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Reference Data

NMR Spectra and Stereochemistry of 1,5- and 1,6-Disubstituted Perhydrooxazolo[3,4-*a*] pyridines*

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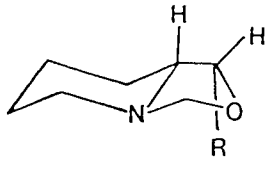
^{13}C and ^{1}H NMR spectroscopy showed that with the exception of *r*-1,*t*-6,*t*-8a-1-alkyl-6-ethylperhydrooxazolo[3,4-*a*] pyridines (alkyl = ethyl, isopropyl) which adopt the *O*-inside *cis*-fused conformation, all the other 1-alkyl-6-ethyl- and 1-alkyl-*cis*(H-5, H-8a)-5-methyl-perhydrooxazolo[3,4-*a*] pyridines adopt *trans*-fused conformations ($CDCl_3$, 298 K).

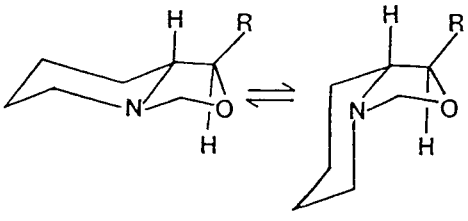
KEY WORDS Perhydrooxazolo[3, 4-*a*]-pyridines Conformation ^{1}H and ^{13}C NMR

INTRODUCTION

Whereas the *cis*-(H-1,H-8a)-1-alkylperhydrooxazolo [3,4-*a*] pyridines **1** and **3** adopt the *trans*-fused conformation **1a** and **3a**, the *trans*-(H-1,H-8a)- isomers **2** and **4** adopt 73% *trans*-fused (**2a**, **4a**)⇌27% *O*-inside *cis*-fused (**2b**, **4b**) conformational equilibria ($CDCl_3$, 298 K).[2] In order to assess the influence of ring A substitution on equilibria positions in these systems, and to provide ^{13}C NMR substituent effect data, the 1,5- and 1,6-derivatives **6**–**17** were synthesized for study.

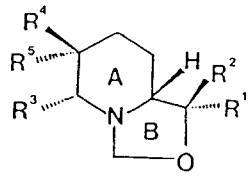


1a R = ethyl
3a R = isopropyl



2a R = ethyl **2b** R = ethyl
4a R = isopropyl **4b** R = isopropyl

* Part 59 in the series 'Compounds with Bridgehead Nitrogen'. For Part 58, see Ref. 1.



R^n = H unless otherwise stated

1 R^1 = ethyl
2 R^2 = ethyl
3 R^1 = isopropyl
4 R^2 = isopropyl
5 R^3 = methyl
6 R^3 = methyl, R^1 = ethyl
7 R^3 = methyl, R^2 = ethyl
8 R^3 = methyl, R^1 = isopropyl
9 R^3 = methyl, R^2 = isopropyl
10 R^4 = ethyl, R^1 = ethyl
11 R^4 = ethyl, R^2 = ethyl
12 R^4 = ethyl, R^1 = isopropyl
13 R^4 = ethyl, R^2 = isopropyl
14 R^5 = ethyl, R^1 = ethyl
15 R^5 = ethyl, R^2 = ethyl
16 R^5 = ethyl, R^1 = isopropyl
17 R^5 = ethyl, R^2 = isopropyl

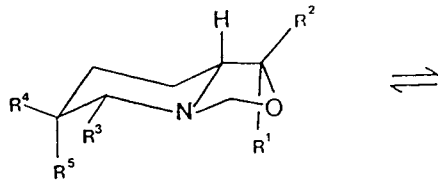
RESULTS AND DISCUSSION

The ^{1}H and ^{13}C NMR spectra of all the compounds are summarized in Tables 1 and 2, respectively. The assignments were aided by reference to the spectra of **1**–**4**[2] and, in the case of **6**–**9**, to that of **5**. The data for all the compounds, with the exception of **15** and **17**, are consistent with the adoption of the *trans*-fused conformation. The ^{1}H NMR spectra of **15** and **17** show striking differences from those of the other members of the set, particularly in the values of J(3ax′, 3eq′) (−5.9 to −5.6 Hz) and of Δ(3ax′, 3eq′)(0.03–0.1 ppm). These values also differ from those for the monosubstituted analogues **2** and **4** [J(3ax′, 3eq′) −2.5 to −2.8 Hz and Δ(3ax′, 3eq′) 0.4 ppm],[2] and comparison of the data with those for conformationally biased systems[2] indicates the preference for the *O*-inside *cis*-fused conformation (**15b**, **17b**).

With the exception of the J(3ax′, 3eq′) values of −2.5 Hz, the ^{1}H NMR spectra of **14** and **16** are consistent with the *trans*-fused conformation (**14a**, **16a**). This change in the J(3ax′, 3eq′) value may be due to some slight distortion of the ring A chair conformation by the C-6 axial ethyl substituent.

The ^{13}C NMR data are consistent with the assignments based on ^{1}H NMR data. In particular, the predominance of the *O*-inside *cis*-conformations (**15b**, **17b**) for **15** and **17** is supported by the γ-axial shieldings of C-1 and C-7 relative to **11a** and **13a** (7.5 and 7.2 ppm, respectively, for **15**).

In conclusion, C-5 equatorial methyl substitution in **2a**(**4a**) and in **7** and **9** shifts the 73% **2a**(**4a**)⇌27% **2b**(**4b**) equilibrium entirely towards the *trans*-conformation **7a** and **9a** and a similar shift is effected by C-6 equatorial ethyl substitution (see **11** and **13**). Axial ethyl substitution at C-6 as in **15a** and **17a**, however, shifts the **2a**(**4a**)⇌**2b**(**4b**) equilibrium entirely towards the *cis*-conformations **15b** and **17b**. Pseudo-axial alkyl substitution at C-1 shifts the predominance of the *cis*-conformer for *cis*(H-6, H-8a)-6-ethylperhydrooxazolo[3,4-*a*]pyridine back towards the *trans*-conformer (see **14a**).



1a–17a ⇌ **1b–17b**

EXPERIMENTAL

The ^{1}H NMR spectra were recorded as 10% solutions in $CDCl_3$ with tetramethylsilane (TMS) as internal reference, on a Bruker WH270 spectrometer. Accumulated scans over 4K data points were normally 100, and the resultant FID was Fourier transformed over 8K data points after application of a trapezoidal window filter to the FID signal; the resulting peak-to-peak resolution was 0.1 Hz, with an error of ±0.7 Hz when the sweep width was *ca* 3 kHz (3012 Hz). The ^{13}C NMR spectra were recorded on a Jeol FX90Q (22.5 MHz) Fourier transfer spectrometer as *ca* 10% solutions with TMS as internal reference; pulse length 6 μs, pulse interval 2 s, 2000 scans. ^{13}C chemical shifts are considered to be accurate to ±0.05 ppm.

Substituted pyridin-2-ylakanols

General procedure

To a cooled ethereal solution of alkyl-

Table 1. ^{1}H NMR spectra of perhydrooxazolo[3,4-*a*]pyridines in $CDCl_3$

	Chemical shifts (δ)											Coupling constants (Hz)					
Compound	1'eq'	1'ax'	3'eq'	3'ax'	5eq	5ax	8a	5-Me	6-CH_2Me	1-Alkyl		3'ax', 3'eq'	1'eq', 8a	1'ax', 8a	5eq, 5ax	5eq, 6ax	5ax, 6ax
5	3.99	3.49	4.75	3.79	—	1.80	2.23	1.08	—	—		−0.9	6.6	10.0	—	—	—
6	3.91	—	4.73	3.73	—	2.13	2.29	1.06	—		0.96[c]	−1.5	7.2	—	—	—	—
7	—	3.59	4.75	3.82	—	2.17	1.84	1.07	—	—	0.96[c]	−0.9	—	8.75	—	—	—
8	3.70	—	4.68	3.83	—	2.24	2.45	1.06	—	0.96[d]	0.88[d]	−0.9	6.6	—	—	—	—
9	—	3.44	4.71	3.77	—	2.20	1.98	1.07	—	0.97[d]	0.95[d]	−0.9	—	8.8	—	—	—
10	3.90	—	4.57	3.71	3.07	1.65	2.20	—	0.94	—	0.89[c]	−1.25	6.7	—	−10.3	2.5	10.3
11	—	3.55	4.58	3.80	3.03	1.69	1.88	—	0.99	—	0.90[c]	−1.25	—	8.8	−10.6	3.1	10.6
12	3.69	—	4.56	3.85	3.04	1.78	2.38	—	0.89	0.97[d]	0.88[d]	−1.25	6.8	—	−11.25	3.1	11.25
13	—	3.39	4.55	3.77	3.02	1.71	1.91	—	0.89	0.96[d]	0.92[d]	−1.25	—	8.8	−10.0	3.1	10.0
14	3.84	—	4.51	3.78	2.77	2.22	2.41	—	0.97		0.90[c]	−2.5	6.7	—	−10.6	2.0[a]	2.8[b]
15	—	3.63	4.39	4.36	2.73	2.38	2.79	—	1.03		0.90[c]	−5.9	—	8.75	−10.6	3.4	10.6
16	3.70	—	4.52	3.66	2.84	2.06	2.25	—	0.90	0.95[d]	0.93[d]	−2.5	6.7	—	−10.0	2.0[a]	2.5[b]
17	—	3.54	4.36	4.26	2.70	2.37	2.90	—	0.90	0.98[d]	0.95[d]	−5.6	—	8.75	−10.0	3.1	10.0

[a] J(5eq, 6eq).
[b] J(5ax, 6eq).
[c] Me protons of 1-ethyl substituent.
[d] Me protons of 1-isopropyl substituent.

Reference Data

Table 2. ^{13}C NMR spectra of perhydrooxazolo[3,4-*a*]pyridines in $CDCl_3$

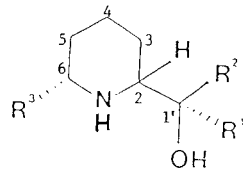
	Chemical shifts (δ)											
Compound	C-1	C-3	C-5	C-6	C-7	C-8	C-8a	C-5-Me	C-6-Et		C-1-alkyl	
5	71.8	84.8	55.1	33.6	24.0	26.5	62.4	20.9	—			
6	81.7	84.8	56.0	33.5	24.9[a]	24.5[a]	64.9	20.9	—		24.7[a]	10.3
7	84.1	84.1	55.3	33.6	24.1[a]	26.9[a]	67.4	20.7	—		25.9[a]	10.2
8	85.1	84.6	55.9	33.1	24.7	24.7	64.6	20.9	—		29.4 20.6	18.6
9	87.5	84.1	55.1	33.6	24.2	27.9	65.4	20.7	—		31.1 19.0	18.5
10	81.4	85.6	53.8	37.0	31.0	24.8	64.7	—	27.1	11.7	24.4	10.3
11	83.8	85.2	53.3	37.2	30.6	26.0	67.3	—	27.0[a]	11.5	26.7[a]	10.2
12	84.3	84.9	52.4	34.8	30.0	22.9	62.7	—	26.1	10.4	28.2 19.2	17.9
13	85.1	87.3	53.2	37.1	30.8	27.8[a]	65.3	—	27.1[a]	11.5	31.3 18.9	18.7
14	81.2	86.3	52.2	35.5	27.9[a]	21.0	63.9	—	25.8	12.3	24.9[a]	10.8
15	76.3	87.1	53.8	37.3	23.4	26.5[a]	63.7	—	27.0	11.4	25.8[a]	10.8
16	84.7	86.5	52.0	35.1	28.0	20.8[a]	65.0	—	24.7	12.5	29.8 20.1[a]	18.4
17	79.8	87.2	53.8	37.2	24.3	25.9	61.5	—	27.0	11.4	31.3 19.6	18.3

[a] Assignments may be reversed.

magnesium bromide [prepared by addition of the appropriate alkyl bromide (0.2 M) in dry diethyl ether (50 ml) to magnesium turnings (4.8 g) in the presence of a trace amount of iodine] was added a solution of 5-ethyl- or 6-methyl-pyridine-2-carboxaldehyde (0.19 M) in dry diethyl ether (50 ml) and, after completion of the addition, the mixture was boiled under reflux for 1 h. The solution was then acidified with 10% hydrochloric acid and basified with sodium carbonate. The resulting mixture was then extracted with diethyl ether (5 × 200 ml), the ether extracts were combined, dried (Na_2SO_4) and evaporated and the residue was distilled under reduced pressure. This gave 1-(6-methylpyridin-2-yl)propan-1-ol, b.p. 89–92 °C at 1.5 mmHg, found C 71.2, H 8.5, N 9.2, $C_9H_{13}NO$ requires C 71.5, H 8.7, N 9.3%; 1-(6-methylpyridin-2-yl)-2-methylpropan-1-ol, b.p. 74 °C at 0.01 mmHg, found C 72.7, H 9.2, N 8.6, $C_{16}H_{15}NO$ requires C 72.7, H 9.2, N 8.5%; 1-(6-ethylpyridin-2-yl)propan-1-ol, b.p. 74–75 °C at 0.1 mmHg, found C 72.5, H 9.5, N 8.8, $C_{10}H_{15}NO$ requires C 72.7, H 9.2, N 8.5%; and 1-(6-ethylpyridin-2-yl)-2-methylpropan-1-ol, b.p. 88–90 °C at 0.04 mmHg, found C 73.3, H 9.5, N 8.1, $C_{11}H_{17}NO$ requires C 73.7, H 9.6, N 7.8%.

Substituted piperidin-2-ylalkanols
General procedure

A solution of the substituted 2-pyridin-2-ylalkanol (0.1 M) in glacial acetic acid (150 ml) was shaken with Adams catalyst (PtO_2, 0.75 g) in a Parr hydrogenator until the calculated uptake of hydrogen had been accomplished. The catalyst was removed by filtration, the acetic acid in the filtrate was evaporated *in vacuo* and the residue was basified with 30% sodium hydroxide. The solution was extracted with diethyl ether (3 × 200 ml), dried (Na_2SO_4), the solvent evaporated and the residue distilled under reduced pressure to yield the substituted piperidin-2-ylalkanols. The separation of the isomers of the 6-methylpiperidin-2- alkanols was effected by formation of the picrate derivative. A hot solution of the piperidin-2-ylalkanol (0.015 M) in ethanol (10 ml) was mixed with a hot solution of picric acid (0.02 M) and the mixture allowed to crystallize. The crude picrate was filtered off and fractionally recrystallized from ethanol to yield the separated diastereoisomeric picrates. The amino alcohols were regenerated from the picrates by treatment with aqueous NaOH (50 ml) and extraction with diethyl ether (5 × 200 ml). The combined extracts were dried (Na_2SO_4) and evaporated and the residue was recrystallized from light petroleum (b.p. 40–60 °C) to yield the pure diastereoisomers. The physical properties of these are listed in Table 3 and the ^1H and ^{13}C NMR spectral data are shown in Table 4.



18 R^3 = methyl, R^1 = ethyl
19 R^3 = methyl, R^2 = ethyl
20 R^3 = methyl, R^1 = isopropyl
21 R^3 = methyl, R^2 = isopropyl

The mixtures of isomeric 1-(5-ethylpiperidin-2-yl)propan-1-ols and of isomeric 1-(5-ethylpiperidin-2-yl)-2-methylpropan-1-ols were not separated but were obtained as colourless oils, b.p. 80–82 °C at 0.15 mmHg, found C 70.4, H 12.0, N 8.3, $C_{10}H_{21}NO$ requires C 70.1, H 12.4, N 8.2%, and b.p. 95–100 °C at 0.07 mmHg, found C 71.4, H 12.6, N 7.7, $C_{11}H_{23}NO$ requires C 71.3, H 12.5, N 7.6%, respectively.

Dialkylperhydrooxazolo[3,4-*a*]pyridines

The 6-methylpiperidin-2-alkanols (3 g) were shaken with a 40% aqueous solution of form-

Table 3. Physical data for substituted 2-piperidinylalkanols

Compound	M.p. (°C)	Picrate m.p. (°C)	(%) C	(%) H	(%) N
18	99–100	159–162	69.9	12.6	8.6[a]
19	79	185	69.6	12.4	8.6[a]
20	81–82	187–190	69.9	12.3	8.2[b]
21	65	160–165	70.0	12.1	8.3[b]

[a] $C_9H_{19}NO$ requires C 69.7, H 12.2, N 8.9%.
[b] $C_{10}H_{21}NO$ requires C 70.1, H 12.4, N 8.2%.

Reference Data

Table 4. ^1H and ^{13}C NMR data for the substituted piperidin-2-ylalkanols

	^1H NMR shifts (δ)				^{13}C NMR shifts (δ)							
Compound	2ax	6ax	6-Me	Alkyl	C-1′	C-2	C-3	C-4	C-5	C-6	6-Me	1′-Alkyl
18	2.60	2.68	1.06	0.96[a]	75.3	60.7	25.9[b]	24.5[b]	34.4	52.5	23.1	24.6[b,c] 10.7[d]
19	2.42	2.60	1.07	0.99[a]	75.1	61.3	26.6[b]	24.6[b]	34.0	52.5	22.9	28.7[b,c] 10.2[d]
20	2.73	2.73	1.06	1.69[e] 1.02[f] 0.86[f]	78.9	58.3	24.4	24.0	34.4	52.3	23.2	30.0[g] 19.0[h] 19.7[h]
21	2.56	2.63	1.08	1.77[e] 0.99[f] 0.91[f]	78.4	56.7	28.4	24.5	34.1	52.1	23.0	29.3[g] 20.4[h] 15.6[h]

[a] $CH_2\underline{CH}_3$.
[b] Assignments may be reversed.
[c] $\underline{CH}_2CH_3$.
[d] $\overline{CH}_2CH_3$.
[e] $\underline{CH}(\overline{CH}_3)_2$.
[f] $\overline{CH}(\underline{CH}_3)_2$.
[g] $\underline{CH}(CH_3)_2$.
[h] $\overline{CH}(\underline{CH}_3)_2$.

Table 5. Physical properties of dialkylperhydrooxazolo[3,4-*a*]pyridines

Compound	B.p. (°C)	(%) C	(%) H	(%) N
6	56–57 at 0.3 mmHg	69.8	11.6	8.2[a]
7	70–71 at 0.5 mmHg	70.0	11.4	8.5[a]
8	60–64 at 0.1 mmHg	72.0	11.5	7.8[b]
9	80–83 at 0.5 mmHg	72.4	11.3	7.5[b]
10	58–62 at 0.2 mmHg	72.0	11.8	7.6[b]
11	71–73 at 0.2 mmHg	71.8	11.4	7.5[b]
12	128–130 at 28 mmHg	73.0	11.5	7.0[c]
13	135–139 at 30 mmHg	72.9	11.6	7.4[c]
14	65–68 at 0.2 mmHg	72.4	11.3	7.3[b]
15	84–87 at 0.5 mmHg	71.9	11.6	7.7[b]
16	142–144 at 28 mmHg	73.3	11.5	7.4[c]
17	130–131 at 29 mmHg	73.1	11.9	7.2[c]

[a] Calculated for $C_{10}H_{19}NO$: C 70.1, H 11.3, N 8.3%.
[b] $C_{11}H_{21}NO$ requires C 72.1, H 11.6, N 7.6%.
[c] $C_{12}H_{23}NO$ requires C 73.0, H 11.8, N 7.1%.

aldehyde (3 ml) for 30 min. The mixture was then basified with 30% NaOH solution and extracted with diethyl ether (5 × 25 ml). The combined extracts were dried (Na_2SO_4) and evaporated and the residue was distilled under vacuum to yield the 5-methylperhydrooxazolo[3,4-*a*]pyridines.

The mixtures of 6-ethylperhydrooxazolo[3,4-*a*]pyridines prepared in a similar way from the mixture of substituted piperidin-2-ylalkanols were separated by column chromatography over Woelm neutral alumina using diethyl ether—light petroleum as eluent. Physical data for the compounds are given in Table 5.

Acknowledgements

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References

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