

The Stereochemistry of 1,6,7,12b-Tetrahydro-2*H*,4*H*-[1,2]oxazino[3',4':1,2]-pyrido[3,4-*b*]indole and of 1,2,3,6,7,12b-Hexahydro-3-methyl-4*H*-pyrimido[3',4':1,2]pyrido[3,4-*b*]indole (1)

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From an analysis of nmr spectral data, 1,6,7,12b-tetrahydro-2*H*,4*H*-[1,3]oxazino[3',4':1,2]-pyrido[3,4-*b*]indole is shown to exist in solution at room temperature almost entirely in the *cis*-fused ring conformation with the nitrogen lone pair bisecting the C4 methylene group whereas under the same conditions 1,2,3,6,7,12b-hexahydro-3-methyl-4*H*-pyrimido[3',4':1,2]pyrido[3,4-*b*]indole exists as an approximately 50:50 equilibrium mixture of the *cis* and *trans*-fused ring conformations.

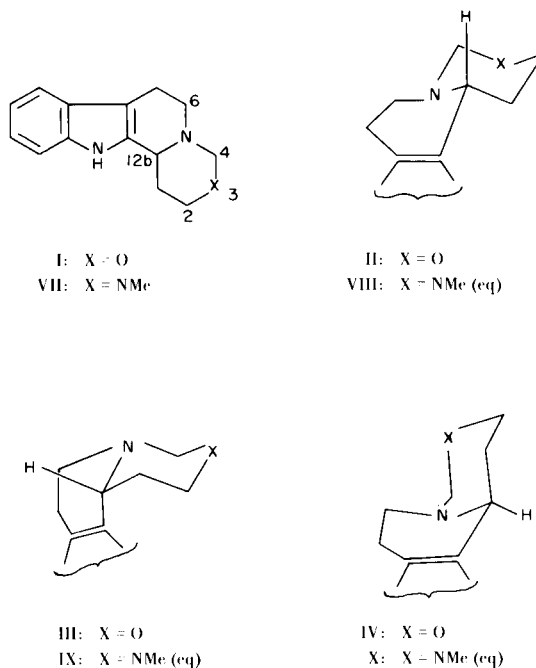
The synthesis of 1,6,7,12b-tetrahydro-2*H*,4*H*-[1,3]oxazino[3',4':1,2]pyrido[3,4-*b*]indole (1) has been described (2,3) and, on the basis of the presence of bands in the 2800-2600 cm^{-1} region of its ir spectrum, has been assigned (2,4) a conformation in which the angular 12b hydrogen is axial.

Our interest (5) in the proton magnetic resonance spectra and the stereochemistry of systems possessing bridge-head nitrogen atoms led us to prepare I and to examine its nmr spectrum since, *inter alia*, knowledge of the geminal coupling constant (J_{gem}) and chemical shifts of the C4 methylene protons (both parameters being dependent (6,7) upon heteroatom lone pair - CH dihedral angle) should permit ready differentiation between the conformations II, III, and IV. Thus IV in which the nitrogen lone pair bisects the C4 methylene H-H internuclear axis will exhibit a more negative J_{gem} than will the alternative *cis* conformation III or the *trans* conformation II in which the nitrogen lone pair and a C4-H bond are parallel. In addition the difference in chemical shift between the C4 methylene protons will be much smaller for IV than for II and III since IV does not possess the necessary *trans* diaxial relationship between the nitrogen lone pair and C4H_{ax} together with the N-methylene group skew to H4_{ax} both necessary for increased shielding of this proton (8).

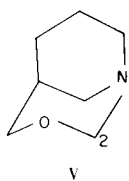
In fact the nmr spectrum of I showed an AB quartet for the C4 methylene protons with J_{gem} -10.5 Hz (9) and δ values of 4.41 and 4.66, consistent with the existence of I in the *cis* fused conformation IV. These values are very similar to those observed (10) for the C2 methylene protons in V ($J = -10.5$ Hz, δ 4.55 and 4.66) which also possesses the CH₂ bisecting lone pair geometry but are rather different from those observed (11) for VI ($J = -8$ Hz δ 3.65 and 4.35) which possesses the parallel lone pair - CH

geometry.

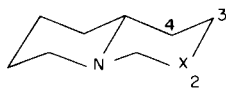
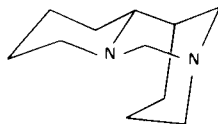
In stereochemical studies on benzo[*a*]- and indolo[*a*]-quinolizidines the angular proton has been found (12) to absorb to lower field of δ 3.8 when the ring fusion is *cis* and to higher field in *trans* fused compounds. The corres-



ponding angular 12b proton signals could not be identified in the nuclear magnetic resonance spectrum of I because of overlapping with the C2 methylene signals. The C2 diduterated derivative of I was therefore prepared by lithium aluminium deuteride reduction of 1-carbomethoxy-methyl-1,2,3,4-tetrahydro- β -carboline followed by ring clo-



V


 VI: X O
 XI: X NMe (eq)


XII

sure with formaldehyde. The H₂b proton signals were now visible at δ 3.9 and this low field absorption confirmed the stereochemistry depicted in IV as did the values of the vicinal coupling constants, between H₁₂b and H₁ ($J_{ax,ax} = 11.5$ Hz, $J_{ax,eq} = 2$ Hz).

The intensity of absorption in the 2800-2600 cm^{-1} region of the ir spectra of quinolizidine derivatives has been shown (13) to be roughly proportional to the number of CH bonds α to the nitrogen atom and possessing a *trans*-axial relationship with the nitrogen lone pair. An examination of the ir spectrum of I in the 2800-2600 cm^{-1} region (14) showed only a set of weak bands in agreement with structure IV which possesses only one correctly orientated α -CH bond (H_{6ax}) but incompatible with the *trans* fused structure II which has three such CH bonds (H_{6ax}, H_{4ax} and H_{12bax}) and should therefore exhibit marked absorption in this region. Thus the combined nmr and ir spectral evidence demonstrates unequivocally that the preferred conformation of I in solution at room temperature is the *cis* fused ring structure IV.

The nmr spectrum of 1,2,3,6,7,12b-hexahydro-3-methyl-4*H*-pyrimido[3',4':1,2]pyrido[3,4-*b*]indole (VII) prepared as described by deStevens (2) showed an AB quartet (δ 3.0 and 3.8, $J = -9.8$ Hz) for the C4 methylene protons and a singlet at δ 2.25 corresponding to an equatorial N-Me group (compare δ 2.24 for equatorial NMe in XI in contrast to δ 2.46 for an axial N-Me in a similar system) (15).

The J_{gem} of -9.8 Hz is intermediate between that in XI (-8.4 Hz) in which both lone pairs are axial and that in XII (-11.3 Hz) (7) in which one of the lone pairs bisects the N-CH₂-N methylene group. This suggests that VII exists as an approximately 50:50 equilibrium mixture of X (one nitrogen lone pair bisecting C4 methylene) and VIII (both nitrogen lone pairs axial and *trans* to C4H_{ax}). *trans*-4a,8-H-2,8-Dimethyl-octahydro-3*H*-pyrido[1,2-*c*]pyrimidine which exists as a similar equilibrium mixture shows a very similar J_{gem} (C1 methylene) of -9.9 Hz to that in VII. VII shows bands in the 2800-2600 cm^{-1} region of its ir spectrum which are much reduced in intensity to those shown by XI (15).

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