COMPOUNDS WITH BRIDGEHEAD NITROGEN PART 74[1]. NMR SPECTRA AND STEREOCHEMISTRY OF 1,3,10,10a-TETRAHYDRO-5*H*-OXAZOLO[3,4-*b*]ISOQUINOLINE AND 1,5,6,10b-TETRAHYDRO-3*H*-OXAZOLO[4,3-*a*]ISOQUINOLINE

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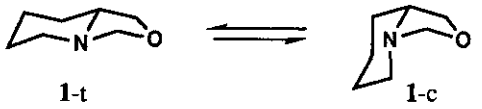
Abstract - Whereas 1,3,10,10a-tetrahydro-5*H*-oxazolo[3,4-*b*]isoquinoline adopts an equilibrium in $CDCl_3$ solution at 295 K in which the *trans*-fused conformation predominates, 1,5,6,10b-tetrahydro-3*H*-oxazolo[4,3-*a*]isoquinoline adopts the *O*-inside *cis*-fused conformation. This difference in conformational preference has been explained partly in terms of ring-fusion strain.

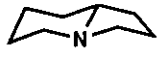
Perhydro-oxazolo[3,4-*a*]pyridine adopts a conformational equilibrium[2] in $CDCl_3$ solution at 298 K between 67% *trans*-fused conformer (**1**-t) and 33% *O*-inside *cis*-fused conformer (**1**-c) whereas indolizidine shows[3] an extreme preference for the *trans*-conformer (**2**-t). In addition to differences in non-bonded interactions between the two systems[4] and the generalised anomeric effect[5] in **1**, ring fusion strain (*cf. trans*-hydrindane[6]) may also be partially responsible for the difference in positions of conformational equilibria. Any ring fusion strain present in *trans*-indolizidine (**2**-t) is expected[4,7] to increase in *trans*-perhydro-oxazolo[3,4-*a*]pyridine (**1**-t) as a result of the shorter C-O bonds (1.43Å) in **1**-t compared to the corresponding C-C bonds (1.54Å) in **2**-t. The magnitude of such strain should be affected by changes in the conformation of the six-membered ring and accordingly 1,3,10,10a-tetrahydro-5*H*-oxazolo[3,4-*b*]isoquinoline (**3**) and 1,5,6,10b-tetrahydro-3*H*-oxazolo[4,3-*a*]isoquinoline (**4**) containing non-chair piperidine rings were chosen for study.

Results and Discussion

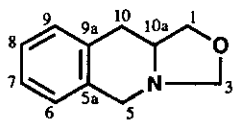
1,3,10,10a-Tetrahydro-5*H*-oxazolo[3,4-*b*]isoquinoline (**3**) may exist in solution as an equilibrium between a *trans*-fused conformer (**3**-t), an *O*-inside *cis*-fused conformer (**3**-c_1) and an *O*-outside *cis*-fused conformer (**3**-c_2). The ^{1}H nmr spectrum of **3** at 295 K shows an AB quartet (δ 3.98, 4.70; J_{gem} −2.2 Hz) for the C-3 methylene protons and comparison of the corresponding C-3 methylene parameters for **1**-t and **1**-c (spectral parameters obtained at 183 K) of δ 3.68, 4.50 (J = 0 Hz) and δ 4.27, 4.33 (J = −5.8 Hz) respectively,[2] clearly demonstrates a conformational equilibria between the *trans*-fused conformation (**3**-t) and the *O*-inside *cis*-fused conformation (**3**-c_1) but in which **3**-t predominates. This is supported by strong ir absorption (Bohlmann bands[8]) in the 2800-2600 cm^{-1} region of the spectrum characteristic of **3**-t.



1-t **1**-c



2-t



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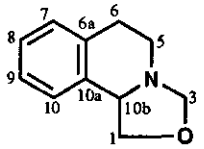

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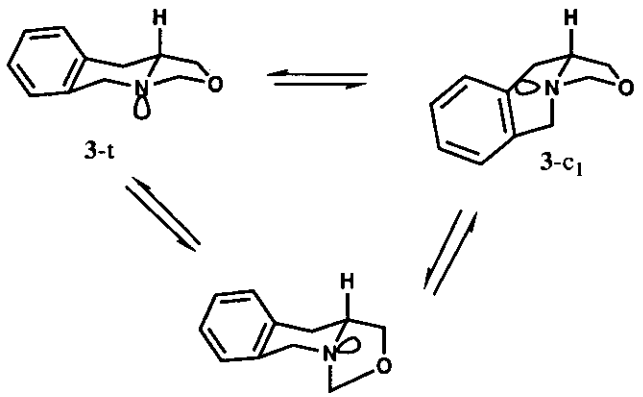
The ^{1}H nmr spectrum of **3** at 173 K did not show freezing out of the **3**-t ⇋ **3**-c_1 equilibrium unlike the situation for the **1**-t ⇋ **1**-c equilibrium. This must be due to a lower energy of activation for ring inversion in the conformers of **3** (*cf.* conformational barrier of 5.3 kcal mol^{-1} in half-chair cyclohexene and the ring inversion barrier of 10-11 kcal mol^{-1} in chair cyclohexane[9]). Temperature dependent spectral changes were, however, observed. In particular, the J_{gem} of the C-3 methylene protons increased to −1.8 Hz at 193 K consistent with an increase in the proportion of the *trans*-fused conformer (**3**-t) at low temperatures.

Since the dihedral angles between H-10a and the C-1 methylene bonds are the same (*ca.* 30° and 150°) in

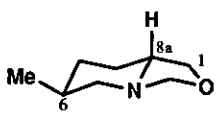
Table 1 ^{1}H Nmr chemical shifts (δ) and coupling constants (J/Hz) of 1,3,10,10a-tetrahydro-5*H*-oxazolo[3,4-*b*]isoquinoline (**3**) 1,5,6,10b-tetrahydro-3*H*-oxazolo[4,3-*a*]isoquinoline (**4**)[a]

Proton	Chemical shifts (δ) and coupling constants (J/Hz)					
	3[b,c]		**3**[d]		**4**[b,e]	
	δ	J	δ	J	δ	J
H-1eq'	4.08	1eq'1ax' −7.1 1eq'10a 6.2	4.18	1eq'1ax' −7.2 1eq'10a 6.4	4.06	1eq'1ax' −6.8 1eq'10b 8.2
H-1ax'	3.53	1ax'10a 8.5	3.60	1ax'10a 9.0	3.50	1ax'10b 9.4
H-3eq'	4.70$^+$	3ax'3eq' −2.2	4.79$^+$	3ax'3eq' −1.8	4.66$^+$	3ax'3eq' −6.4
H-3ax'	3.98$^+$		3.91$^+$		4.64$^+$	
H-5eq'	3.99*	5eq'5ax' −14.1	4.05*	5eq'5ax' −14.1	2.85	5eq'5ax' −11.5 5eq'6eq' 2.6 5eq'6ax' 5.0
H-5ax'	3.51*		3.48*		2.87	5ax'6eq' 2.6 5ax'6ax' 11.5
H-6eq'					2.60	6eq'6ax' −15.7
H-6ax'					3.06	
H-10eq'	2.94	10eq'10ax' −14.3 10eq'10a 3.8	2.97	10eq'10ax' −17.0 10eq'10a 5.0		
H-10ax'	2.74	10eq'10a 8.8	2.74	10ax'10a 10.1		
H-10a	2.86		2.77			
H-10b					4.36	
H-Ar	7.05-7.6		7.11-7.21		7.0-7.2	

a Spectra of **3** in 1:1 $CFCl_3$: CD_2Cl_2; spectra of **4** in $CDCl_3$
b Spectrum obtained at 295 K
c Chemical shifts and coupling constants of C-10, C-10a and C-1 protons obtained by computer simulation
d Spectrum obtained at 197 K
e Chemical shifts and coupling constants of C-5, C-6 methylene protons obtained by computer simulation
$^{+*}$ Respective signals may be interchanged.



both the **3**-t and **3**-c_1 conformers of **3** whereas in **3**-c_2 these are *ca.* 30° and 90°, then marked changes with temperature in the magnitude of the vicinal coupling constants involving the C-10 methylene protons are to be expected if **3**-c_2 is involved in the equilibria. The observation that the coupling constants (obtained from simulation of the five-spin system (C-1 to C-10) at 295 K (J = 8.5 Hz and 6.2 Hz) and at 193 K (J = 9.0 Hz and 6.4 Hz) are very similar point to the absence of **3**-c_2. In addition, the values of $J_{10a,\ 1ax'}$ and $J_{10a,\ 1eq'}$ of 8.5 and 6.2 Hz respectively (Table 1) compare closely with the corresponding couplings($J_{1ax',8a}$ = 9.5 Hz, $J_{1eq',8a}$ = 6.5 Hz)[10] between H-8a and the C-1 methylene protons in the *trans*-fused *trans*-(H-6, H-8a)-6-methylperhydro-oxazolo[3,4-*a*]pyridine (**5**) . A distinction between conformers (**3**-t) and (**3**-c_1) cannot be made on the basis of these couplings since they are of similar magnitude in both systems.



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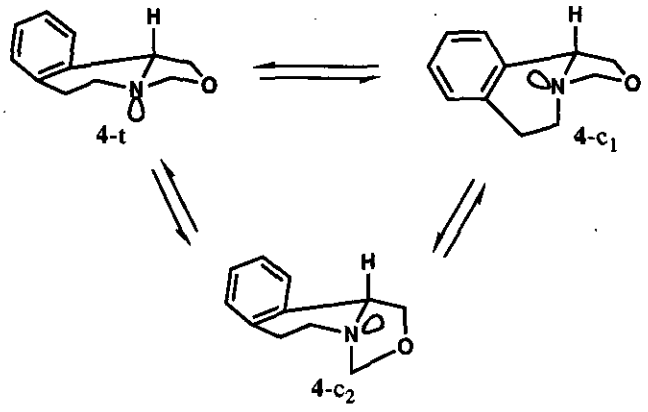
Dreiding models show a pseudoaxial/equatorial relationship between the C-10 methylene protons and axial H-10a in both **3**-t and **3**-c_2 which should give rise to one large vicinal coupling constant $J_{10a,\ 10ax'}$ and one small coupling constant $J_{10a,10eq'}$. In **3**-c_1, however, the C-10a–H bond approaches bisection of the C-10 methylene group and such a conformation would be characterised by two small vicinal coupling constants. The vicinal couplings $J_{10a,10ax'}$ and $J_{10a,10eq'}$ obtained by simulation of the spectra increased from 8.1 to 10.1 Hz and from 3.8 to 5.0 Hz respectively with reduction in temperature indicating a significant proportion of **3**-c_1 in the conformational equilibrium at 295 K.

This conclusion is supported by the changes in the magnitude of the J_{gem} of the C-10 methylene protons with temperature. The observed value of −17 Hz at 193 K is consistent with conformation (**3**-t) in which there is a near bisection of the C-10 methylene protons by the plane of the aromatic ring in which a significant negative contribution to J_{gem} is expected.[11] Conformation (**3**-c_1), however, readily accommodates a very small angle between the plane of the aromatic ring and one of the C-10–H bonds consistent with a very small ΔJ contribution from the π system and consequently an expected J_{gem} of *ca.* −11 Hz. The J_{gem} of −14.3 Hz observed at 295 K falls between these extreme values.

The predominance of **3**-t in the equilibrium for **3** is confirmed by comparison of the ^{13}C nmr parameters (Table 2) of **1**-t and **3**-t. The chemical shifts for C-1 and C-3 (δ 72.0 and 87.2 respectively) of **3**-t in particular are very close to the values (δ 71.6 and 85.8 respectively)[2] of **1**-t. Thus all the spectral data indicates an equilibrium for **3** between **3**-t and **3**-c_1 in which **3**-t predominates and in which the proportion of **3**-t increases with decreasing temperature.

In contrast to the J_{gem} of the NCH_2O protons of −2.2 Hz in **3**, the J_{gem} value for the C-3 methylene protons in **4** is −6.4 Hz (*cf.* −5.8 Hz for **1**-c). This together with the absence of Bohlmann bands[8] in the ir spectrum indicates the exclusive existence of **4** in the *O*-inside *cis*-fused conformation (**4**-c_1). In addition the ^1H nmr spectrum of **4** showed an ABX system for H-10b (δ 4.36) and the C-1 methylene protons (δ 3.50, 4.06; $J_{1eq',1ax'} = -6.8$ Hz, $J_{1eq',\ 10b} = 8.2$ Hz and $J_{1ax',\ 10b} = 9.4$ Hz) consistent with conformation (**4**-c_1). The preference for **4**-c_1 was confirmed from the ^{13}C nmr chemical shifts of **4** in which the resonance of C-3 (δ 88.6) closely matches that (δ 88.5)[2] of the corresponding carbon of **1**-c. The chemical shift (δ 68.1) of C-1 in **4** is relatively downfield of that (δ 62.9) in **1**-c since the γ_{ax} effect between the C-1 methylene group and the C-7 methylene group in **1**-c has been replaced in **4**-c_1 by an interaction involving the sp^2 C-6a. Analysis of the 4-spin $C(5)H_2$-$C(6)H_2$ system gave the ^1H nmr couplings quoted in Table 1 which are in accord with a fully staggered geometry.



CONCLUSION

Comparison of the J_{gem} values for the NCH_2O protons ($CDCl_3$ solution, 298 K) of −2.5 Hz for **1**-t ⇋ **1**-c and of −2.2 Hz for **3**-t ⇋ **3**-c_1 indicates a slight increase in preference (*ca.* 5%) of **3** for the *trans*-fused conformation (**3**-t). Since the destabilising gauche butane interaction (C-1–C-7) present in **1**-c is replaced in **3**-c_1 by the more favourable interaction between the C-1 methylene and the sp^2 centre at C-9a, a shift of the equilibrium towards the *cis*-fused conformation (**3**-c_1) is expected. Accordingly the observed reverse shift towards **3**-t may mean a relief (relative to **1**-t) of ring fusion strain due to the flexibility of the half-chair type B-ring in **3**-t.

Whereas **3** prefers the *trans*-fused conformation (**3**-t), the alternative benzo-fused compound (**4**) prefers the *O*-inside *cis*-fused ring conformation (**4**-c_1). The *trans*-fused conformer (**4**-t), is destabilised by a peri-type interaction between H-10 and H-1 which is relieved in the *O*-inside *cis*-conformer (**4**-c_1). This latter is stabilised by the generalised anomeric effect[5] and by the replacement of a gauche butane interaction in *O*-inside *cis*-fused **1**-c by the less demanding interaction involving the C-1 methylene and the sp^2 C-6a. These interactions are not, however, sufficient to account for the preference of **4** for the *O*-inside *cis*-fused conformer. Dreiding models of the *trans*-conformers (**4**-t) and (**3**-t) suggest differing resistance of the B ring to fusion with the oxazolidine ring C. If half-chair type B-rings are considered for both, then *trans*-fusion as in **3**-t involves di-equatorial bonds, whereas in **4**-t, one equatorial bond and one pseudo-equatorial bond is required. In the latter case the dihedral angle between the two bonds is greater than 60^o and in order to accommodate ring fusion to the oxazolidine C ring these bonds have to be moved together against a relatively

hard potential barrier (*cf.* hydrindane[6]). This provides an explanation for the extreme bias towards the *O*-inside *cis*-fused conformer for **4**.

Table 2 ^{13}C Nmr chemical shifts (δ, $CDCl_3$ 295K) of 1,3,10,10a-tetrahydro-5*H*-oxazolo[3,4-*b*]isoquinoline (**3**) and 1,5,6,10b-tetrahydro-3*H*-oxazolo[4,3-*a*]isoquinoline (**4**)

	chemical shifts	
Carbon	3	4
1	72.0	68.1
3	87.2	88.8
5	51.1	45.4
5a	134.3[a]	-
6	126.4[b]	29.6
6a	-	133.8[a]
7	126.8[b]	128.6[b]
8	127.0[b]	126.9[b]
9	129.3[b]	126.6[b]
9a	135.0[a]	-
10	31.9	126.1[b]
10a	58.8	133.7[a]
10b	-	60.7

a,b Respective signals may be interchanged

EXPERIMENTAL

^1H and ^{13}C nmr spectra were recorded in $CDCl_3$ or $CFCl_3$:CD_2Cl_2(1:1) in 5 mm tubes on a JEOL GSX-270 (^1H, ^{13}C) fourier transform spectrometer at 270.16 Hz (^1H) and 67.97 MHz (^{13}C), using the deuterium signal of the solvent as the lock and TMS as internal standard. The most important measurement parameters were as follows: sweep width, 3 KHz (^1H) and 18 KHz (^{13}C); pulse width, 3 μs (^1H) and 4.2 μs (^{13}C) (*ca.* 40 and *ca* . 45 flip angle, respectively); acquisition time, 5.459 or 0.901s; number of scans, 16-320 (^1H) and 1-20 K

(^{13}C); and computer memory, 32K. ^{1}H Nmr parameters were obtained by an nmr spin simulation/interaction programme V2.10 (JEOL NMR COMIC programme).

*1,3,10,10a-Tetrahydro-5*H-*oxazolo[3,4-*b*]isoquinoline* (3).—The1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid[12] (17.7 g, 0.1 mol) was added in small amounts to lithium aluminium hydride (10 g, 0.25 mol) in dry tetrahydrofuran (200 ml). After completion of the addition, the mixture was heated on a water-bath for 1 h. The usual work up gave a viscous oil which solidified on freezing to give the crude required alcohol (11.0 g, 69%). The whole of this was shaken with excess 36% aqueous formaldehyde solution for 0.5 h when the mixture was basified (aqueous 10% NaOH) and extracted three times with ether. The ether solution was dried (Na_2SO_4) and evaporated to leave a viscous oil which was dissolved in petroleum ether (bp 40-60°C) and passed through a short column of alumina. The solid thus obtained was purified by sublimation at 30-35°C at 0.1 mmHg to give 9.4 g (80 %) of *1,3,10,10a-tetrahydro-5*H-*oxazolo[3,4-*b*]isoquinoline* as fine colourless crystals, mp 49-50°C. (Anal.Calcd for $C_{11}H_{13}NO$: C, 75.4; H, 7.5; N, 8.0%. Found: C, 75.2; H, 7.5; N, 7.8) :ν_{max} (cm^{-1}) 2808 ε^a (60), 2772 (55), 2750 (55), 2697 (20). Picrate, mp 170-171°C (Anal.Calcd for $C_{17}H_{16}N_4O_7$: C, 50.5; H, 4.0; N, 13.9. Found C, 50.3; H, 4.1; N, 13.8).

1,5,*6,10b-Tetrahydro-3*H-*oxazolo[4,3-*a*]isoquinoline* (4).— A solution of ethyl isoquinaldinate (11.3 g, 0.056 mol) in dry tetrahydrofuran (100 ml) was added dropwise to lithium aluminium hydride (4.26 g, 0.112 mol) in dry tetrahydrofuran (250 ml) with stirring. The mixture was then refluxed for 1.5 h, cooled and the excess hydride destroyed by the addition of water. The mixture was basified (10% aqueous NaOH), filtered, and the tetrahydrofuran was removed under vacuum. The residue was extracted with chloroform and dried (Na_2SO_4). The solvent was removed under vacuum to give 1-isoquinolylcarbinol (7.5 g, 75%) as a dark red viscous oil. The alcohol (7.5 g) in glacial acetic acid (150 ml) was hydrogenated at atmospheric pressure in the presence of PtO_2 catalyst (0.8 g) until the calculated volume of hydrogen had been absorbed. After work up in the usual way, the 1-(1,2,3,4-tetrahydroquinolyl)carbinol was obtained as a dark brown viscous oil (5.3 g, 71%). A solution of the alcohol (5.3 g) dissolved in absolute ethanol (20 ml) was shaken with excess 36% aqueous formaldehyde for 5 h. After removal of the alcohol *in vacuo*, the residue was treated with excess 10% aqueous NaOH and extracted three times with chloroform. The chloroform solution was dried (Na_2SO_4) and the solvent removed to leave a dark brown viscous residue (3.8 g, 68%). This was dissolved in petroleum ether (bp 40-60°C), and was passed through a short column containing alumina to give a yellow

viscous oil which was sublimed at 90° at 0.1 mmHg to give 3.1 g (55 %) of *1,5,6,10b-tetrahydro-3H-oxazolo[4,3-a]isoquinoline* as fine colourless crystals, mp 42.5-44.5°C. (Anal.Calcd for $C_{11}H_{13}NO$: C, 75.4; H, 7.4; N, 8.0.Found: C, 75.4; H, 7.6; N, 8.1): ν_{max} (cm^{-1}) 2835 ε^a (45), 2803 (12).

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