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PROTON MAGNETIC RESONANCE STUDIES OF COMPOUNDS WITH BRIDGEHEAD NITROGEN ATOMS—VI*

CONFIGURATIONAL AND CONFORMATIONAL STUDIES WITH DERIVATIVES OF OCTAHYDROPYRIDO [1,2-c] 1,3-OXAZINES

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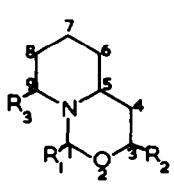
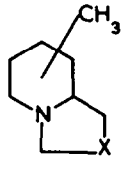
Abstract—The configurations and preferred conformations of some substituted octahydropyrido[1,2-c]1,3-oxazines have been deduced on the basis of NMR spectra and the 2700–2850 cm^{-1} region of the IR spectra. The configurations of (±) sedridin and (±) sedamin have been confirmed. The importance of dipole interactions in determining the preferred conformations of this system have been illustrated.

THE reliability of the Bohlmann IR criterion in the determination of the preferred conformations of quinolizidines has been questioned[1] and its inability to determine the presence of *cis* fused ring conformations is recognized. There has also been some discussion on the conformation of compounds of type I (R_2 = Me, R_3 = H, R_1 = *p*-substituted phenyl) with regard to the configuration of sedridin.[2] We therefore felt that the results of our studies on the configurations and preferred conformations of some compounds in this series would be of interest. In previous papers[3–5] we have demonstrated the utility of geminal coupling constants (J_{gem}) in solving conformational problems with compounds of type II (X = O,S).

The first group of compounds investigated are of type III with a C_1 methylene group. Two racemic epimers are possible for each of the substituted compounds in addition to which each epimer may exist as an equilibrium mixture of the *trans* IV and *cis* fused ring conformation (V and VI).



I



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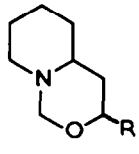
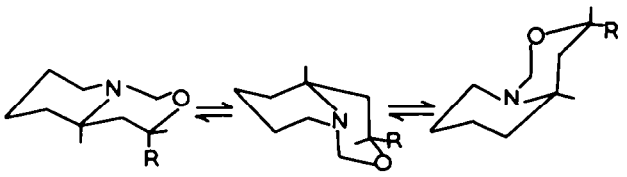


III

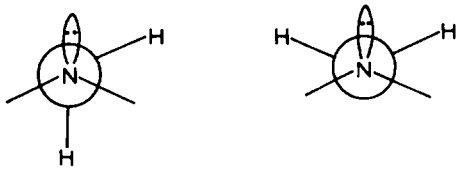
* Part V. P. J. Chivers, T. A. Crabb and R. O. Williams, *Tetrahedron* in press.



IV V VI

Different conformations in these compounds should be reflected in the 2850–2600 cm^{-1} region of the IR spectrum,[6,7] thus conformations V and VI are not expected to produce Bohlmann's bands since they do not allow two C—H bonds adjacent to the N to be *trans* and axial to the N lone pair of electrons.

The J_{gem} for the C_1 methylene protons will also vary with different conformations since this depends on the degree of overlap between the molecular orbitals of the methylene group and the lone pairs of electrons on the adjacent heteroatoms.[8,9] Thus conformations IV and V, in which one of the C—H bonds of the C_1 methylene group is orientated *trans* and axial with respect to the lone pair of electrons on the N as depicted in VII, should allow a more efficient overlapping between the C_1 methylene group and the N lone pair of electrons[4,10,11] than is possible in conformation VI in which the relative positions of the N lone pair and the methylene group are as in VIII. Conformers of type IV and V would therefore be expected to have a more positive* J_{gem} for the C_1 methylene group than conformers of type VI. The orientation of the lone pairs of electrons on the O atom with respect to the C_1 methylene group is the same in IV, V and VI. In addition to changes in the ring fusion the J_{gem} for the C_1 methylene group should also be sensitive to distortion of the tetrahydro 1,3-oxazine ring induced by the presence of axial groups.



VII VIII

As may be seen from Table 1, all the compounds III have a J_{gem} for the C_1 methylene group of ca. −8·0 c/s suggesting that the conformation of the tetrahydro 1,3-oxazine ring is similar in all five compounds. J_{gem} for the C_2 methylene group in tetrahydro 1,3-oxazines varies from −7·7 to −10·0 c/s.[9,11] Since Urbanski[12] has shown from dipole moment data that 5-nitro, 5-methyl, 3-t-butyl, tetrahydro 1,3-oxazine exists in the chair conformation IX with the t-butyl group equatorial and this compound has a J_{gem} for the C_2 methylene protons of −7·7 c/s, it follows that

* All values of J_{gem} are assumed to be negative.

TABLE 1. NMR SPECTRA OF OCTAHYDROPYRIDO [1,2-c] 1,3-OXAZINES

	Coupling constants (c/s)*						
	J_{1a1e}	J_{3a3e}	J_{3a4e}	J_{3a4a}	J_{3e4a}	J_{3e4e}	J_{9a9e}
Octahydropyrido[1.2-c]1,3-oxazine	−8·0	−11	3	11	5	ca. 1	ca. 10
cis-1,5-*H*-1-Methyloctahydropyrido[1.2-c]1,3-oxazine	—	−11	3	11	5	ca. 1·5	ca. 10
cis-1,5-*H*-1-Phenyloctahydropyrido[1.2-c]1,3-oxazine	—	−11	3	11	5	1·5	ca. 10
trans-1, *cis*-9,5-*H*-1-9-Dimethyloctahydropyrido[1.2-c]1,3-oxazine	—	−11	3·5	11	—	—	—
cis-9,5-*H*-9-Methyloctahydropyrido[1.2-c]1,3-oxazine	−8·0	−10	3	11	4·8	ca. 1	—
trans-9,5-*H*-9-Methyloctahydropyrido[1.2-c]1,3-oxazine	−10·0	−11·3	3	11·3	4·5	ca. 1	—
cis-3,5-*H*-3-Methyloctahydropyrido[1.2-c]1,3-oxazine	−8·0	—	—	—	—	—	ca. 10
trans-3,5-*H*-3-Methyloctahydropyrido[1.2-c]1,3-oxazine	−8·0 (benzene)	—	—	—	ca. 3·0	ca. 1	ca. 10
cis-3,5-*H*-3-Phenyloctahydropyrido[1.2-c]1,3-oxazine	−8·3	—	ca. 1	8·5	—	—	ca. 10
trans-3,5-*H*-3-Phenyloctahydropyrido[1.2-c]1,3-oxazine	−8·3	—	—	—	3	3	ca. 10

* ±0·3 c/s.

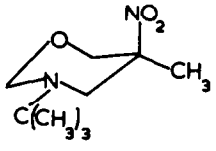
all the compounds III with $J_{gem} = -8{\cdot}0$ c/s exist with the tetrahydro 1,3-oxazine ring in a chair conformation.

Additional evidence for the chair conformation of the tetrahydro 1,3-oxazine ring may be obtained from studying vicinal coupling constants (J_{vic}) and chemical shift data. In III (R = H) a complete first order analysis of the coupling constants in the

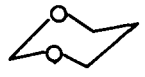
TABLE 2. COUPLING CONSTANTS IN 1,3-DIOXANS c/s

J_{4a5a}	9 to 11·6	J_{4e5e}	1·3 to 1·76
J_{4a5e}	2·6 to 4·4	J_{6a6e}	−11·2
J_{4e5a}	3·3 to 5·9		

tetrahydro 1,3-oxazine ring is possible. The coupling constants obtained (Table 1) compare closely with the analogous couplings observed in 1,3-dioxans[13] (Table 2) which are known to exist in chair conformations (X).



IX



X

All but one of the compounds in the present series had Bohlmann's bands in their IR spectrum (Table 3) indicating the presence of the *trans* fused ring conformation IV. The exception was the *trans*-9,5-*H*-9-methyl compound. In this compound however (if one assumes a *trans*-ring fusion) one of the axial protons next to the N atom

TABLE 3. IR SPECTRA OF OCTAHYDROPYRIDO [1,2-c] 1,3-OXAZINES

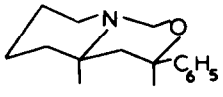
Compound	cm^{-1}	ε_a
Octahydropyrido[1.2-c]1,3-oxazine	2682	52
	2725	50
	2739	44
	2762	84
	2776	68
	2813	50
cis-1,5-*H*-1-Methyloctahydropyrido[1.2-c]1,3-oxazine	2615	19
	2660	26
	2671	28
	2713	54
	2724	48
	2745	50
	2755	48
	2785	84

TABLE 3—*continued*

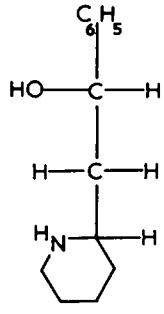
Compound	cm^{-1}	ε_a
cis-1,5-*H*-1-Phenyloctahydropyrido[1.2-c]1,3-oxazine	2658	24
	2715	68
	2747	44
	2760	52
	2786	86
trans-1, *cis*-9,5-*H*-1-9-Dimethyloctahydropyrido[1.2-c]1,3-oxazine	2620	18
	2660	16
	2700	28
	2788	74
	2832	64
cis-9,5-*H*-9-Methyloctahydropyrido[1.2-c]1,3-oxazine	2615	18
	2650	26
	2683	34
	2698	50
	2725	72
	2758	62
	2774	74
	2812	46
trans-9,5-*H*-9-Methyloctahydropyrido[1.2-c]1,3-oxazine	2640	11
	2725	23
	2760	26
cis-3,5-*H*-3-Methyloctahydropyrido[1.2-c]1,3-oxazine	2668	25
	2687	36
	2723	39
	2735	54
	2764	94
	2811	58
trans-3,5-*H*-3-Methyloctahydropyrido[1.2-c]1,3-oxazine	2622	18
	2656	30
	2682	54
	2714	46
	2737	64
	2759	94
	2811	60
cis-3,5-*H*-3-Phenyloctahydropyrido[1.2-c]1,3-oxazine	2610	18
	2652	23
	2682	48
	2715	44
	2733	57
	2762	97
	2812	72
trans-3,5-*H*-3-Phenyloctahydropyrido[1.2-c]1,3-oxazine	2615	14
	2640	18
	2690	30
	2723	48
	2773	97
	2823	58

in the piperidine ring is replaced by a Me group and since the axial proton between the heteroatoms does not significantly contribute to the Bohlmann's bands in this type of system, there is only one effective C—H bond adjacent to the N and *trans*- and axial with respect to the lone pair of electrons. Under these conditions Bohlmann's bands should not be present. Evidence for the correctness of this view is that in the 1,9-dimethyl compound (I, $R_1 = R_3 = Me$, $R_2 = H$) where the axial C_1 proton is replaced by a Me group the Bohlmann's bands are not significantly altered when compared with the unsubstituted parent compound III (R = H).

If, as the J_{gem} for the C_1 methylene protons and the IR spectra signify all the compounds III exist predominantly with a *trans*-fused ring conformation and a chair conformation for the tetrahydro-1,3-oxazine ring, the vicinal coupling constants of the C_3 proton with the C_4 protons in the 3-substituted compounds will serve to distinguish between the two epimers. Thus in *trans*-3,5-*H*-3-phenyloctahydropyrido[1.2-c]1,3-oxazine (IV, R = Ph) the C_3 proton should show an equatorial-axial and an equatorial-equatorial J_{vic} if the Ph group is axial and the ring fusion is *trans*. The C_3 proton in the *cis*-3,5-*H*-3-phenyl compound XI however will show an axial-axial and an axial-equatorial J_{vic} since the Ph group may be assumed equatorial and the ring fusion *trans*. It can be seen that the C_3 proton of one epimer shows two J_{vics} of 3 c/s ($J_{3e4a} \simeq J_{3e4e}$) and this must therefore be *trans*-3,5-*H*-3-phenyloctahydropyrido[1.2-c]1,3-oxazine (IV R = Ph), the other epimer shows one J_{vic} of 8·5 c/s which must be an axial-axial coupling (J_{3a4a}) and another of 1 c/s (J_{3a4e}) and this therefore corresponds to the *cis*-3,5-*H*-3-phenyl compound XI. In addition the



XI



XII

equatorial C_3 proton in IV (R = Ph) comes 0·72 ppm to lower field than the axial C_3 proton in XI, (Table 4). The vicinal couplings in the phenyl epimers are somewhat smaller than those observed in the rest of the series III, this is probably due to the electron withdrawing properties of the Ph group rather than to distortion of the tetrahydro-1,3-oxazine ring since both the epimers are similarly affected, and the epimer with an equatorial Ph group should be free of any ring distortion.

This work also verifies the configuration of (±) sedamine and (±) allosedamine. Lukes *et al.*[14] have shown that (±) norsedamine has a m.p. 98–99° and (±) norallosedamine has a m.p. 112–113° and these have been correlated with (±) sedamine and (±) allosedamine by N-methylation. Thus *cis*-3,5-*H*-3-phenyloctahydropyrido

TABLE 4. NMR SPECTRA OF OCTAHYDROPYRIDO [1,2-c] 1,3-OXAZINES

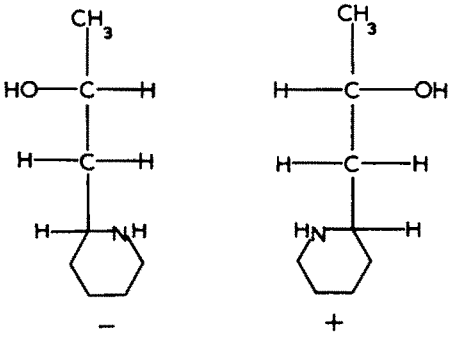
Compound	Chemical shifts (τ)*							
	Solvent	H_{1e}	H_{1a}	H_{3e}	H_{3a}	H_{9e}	H_{9a}	Others
Octahydropyrido[1.2-c]1,3-oxazine	CCl_4	5·82	6·48	6·05	6·64	7·30 (m)	8·05 (m)	
cis-1,5-*H*-1-Methyloctahydropyrido[1.2-c]1,3-oxazine	CCl_4	—	6·48	6·10	6·59	7·20 (m)	8·0 (m)	
cis-1,5-*H*-1-Phenyloctahydropyrido[1.2-c]1,3-oxazine	CCl_4	—	5·78	6·02	6·49	7·65 (m)	7·90 (m)	
trans-1, *cis*-9,5-*H*-1-9-Dimethyloctahydropyrido[1.2-c]1,3-oxazine	CCl_4	5·25	—	6·10 (m)	6·30 (m)	—	7·7 (m)	
cis-9,5-*H*-9-Methyloctahydropyrido[1.2-c]1,3-oxazine	CCl_4	5·42	6·73	6·10	6·67	—	8·0 (m)	
trans-9,5-*H*-9-Methyloctahydropyrido[1.2-c]1,3-oxazine	CCl_4	5·43	6·03	6·04	6·43	—	7·0 (m)	6·90 H_{5a}
cis-3,5-*H*-3-Methyloctahydropyrido[1.2-c]1,3-oxazine	CCl_4	5·75	6·36	—	6·60	7·25 (m)	7·95 (m)	
	Benzene	5·71	6·45	—	6·60	7·45 (m)	8·15 (m)	
trans-3,5-*H*-3-Methyloctahydropyrido[1.2-c]1,3-oxazine	CCl_4	6·13	6·13	5·98	—	7·35 (m)	7·8 (m)	
	Benzene	5·95	6·15	5·80	—	7·45 (m)	8·0 (m)	
cis-3,5-*H*-3-Phenyloctahydropyrido[1.2-c]1,3-oxazine	CCl_4	5·60	6·23	—	5·70	7·25 (m)	7·90 (m)	
trans-3,5-*H*-3-Phenyloctahydropyrido[1.2-c]1,3-oxazine	CCl_4	6·0	6·26	4·98	—	7·35 (m)	7·90 (m)	

* ±0·05 ppm (m) = multiplet measured from centre.

[1.2-c]1,3-oxazine (XI) should be obtained from (±) norsedamine (XII (−) norsedamine) and *trans*-3,5-*H*-3-phenyloctahydropyrido[1.2-c]1,3-oxazine should be obtained from (±) norallosedamine. As can be seen from the experimental section our results are in agreement with these conclusions.

The vicinal coupling constants of the C_3 proton in the 3-methyl substituted compounds could not be extracted due to coupling of this proton with the Me group. It was however possible to assign configurations purely on the basis of chemical shifts. Booth[15] has shown that for cyclohexane derivatives an axial Me group on C_1 may deshield the axial protons on C_3 and C_5 by up to 0·25 ppm, whereas an equatorial Me group on C_1 has little effect on either of the C_3 or C_5 protons. Thus in *trans*-3,5-*H*-3-methyloctahydropyrido[1.2-c]1,3-oxazine (IV, R = Me), where the Me group is axial, the axial proton on C_1 should be deshielded. In the *cis*-3,5-*H*-3-Me compound with an equatorial Me group the chemical shifts for the C_1 protons should be similar to those observed for the parent compound.

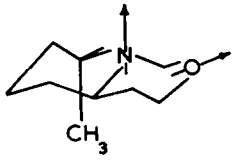
In carbon tetrachloride solution one of the 3-methyl isomers III (R = Me) showed a singlet at 6·13 τ for the C_1 methylene protons and this represents a deshielding of the axial proton of 0·35 ppm and a shielding of the equatorial proton of 0·31 ppm compared with III (R = H). The other 3-Me isomer showed a quartet for the C_1 methylene protons, the axial proton being deshielded by 0·12 ppm and the equatorial proton by 0·07 ppm compared with III (R = H). The compound giving rise to the latter spectrum was therefore assigned the configuration *cis*-3,5-*H*-3-methyloctahydropyrido[1.2-c]1,3-oxazine. Additional chemical shift evidence for this assignment is that the equatorial C_3 proton in the *trans*-3,5-*H*-3-Me compound comes 0·62 ppm to lower field than the axial C_3 proton in the *cis*-3,5-*H*-3-Me compound. In benzene solution the *trans*-3,5-*H*-3-Me compound showed a J_{gem} of −8·0 c/s for the C_1 methylene protons as did the *cis*-3,5-*H*-3-Me compound in carbon tetrachloride solution.



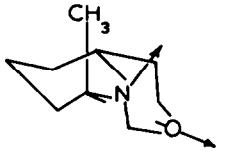
XIII

This work provides an additional confirmation of the configuration of (±) sedridine m.p. 75° which had previously been deduced[16] as XIII. Thus on reacting (±) sedridin with formaldehyde the *trans*-3,5-*H*-3-Me compound IV (R = Me) should be obtained. As seen from the experimental this is the case.

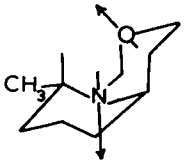
The configurations of the 9-Me isomers were readily assigned since in the *cis*-9,5-*H*-9-Me compound there is no equatorial proton on the C atom next to N at about 7 τ whereas in the *trans*-9,5-*H*-9-Me compound this signal is clearly identifiable. *cis*-9,5-*H*-9-Methyloctahydropyrido[1.2-c]1,3-oxazine would be expected to exist in conformation XVIII with a *trans*-ring fusion and an equatorial Me group. The strong



XIV



XV



XVI

Bohlmann's bands in its IR spectrum, and the J_{gem} for the C_1 methylene protons of −8·0 c/s (Fig. 1) support this view. In addition the complete first order analysis of the J_{vics} in the tetrahydro-oxazine ring show this ring to exist in a chair conformation. (Table 1).

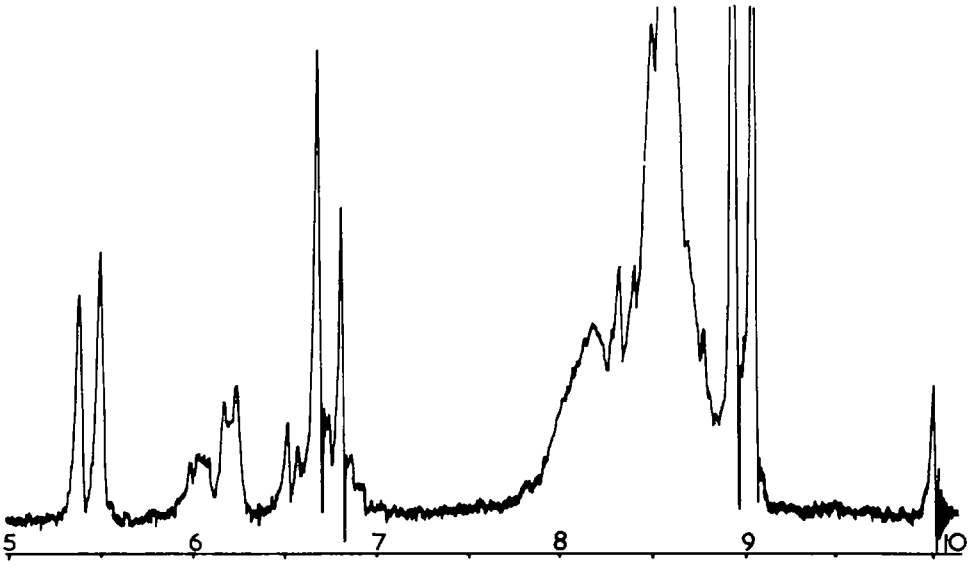


FIG. 1 NMR spectrum of *cis*-9,5-*H*-9-methyloctahydropyrido[1,2-c]1,3-oxazine.

trans-9,5-*H*-9-Methyloctahydropyrido[1,2-c]1,3-oxazine can clearly exist as an equilibrium mixture of XIV with an axial Me group and XVI with an equatorial Me group. J_{gem} for the C_1 methylene group should be ca. −8·0 c/s in conformation XIV and somewhat more negative in conformation XVI since in this case the N lone pair of electrons bisects the C_1 methylene group (VIII) and will not make a contribution to J_{gem}. The *cis*-conformation XV may be neglected since in this conformation the Me group would occupy an axial position. For reasons which have already been discussed it is not possible to assign a preferred conformation to this compound on the basis of its IR spectrum.

The NMR spectrum (Fig. 2), however, clearly shows that the compound exists in the *cis*-fused ring conformation XVI with an equatorial Me group. Thus the J_{gem}

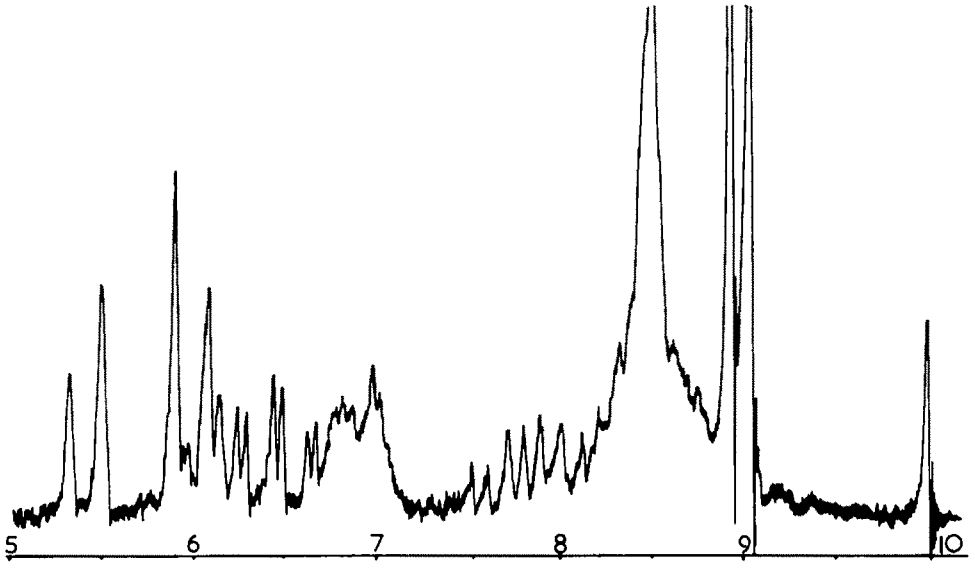
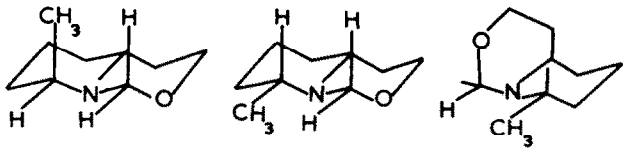


FIG. 2 NMR spectrum of *trans*-9,5-*H*-9-methyloctahydropyrido[1,2-c]1,3-oxazine.

for the C_1 methylene group is −10 c/s, 2 c/s more negative than the rest of the compounds in this series and equal to the most negative value recorded[9] for the NCH_2O protons in a tetrahydro-1,3-oxazine ring. If the preferred conformation is XVI then one would predict J_{gem} for the C_1 methylene group to be ca. −10 c/s since J_{gem} for the C_3 methylene group next to O in these compounds is −11 c/s and the electronegativity effect of the N atom should make an additional small positive contribution.

The spectrum of the *trans*-9,5-*H*-9-Me compound exhibits a broad two proton multiplet at ca. 7 τ. If the compound existed with a *trans*-fused ring junction (XIV) there should only be one proton, the equatorial C_9 proton next to N, at 7 τ. The axial proton on C_5 should be deshielded by ca. 0·45 ppm by the axial Me group on C_9 and should therefore absorb at ca. 7·5 τ. If, however, the ring fusion is *cis*- (XVI) then the C_5 equatorial proton adjacent to the nitrogen atom will come at ca. 7·0 τ. and the axial C_9 proton will suffer two 1–3 deshieldings due to the tetrahydro-1,3-oxazine ring thus accounting for the observed deshielding of this proton of ca.

0·9 ppm. Irradiation of the Me resonance simplifies the multiplet at 7 τ proving that the C_9 proton absorbs in this region. No coupling constants could be extracted however due to the complexity of the signal.



XVII XVIII XIX

Additional proof that this compound exists in a *cis*-fused ring conformation may be obtained from the chemical shifts of the H_1 protons. Thus the equatorial C_1 proton comes at the same field as the equivalent proton in the *cis*-9,5-*H*-9-Me compound. If the ring fusion was *trans*-XVII this proton should come 0·45 ppm to higher field since there is no longer a 1–3 deshielding effect from the Me group (XVIII). If the ring fusion is *cis*- however the 1–3 Me deshielding will still be present (XIX). Deshielding effects from the N atom will be the same in both cases. The chemical shift of the axial C_1 proton can be explained in terms of both *trans*- and *cis*- ring fusions. Thus if the ring fusion is *trans*-XVII the axial C_1 proton should come ca. 0·45 ppm to lower field than the equivalent proton in the *cis*-9,5-*H*-9-Me compound due to the 1–3 deshielding effect of the Me group on C_9. If the ring fusion is *cis*-XIX, however, the axial C_1 proton will no longer be shielded by the N atom (VII) but will be deshielded (VIII) thus bringing it to lower field. The Me doublet absorbs at the same position in both the *trans*-9,5-*H*-9-Me and the *cis*-9,5-*H*-9-Me compounds suggesting that it occupies an equatorial position in both cases.

The conformational preferences in these compounds can be explained in terms of dipole interactions between the N and the O atoms, butane-gauche interactions, and 1,3-diaxial hydrogen interactions. It can be seen that in the *trans*-fused ring conformation (XIV, IV) and in the *cis*-fused ring conformation (XV, V) there is a destabilising dipole–dipole interaction between the heteroatoms which is relieved in the *cis*-fused ring conformation (XVI, VI). A rough calculation indicates that this will stabilise the *cis*-conformation (XVI, VI), with respect to the other two conformations by ca. 2·5 kcal/mole. In the *trans*-9,5-*H*-9-Me compound the *trans*-fused ring conformation XIV is favoured with respect to the *cis*-fused ring conformation XVI by one gauche n-propanol interaction. A comparison of III (R = H) with decalin shows that replacement of the C—H bonds by the N and O lone pairs reduces the number of 1,3-diaxial hydrogen interactions.[17] Thus it is found that the *trans*-conformation XIV of the *trans*-9,5-*H*-9-Me compound is favoured with respect to the *cis*-conformation XVI by one 1,3-diaxial interaction. The *cis*-conformation XVI is however favoured by the dipole interaction between the N and O atoms (ca. 2·5 Kcal/mole) and this make it the preferred conformation for this compound. The other *cis*-conformation (XV) for the *trans*-9,5-*H*-9-Me compound may be neglected since it is not favoured by any of the three interactions.

The *trans*-fused ring conformation (IV) of the *trans*-3,5-*H*-3-Me compound is

favoured with respect to the *cis*-fused ring conformation (V) by one butane–gauche and two 1,3-diaxial hydrogen interactions and since neither of these conformations is favoured with respect to the other by dipole interactions the *trans*-fused ring conformation (IV) will be more stable than the *cis*-fused ring conformation (V). The *cis*-fused ring conformation (VI) of the *trans*-3,5-*H*-3-Me compound will, however, be favoured with respect to the other two conformations (IV, V) by the N–O dipole interaction (ca. 2·5 Kcal/mole) but since this conformation will be destabilised relative to the *trans*-fused ring conformation (IV) by two butane–gauche, one gauche n-propanol interaction, and one 1,3-diaxial hydrogen interaction and since these destabilising factors are greater than the stabilising dipole interaction the *trans*-fused ring conformation (IV) is the preferred one in the *trans*-3,5-*H*-3-Me compound.

Entropy has not been taken into account in this discussion since the two *cis*-conformations are of unequal energy and by analogy with the decalins trivial entropy considerations are small.

cis-1,5-*H*-1-Methyloctahydropyrido[1.2-c]1,3-oxazine (I, $R_3 = R_2 = H$, $R_1 =$ Me) has been assigned a *trans*-fused ring conformation with the Me group in an equatorial position. Evidence for this assignment includes the chemical shift of the C_1 proton, which is the same as that of the axial C_1 proton, in the parent compound, III (R = H) and the strong Bohlmann's bands in the IR spectrum. *cis*-1,5-*H*-1-Phenyloctahydropyrido[1.2-c]1,3-oxazine has also been assigned a *trans*-ring fusion with the Ph group equatorial. The evidence is again the chemical shift of the C_1 proton which is deshielded by 0·7 ppm with respect to the axial C_1 proton in III (R = H), and by 0·04 ppm compared to the equatorial C_1 proton. Since a Ph group deshields a proton on the same C atom the Ph group in the 1-phenyl compound must be equatorially situated. The strong Bohlmann's bands in the IR spectrum show the presence of a *trans*-ring fusion.

The 1-9-dimethyl compound I ($R_1 = R_3 =$ Me, $R_2 = H$) has been assigned a *trans*-fused ring conformation on the basis of its IR spectrum and the lack of an equatorial proton adjacent to nitrogen (ca. 7 τ) in its NMR spectrum. A close examination of the chemical shifts shows that the C_1 Me group is in an axial position. Thus the C_1 proton comes 0·17 ppm to lower field than the equatorial C_1 proton in the *cis*-9,5-H-9-Me compound I ($R_1 = R_2 = H$, $R_3 =$ Me) in addition the axial C_3 proton is deshielded by 0·34 ppm with respect to the axial C_3 proton in III (R = H) and this must be due to a 1-3 deshielding interaction[15] with the C_1Me group.

EXPERIMENTAL

Elemental analysis were carried out by Dr. F. Pascher and E. Pascher, Micro-Analytical Laboratory, Bonn, Germany. M.ps are uncorrected. IR spectra were recorded on a Perkin–Elmer 237 grating instrument as 0·2M solution in CCl_4 using 0·1 mm matched cells and on a Unicam S.P.100 as 0·1M solns in CCl_4 using 0·5 mm matched cells. The NMR spectra were determined on a Perkin–Elmer R10 spectrometer as 10% solns in CCl_4 with TMS as internal reference.

Catalytic hydrogenation of 2-pyridylethanols

General procedure. The pyridylethanol (0·2M), glacial AcOH (200 ml) and PtO_2 catalyst (1 g) were shaken with H_2 at 60 psi until the theoretical uptake of H_2 was complete. The soln was filtered, basified with NaOHaq and ether extracted 3 times. The ether soln was dried (Na_2SO_4) and concentrated and the crude product was distilled.

Hydrogenation of 2-(6-methyl-α-pyridyl) ethanol. 2-(6-methyl-α-piperidyl)ethanol (19·1 g, 90%) was

obtained from 2-(6-methyl-α-pyridyl) ethanol (20 g) as a white crystalline solid, b.p. 125–129°(24 mm. The product recrystallized from ether to give white plates, m.p. 96–97° (Lit.[18] 95–96°). This was the sole product.

Hydrogenation of 1-(α-*pyridyl*)2-*propanol.* An epimeric mixture of the 1-(α-piperidyl)2-propanols (9 g, 86%) was obtained from 1-(α-pyridyl)2-propanol (10 g) as a white crystalline solid m.p., 58–60° from light petroleum. Repeated recrystallization gave epimerically pure sedridin m.p., 72–73° (Lit.[16] 75°) as white needles from light petroleum.

Hydrogenation of 2-(α-*pyridyl*)1-*phenylethanol.* An epimeric mixture of the 2-(α-piperidyl)1-phenylethanols (13·5 g, 88%) was obtained from 2-(α-pyridyl)1-phenylethanol (15 g) as a white crystalline solid. The product recrystallized from diethyl ether to give two types of crystals which were hand separated. The first type (8·5 g) were white rhombs, m.p. 97–98° (Lit.[14] 98–99°) and corresponded to (±) norsedamine. The second type (1·5 g) were white rosettes of needles, m.p. 110–111° (Lit.[14] 112–113°) and corresponded to (±) norallosedamine. In addition an epimeric mixture of the alcohols (2·5 g) and an unexamined aromatic compound (0·7 g) were also obtained.

Sodium-ethanol reduction of 2-(6-*methyl*-α-*pyridyl*) *ethanol*[18]

2-(6-methyl-α-pyridyl) ethanol (80 g) was refluxed in abs EtOH (1500 ml) and Na (240 g) was added in 15 g portions so that the mixture continued to reflux. When the Na had dissolved water (300 ml) was added, and excess EtOH was removed under vacuum. The crude mixture was ether extracted four times, the ether soln was dried (Na_2SO_4) and concentrated. The crude product was recrystallized from ether to give an epimerically pure alcohol (35 g), m.p. 95–96°. The residual oil (4 g) was distilled to give a colourless viscous oil (3·4 g), b.p. 90–92°/0·6 mm.

Preparation of octahydropyrido[1.2-c]1,3-*oxazines*

General procedure. The piperidyl alcohol was shaken with a slight excess of 40% formaldehyde soln for ½ hr. The mixture was basified with NaOH aq and ether extracted 3 times. The ether extract was dried over Na_2SO_4, concentrated, and the crude product was distilled.

Octahydropyrido[1.2-c]1,3-*oxazine* (9 g, 82%) was obtained from 2-(α-piperidyl) ethanol (10 g) as a colourless mobile oil, b.p. 106–108°/29 mm $n_D^{15.5°}$ 1·4805. The picrate formed yellow needles from EtOH, m.p. 166–168° [Lit.[19] 166–167·5°] (Found: C, 45·18; H, 5·09; N, 15·22. Calc. for $C_{14}H_{18}O_8N_4$; C, 45·40; H, 4·73; N, 15·14%).

cis-1,5-*H*-1-*Methyloctahydropyrido*[1.2-c]1,3-*oxazine.* (9·4 g, 61%) was obtained from 2-(α-piperidyl) ethanol (12·9 g) by refluxing with a slight excess of acetaldehyde in benzene on a Dean and Stark apparatus. It was colourless oil, b.p. 106–107°/35 mm $n_D^{15.5}$ 1·4793. (Found: C, 69·47; H, 11·24; N, 9·25. $C_9H_{17}ON$ requires: C, 69·63; H, 11·04; N, 9·02%).

cis-1,5-*H*-1-*Phenyloctahydropyrido*[1.2-c]1,3-*oxazine* (13·3 g, 61%) was obtained from 2-(α-piperidyl) ethanol (12·9 g) by refluxing with a slight excess of benzaldehyde in benzene on a Dean and Stark apparatus. It was a white solid, b.p. 180–182°/24 mm and formed white plates from ether, m.p. 56–58° [Lit.[20] 58–59°.] (Found: C, 77·42; H, 9·01; N, 6·53. Calc. for $C_{14}H_{19}ON$: C, 77·38; H, 8·81; N, 6·45%).

cis-9,5-*H*-9-*Methyloctahydropyrido*[1.2-c]1,3-*oxazine* (4.1 g, 94%) was obtained from 2-(6-methyl-α-piperidyl) ethanol (4 g) made by catalytic reduction. It was a colourless oil, b.p. 55–57°/0·45 mm $n_D^{15.5°}$ 1·4786. (Found: C, 69·87; H, 11·12; N, 9·22. $C_9H_{17}ON$ requires: C, 69·63; H, 11·04; N, 9·02%). The picrate formed dark yellow needles from EtOH, m.p. 168–169°. (Found: C, 46·94; H, 5·34; N, 14·50. $C_{15}H_{20}O_8N_4$ requires: C, 46·87; H, 5·25; N, 14·58%).

trans-9,5-*H*-9-*Methyloctahydropyrido*[1.2-c]1,3-*oxazine.* The 2-(6-methyl α-piperidyl) ethanol (3·4 g) obtained as an oil from the Na-EtOH reduction of 2-(6-methyl-α-pyridyl) ethanol gave an epimeric mixture of *cis*- and *trans*-9,5-*H*-9-methyloctahydropyrido[1.2-c]1,3-oxazine (3·3 g) as a colourless oil, b.p. 102–104°/18 mm. Separation of the mixture was achieved on an Aerograph Autoprep gas chromatogram using a 20% apiezon L column and H_2 carrier gas. *trans*-9,5-*H*-9-methyloctahydropyrido[1.2-c]1,3-oxazine was obtained as a colourless oil, b.p. 100–102°/16 mm. It formed a picrate as yellow needles from EtOH, m.p. 166–167°. (Found: C, 47·12; H, 5·27; N, 14·41. $C_{15}H_{20}O_8N_4$ requires: C, 46·87; H, 5·25; N, 14·58%).

trans-1,cis-9,5-*H*-1,9-*Dimethyloctahydropyrido*[1.2-c]1,3-*oxazine* (3·2 g, 67%) was obtained from 2-(6-methyl-α-piperidyl) ethanol (4·0 g), itself prepared by Catalytic reduction of 2-(6-methyl-α-pyridyl) ethanol, by refluxing with a slight excess of acetaldehyde in benzene on a Dean and Stark apparatus. It was a colourless oil, b.p. 70–71°/1·4 mm $n_D^{15.5°}$ 1·4831. (Found: C, 69·84; H, 11·19; N, 8·72. $C_{10}H_{19}ON$ requires: C, 69·68; H, 10·97; N, 9·03%).

cis- *and* trans-3,5-*H*-3-*Methyloctahydropyrido*[1.2-c]1,3-*oxazine* (9·5 g, 87%) was obtained from 1-α-piperidyl)2-propanol (9·0 g) as a colourless oil, b.p. 98–100°/20 mm [Lit.[21] diasterioisomeric mixture, b.p. 108–111°/28 mm]. The epimeric mixture was separated on an Aerograph Autoprep gas chromatogram using a 20% apiezon L column and H_2 carrier gas.

cis-3,5-*H*-3-*Methyloctahydropyrido*[1.2-c]1,3-*oxazine* was obtained as a colourless mobile oil, b.p. 106–108°/25 mm $n_D^{18·5}$ 1·4712. The picrate formed yellow needles from EtOH, m.p. 144–145°. (Found: C, 47·03; H, 5·26; N, 14·51. $C_{15}H_{20}O_8N_4$ requires: C, 46·87; H, 5·25; N, 14·58%).

trans-3,5-*H*-3-*Methyloctahydrodropyrido*[1.2-c]1,3-*oxazine* was obtained as a colourless oil, b.p. 110–112°/25 mm $n_D^{16·0}$ 1·4782. The picrate formed dark yellow needles from EtOH, m.p. 142–143°. (Found: C, 47·03; H, 5·67; N, 14·71. $C_{15}H_{20}O_8N_4$ requires: C, 46·87; H, 5·25; N, 14·58%). *trans*-3,5-*H*-3-Methyl-octahydropyrido[1.2-c]1,3-oxazine was also obtained when Sedridin, m.p. 72–73° was reacted with formaldehyde.

cis-3,5-*H*-3-*Phenyloctahydropyrido*[1.2-c]1,3-*oxazine* (2·6 g, 82%) was obtained from 2-(α-piperidyl) 1-phenylethanol m.p., 97–98° (3·0 g) as a colourless viscous oil, b.p. 128–129°/0·45 mm. $n_D^{22·5°}$ 1·5443. The picrate formed yellow needles from EtOH, m.p. 141–142°. (Found: C, 53·73; H, 4·98; N, 12·59. $C_{20}H_{22}O_8N_4$ requires: C, 53·81; H, 4·97; N, 12·55%).

trans-3,5-*H*-3-*Phenyloctahydropyrido*[1.2-c]1,3-*oxazine* (0·55 g, 87%) was obtained from 2-(α-piperidyl) 1-phenylethanol, m.p. 110–111° (0·60 g) as a colourless viscous oil, b.p. 89–91°/0·1 mm $n_D^{22·5°}$ 1·5471. It formed a picrate as yellow needles from EtOH, m.p. 159–160°. (Found: C, 53·83; H, 5·03; N, 12·3. $C_{20}H_{22}O_8N_4$ requires: C, 53·81; H, 4·47; N, 12·55%).

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