column, oven 185°, detector 250°, injection block 240°. Sample injection was 0·1 ml with hydrogen as carrier gas at a flow rate of 200/ml/min.

trans syn cis Isomer I (R = H, n = 1) n_D^{11} 1·5092, picrate m.p. 146–148° (Found: 13·65%).

trans anti trans Isomer II (R = H, n = 1) n_D^{11} 1·5058, picrate m.p. 165·5–167° (Found: 13·77%).

trans anti cis Isomer III (R = H, n = 1) n_D^{11} 1·5124, picrate decomposed during recrystallization. $C_{17}H_{22}N_4O_8$ requires: N, 13·65%.

Perhydrocycloheptano [1.2-c] [1.3] *oxazine.* 2-(2-Piperidyl) cycloheptanol (13·1 g) gave a mixture of 3 isomers (8·6 g, 62%) as a colourless oil b.p. 57–59°/0·05 mm. (Found: C, 73·86; H, 10·66; N, 7·24. $C_{13}H_{23}NO$ requires: C, 74·59; H, 11·08; N, 6·69%).

The isomers were separated on a 15% carbowax/chromosorb W., sample injection 0·3 ml with H_2 as carrier gas at a flow rate of 200 ml/mm.

trans syn cis Isomer I (R = H, n = 3) $n_D^{12.5}$ 1·5140

trans anti trans Isomer II (R = H, n = 3) $n_D^{12.5}$ 1·5285.

trans anti cis Isomer III (R = H, n = 3) $n_D^{12.5}$ 1·5223.

2-(6-Methyl-2-pyridyl) cycloalkanols

General procedure. The preparation 2-(6-methyl-2-pyridyl) cyclohexanone was carried out according to the method of Hamana and Noda[14] from 2-picoline-1-oxide and 1-morpholino-cyclohexen-1-amine. This method was also employed in the preparation of 2-(6-methyl-2-pyridyl) cyclopentanone and 2-(6-methyl-2-pyridyl) cycloheptanone from 1-morpholino-cyclopenten-1-amine and 1-morpholino-cyclohepten-1-amine respectively. The ketones were not purified but hydrogenated directly at 60 psi and at room temp with PtO_2 catalyst. The soln was filtered, basified with NaOH aq and ether extracted 3 times. The ether soln was dried (Na_2SO_4) and evaporated to give the crude 2-(6-methyl-2-piperidyl) cycloalkanols.

2-(6-Methyl-2-piperidyl) cyclohexanol. The product obtained by reduction of 2-(6-methyl-2-pyridyl) cyclohexanone was recrystallized from light petroleum–benzene to give 2-(6-methyl-2-piperidyl) cyclohexanol as colourless needles m.p. 115–116°. (Found: C, 73·52; H, 11·86; N, 7·09. $C_{12}H_{23}NO$ requires: C, 73·04; H, 11·75; N, 7·10%).

2-(6-Methyl-2-piperidyl) cyclopentanol. The product from 2-(6-methyl-2-pyridyl) cyclopentanone was recrystallized from light petroleum–benzene to give 2-(6-methyl-2-piperidyl) cyclopentanol as a felt of soft colourless needles m.p. 138–139°. (Found: C, 72·15; H, 11·54; N, 7·54. $C_{11}H_{21}NO$ requires: C, 72·08; H, 11·55; N, 7·64%).

2-(6-Methyl-2-piperidyl) cycloheptanol. 2-(6-Methyl-2-piperidyl) cycloheptanol was obtained as a colourless viscous oil b.p. 115–124°/0·03 mm which because of the occurrence of decomposition on further fractionation was not obtained analytically pure.

4-Methylperhydrobenzo [e]-*pyrido* [1.2-c] [1.3] *oxazine*

2-(6-Methyl-2-piperidyl) cyclohexanol (12 g) on treatment with formaldehyde gave a mixture of 3 isomers (9·5 g) as a colourless oil b.p. 92–99°/0·3 mm. (Found: C, 74·63; H, 11·21; N, 7·12. $C_{13}H_{23}NO$ requires: C, 74·59; H, 11·08; N, 6·69%). The mixture was separated into a mixture of 2 isomers and one pure isomer, m.p. 35–36·5°. (Found: C, 74·69; H, 10·97; N, 6·75. $C_{13}H_{23}NO$ requires: C, 74·59; H, 11·08; N, 6·69%), by preparative GLC using a diethylene glycol succinate column, oven 180°. Sample injection was 0·20 ml with H_2 as carrier gas at a flow rate of 200 ml/min.

The binary mixture of isomers was chromatographed over Woelm Alumina to give II (R = Me, n = 2) m.p. 51–52° from petroleum ether. (Found: C, 74·84; H, 11·32; N, 6·63. $C_{13}H_{23}NO$ requires: C, 74·59; H, 11·08; N, 6·69%).

4-Methylperhydrocyclopentano [e] *pyrido* [1.2-c] [1.3] *oxazine*

2-(6-Methyl-2-piperidyl) cyclopentanol (52·2 g) on treatment with formaldehyde gave a mixture of 3 isomers as a colourless oil b.p. 76–78°/0·28 mm. (Found: C, 73·79; H, 10·86; N, 7·38. $C_{12}H_{21}NO$ requires: C, 73·79; H, 10·84; N, 7·17%).

The isomers were separated on a diethylene glycol succinate column, oven 150°, with a sample injection of 0·1 ml.

4-Methylperhydrocyclohepta [e] *pyrido* [1.2-c] [1.3] *oxazine*

2-(6-Methyl-2-piperidyl) cycloheptanol (22·5 g) on treatment with formaldehyde gave a mixture of 2 isomers (20 g) as a colourless oil b.p. 83–94°/0·08 mm. (Found: C, 75·16; H, 11·32; N, 6·30. $C_{14}H_{25}NO$ requires: C, 75·28; H, 11·28; N, 6·27%).

The isomers were separated on a diethylene glycol succinate column, oven 200°, with a sample injection of 0·1 ml and H_2 as carrier gas at a flow rate of 200 ml/min.

2-(2-Piperidyl) propanol

2-(2-Pyridyl) propanol[9] (40·5 g) was hydrogenated at 60 psi and at room temp in glacial AcOH (300 ml) with PtO_2 (1 g) as catalyst. The catalyst was filtered off and AcOH was removed *in vacuo*. The soln was basified with NaOH aq and extracted several times with ether. The dried (Na_2SO_4) ether extract was evaporated to leave a viscous liquid which solidified after prolonged freezing. The solid on recrystallization from light petroleum–benzene gave 2-(2-piperidyl) propanol (30 g) as aggregates of colourless needles m.p. 58–59°. (Found: C, 67·26; H, 11·83; N, 10·04. $C_8H_{17}NO$ requires: C, 67·09; H, 11·96; N, 9·78%).

4-Methyloctahydropyrido [1.2-c] [1.3] *oxazine*

2-(2-Piperidyl) propanol was shaken with excess 36% formaldehyde soln for ½ hr. The reaction mixture was worked up in the usual way to yield on distillation 4-methyloctahydropyrido [1.2-c] [1.3] oxazine as a mixture of 2 isomers b.p. 28–31°/0·02 mm. (Found: C, 69·42; H, 10·98; N, 9·04. $C_9H_{17}NO$ requires: C, 69·63; H, 11·04; N, 9·02%).

The mixture was separated by preparative GLC using a diethylene glycol succinate column, oven 150°, with sample injection of 0·1 ml and H_2 as carrier gas at a flow rate of 200 ml/min. The isomers present in an approximately 50/50 ratio were collected in the following order:

cis-4,5-H-4-Methyloctahydropyrido [1.2-c] [1.3]oxazine b.p. 30–32°/0·03 mm. (Found: C, 70·02; H, 11·12; N, 8·33. $C_9H_{17}ON$ requires: C, 69·63; H, 11·04; N, 9·02%).

trans-4,5-H-4-Methyloctahydropyrido [1.2-c] [1.3] oxazine b.p. 28–31°/0·03 mm. (Found: C, 69·62; H, 10·89; N, 9·11. $C_9H_{17}ON$ requires: C, 69·63; H, 11·04; N, 9·02%).

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