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Synthesis and conformational properties of *N*-monoalkyl 1,5-diaza-*cis*-decalins

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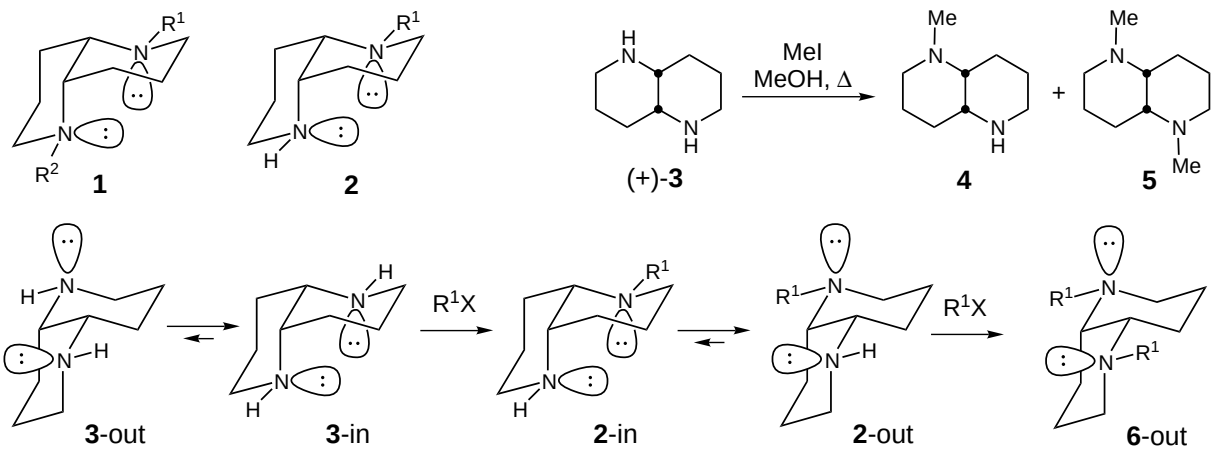
Abstract—*N*-Monoalkyl 1,5-diaza-*cis*-decalins were synthesized in high yield and purity by derivatization of tetrahydronaphthyridine followed by reduction to the saturated system. The position of the conformational equilibrium between the chair–chair inversion forms of a series of four *N*-monoalkyl of 1,5-diaza-*cis*-decalins was measured and was directly related to the size of the *N*-alkyl group. © 2001 Elsevier Science Ltd. All rights reserved.

Previous efforts in our laboratories have identified the 1,5-diaza-*cis*-decalins (**1**) as useful ligands for asymmetric synthesis.[1,2] In order to determine the effect of different *N*-alkyl groups on the selectivity of these ligands, monosubstituted derivatives such as **2** were required (Scheme 1). While many methods have been devised for the monoalkylation and monoacylation of diamines,[3] none of the reported protocols allowed efficient monoderivatization of **3**. The best of these methods, simple rapid alkylation under dilute conditions with a substoichiometric amount of MeI produced a mixture of **3**, **4**, and **5**. The difficulty in monoderivatization of **3** appears to be a consequence of the conformational equilibria of 1,5-diaza-*cis*-decalins.[4] The parent **3** exists mainly in the **3**-in conformation, but the product of the first alkylation/acylation **2** favors the **2**-out conformation. The amine lone pair of **2**-out is less hindered than in the major form of the starting material **3**-in. The net result is that alkylation/acylation of the *N*-monoalkylated intermediate **2** proceeds more rapidly than that of the starting diamine **3**.

In order to generate the *N*-monoalkyl 1,5-diaza-*cis*-decalins (**2**), an alternative route has been devised utilizing tetrahydronaphthyridine **8** (Scheme 2). Naphthyridine (**7**) was previously used to synthesize the decahydro compound **3**[1] by hydrogenation at 1000 psi at rt using Rh/Al_2O_3. By performing the hydrogenation at atmospheric pressure the partially hydrogenated intermediate tetrahydronaphthyridine (**8**) could be



Scheme 1.

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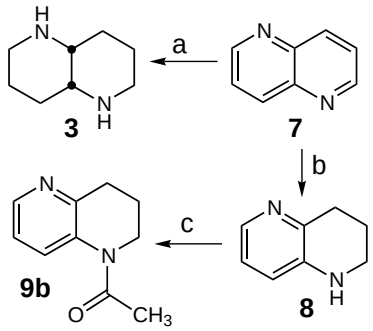


Scheme 2. (a) Rh/Al_2O_3, 1000 psi H_2, rt, 90:10 *cis*:*trans* mixture produced, 95%; (b) Rh/Al_2O_3, H_2, rt, 59%; (c) AcCl, 86%.

obtained readily.[5] Treatment of **8** with acetyl chloride produced a single new compound which was presumably *N*-acyl **9b**.

In the NMR spectra of *N*-acyl **9b** in $CDCl_3$, one proton signal and three carbon signals were conspicuously absent. Closer analysis of the ^1H NMR spectrum of **9b** revealed the presence of a *very* broad (2 ppm) C8 hydrogen signal center at a 7.8 ppm (Fig. 1). In DMSO-d_6 at 60°C all the signals could be observed although some signals were still broad. The localized broadening of select signals for compound **9b** arises from a slow equilibration between the *cis* and *trans* amide rotamers (Fig. 2) combined with large chemical shift differences for the affected signals in the different rotamers.[6] The complete broadening of some signals while other are unaffected is an unusual extreme.[7] Interestingly, the spectral anomalies found in **9b** were not observed in *N*-acyltetrahydroisoquinoline **10** (Fig. 2) under identical conditions, indicating that the pyridyl nitrogen is responsible for the large chemical shift differences.[8]

With *N*-acyl **9b** in hand, other derivatives including the methoxyacetyl (**9c**), pivaloyl (**9d**), and trifluoroacetyl (**9e**) were prepared in a similar manner (Scheme 3). Reduction of these *N*-acyl derivatives to the *N*-alkyl analogs **11b–d** was then attempted. Surprisingly, treatment of **9b** with $LiAlH_4$ resulted in low yields of *N*-alkyl **11b**. The intermediate iminium ion formed during the reduction is likely unstable due to allylic steric interactions with the *peri*-hydrogen of the pyridine ring. A more efficient reduction was obtained with BH_3; however, the isolated product was the very stable pyridinium–borane adduct of **11b**. This adduct was cleaved by heating in 6N HCl to provide **11b** in good overall yield (73%). A similar procedure was applied to

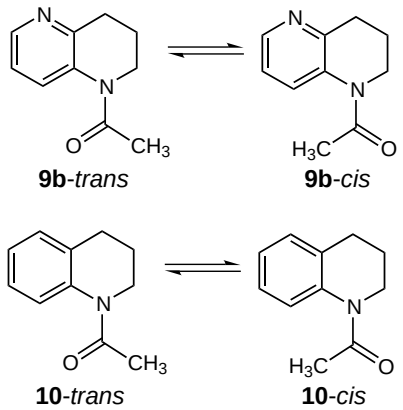
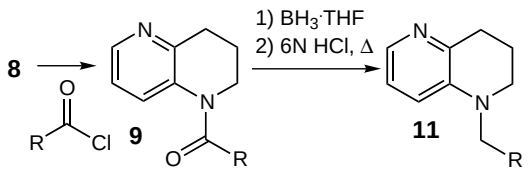


Figure 2.



R =	Me (**b**)	CH_2OMe (**c**)	tBu (**d**)	CF_3 (**e**)
8 → **9**	86%	73%	88%	75%
9 → **11**	73%	62%	60%	

Scheme 3.

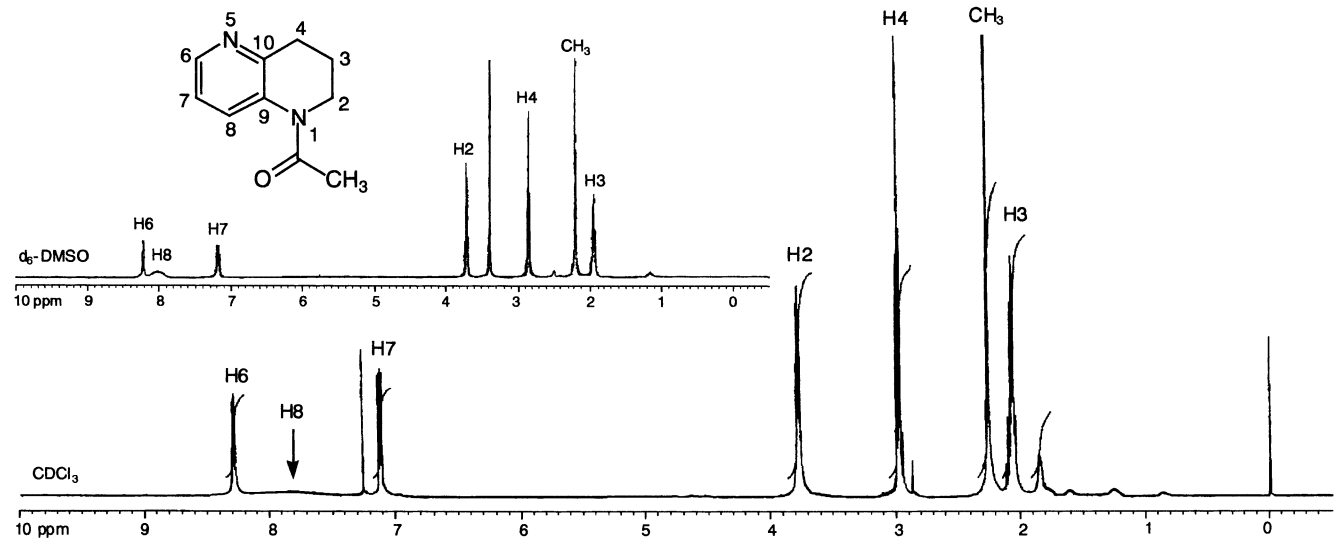
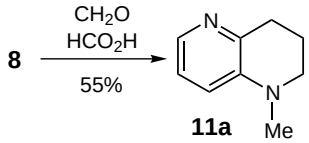


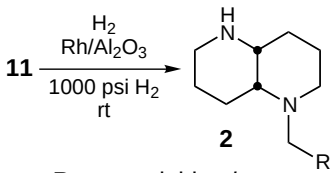
Figure 1. ^1H NMR spectra of **9b**.

obtain **11c** and **11d**, but proved unsuccessful for the reduction of the trifluoroacyl derivative **9e**. The greater lability of the trifluoroacetyl combined with the steric strain induced by the *peri*-hydrogen resulted in rapid cleavage of the trifluoroacetyl group to generate **8**.

To obtain the *N*-Me analog **11a**, Eschweiler–Clarke methylation of **8** was undertaken (Eq. (1)). Hydrogenation of the pyridine ring of **11a–d** with a Rh/Al_2O_3 catalyst proceeded uneventfully to yield predominantly the *cis* ring fused *N*-monoalkyl compounds **2a–d** (Eq. (2)).



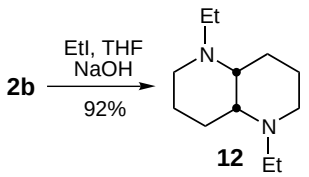
(1)



(2)

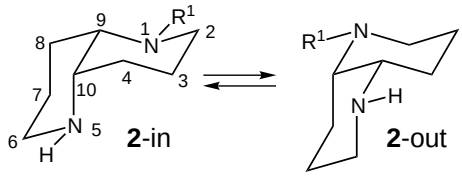
	R	yield	*cis:trans*
a	H	62%	72:18
b	Me	84%	74:16
c	CH_2OMe	62%	73:17
d	tBu	54%	73:17

The NMR spectra of **2a–d** were complex, presumably due to chair–chair inversion occurring on the NMR time scale, and did not permit an unambiguous assignment of these compounds. As such, compound **2b** was converted to the known *N*,*N*′-diethyl-1,5-diaza-*cis*-decalin **12** with EtI (Eq. (3)). The *N*,*N*′-dialkyl **12** was identical in all respects to the material generated directly from **3**.



(3)

With the monoalkyl derivatives **2a–d** in hand, the conformational equilibria of these compounds were investigated by means of NMR spectroscopy. At room temperature, the spectra were broadened indicating rapid interchange between the *N*-in and *N*-out forms (Fig. 3). At lower temperatures (250 K), the ^1H NMR spectra were still very complex, but two distinct sets of peaks were observed in the ^{13}C NMR spectra of **2a–d**. Furthermore, the *N*-in and *N*-out conformations could be assigned on the basis of the ^{13}C NMR chemical shifts[9] and the relative populations of the conformational isomers could be measured (Fig. 3).[10] Similar trends were observed for these derivatives as had been observed for the *N*,*N*′-dialkyl compounds.[4,11] Increasing the steric bulk of the *N*-alkyl group caused a shift toward the *N*-out form due to torsional interactions



	R^1	2-in:2-out
a	Me	>90 : 10
b	Et	75 : 25
c	CH_2CH_2OMe	75 : 25
d	CH_2tBu	<10 : 90

Figure 3.

between R^1 and C8;[4] however, these compounds possessed a greater tendency to populate the *N*-in conformer compared to the *N*,*N*′-dialkyl compounds, indicating their potential utility as stable chelating diamine ligands.

An efficient synthesis of monoalkyl derivatives of **3** has been achieved. This method will also allow the synthesis of unsymmetric *N*,*N*′-dialkyl-1,5-diaza-*cis*-decalins which may have applications as chiral ligands. A rare example of chemical exchange causing the absence of certain signals in otherwise normal NMR spectra is reported.

Acknowledgements

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5. Satisfactory characterization was obtained for all new compounds. **8**: mp 107–109°C; ^1H NMR (200 MHz, $CDCl_3$) δ 1.96–2.08 (m, 2H), 2.92 (t, 6.5 Hz, 2H), 3.30 (t, 4.8 Hz, 2H), 3.81 (brs, 1H), 6.72 (dd, 8.0 Hz, 1.4 Hz, 1H), 6.88 (dd, 7.9 Hz, 4.5 Hz, 1H), 7.85 (dd, 4.6 Hz, 1.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 30.2, 41.4, 120.0, 121.7, 137.7, 140.9, 142.6; IR (film) 3229, 2949,

1456 cm^{-1}; HRMS (ES) calcd for $C_8H_{11}N_2$ (MH^+) 135.0922, found 135.0927. **9b**: oil; ^1H NMR (500 MHz, $CDCl_3$) δ 2.08 (m, 2H), 2.27 (s, 3H), 2.99 (t, 6.8 Hz, 2H), 3.79 (t, 5.9 Hz, 2H), 7.13 (dd, 8.2 Hz, 4.7 Hz, 1H), 8.3 (d, 4.1 Hz, 1H); ^1H NMR (360 MHz, DMSO-d_6, rt) δ 1.92–1.99 (m, 2H), 2.20 (s, 3H), 2.86 (t, 6.7 Hz, 2H), 3.71 (t, 6.1 Hz, 2H), 7.17 (dd, 8.2 Hz, 4.7 Hz, 1H), 8.00 (brs, 1H), 8.21 (dd, 4.3 Hz, 1.1 Hz, 1H); ^1H NMR (360 MHz, DMSO-d_6, 60°C) δ 1.93–2.02 (m, 2H), 2.20 (s, 3H), 2.87 (t, 6.7 Hz, 2H), 3.72 (t, 6.1 Hz, 2H), 7.17 (dd, 8.2 Hz, 4.7 Hz, 1H), 8.00 (d, 8.2 Hz, 1H), 8.21 (dd, 4.3 Hz, 1.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.2, 30.3, 121.0, 131.6, 145.2, 169.9; ^{13}C NMR (125 MHz, DMSO-d_6) δ 23.5, 23.6, 30.7, 45.1, 121.8, 132.2, 135.6, 145.3, 151.3, 170.6; IR (film) 2931, 1661 cm^{-1}; HRMS (ES) calcd for $C_{10}H_{13}N_2O$ (MH^+) 177.1028, found 177.1030. **11b·BH$_3$**: mp 102–104°C; ^1H NMR (200 MHz, $CDCl_3$) δ 1.10 (t, 7.1 Hz, 3H), 1.98 (tt, 6.6 Hz, 6.6 Hz, 2H), 3.17–3.38 (m, 6H), 6.93–7.04 (m, 2H), 7.93–7.96 (m, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 10.2, 20.4, 27.4, 45.4, 47.2, 118.4, 122.3, 135.2; IR (film) 2959, 2324, 1185 cm^{-1}; anal. calcd for $C_{10}H_{17}BN_2$: C, 68.22; H, 9.73; N, 15.91; found C, 68.17; H, 10.24; N, 15.98. **11b**: oil; ^1H NMR (200 MHz, $CDCl_3$) δ 1.06 (t, 7.1 Hz, 3H), 1.92–2.04 (m, 2H), 2.86 (t, 6.6 Hz, 2H), 3.08–3.31 (m, 4H), 6.75 (d, 8.3 Hz, 1H), 6.89 (dd, 8.3 Hz, 4.6 Hz, 1H), 7.72 (d, 4.6 Hz, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 10.4, 18.4, 31.1, 44.6, 47.8, 116.1, 121.9, 135.7, 140.9, 141.3; IR (film) 2967, 1577, 1456 cm^{-1}; HRMS (ES) calcd for $C_{10}H_{15}N_2$ (MH^+) 163.1235, found 163.1232. **2a**: oil, ^1H NMR (500 MHz, $CDCl_3$) δ 1.19–1.23 (m, 1H), 1.37–1.49 (m, 3H), 1.56–1.63 (m, 1H), 1.67–1.76 (m, 2H), 1.89 (br., 1H), 1.98–2.11 (m, 2H), 2.17 (m, 4H), 2.61–2.69 (m, 2H), 2.74–2.76 (m, 1H), 3.05–3.07 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, rt) δ 21.2, 21.6, 24.4, 29.1, 42.5, 46.9, 54.7, 56.8, 59.8, 61.7; ^{13}C NMR (125 MHz, $CDCl_3$, 250 K) 20.3, 21.0, 27.7, 30.5, 42.5, 46.7, 54.0, 57.2, 61.3; IR (film) 2933 cm^{-1}; HRMS (ES) calcd for $C_9H_{19}N_2$ (MH^+) 155.1548, found 155.1547. **2b**: oil, ^1H NMR (500 MHz, $CDCl_3$) δ 0.96 (t, $J=7.1$ Hz, 3H), 1.05–1.29 (m, 3H), 1.42–1.50 (m, 3H), 1.62–1.78 (m, 3H), 2.06 (br., 1H), 2.20–2.78 (m, 6H), 3.03–3.06 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, rt) δ 9.0, 22.1, 29.7, 46.4, 54.7, 57.3; ^{13}C NMR (125 MHz, $CDCl_3$, 250 K) *N*-in: 7.0, 20.5, 21.1, 27.2, 30.6, 45.8, 46.8, 51.8, 54.3, 55.7; *N*-out: 12.6, 14.6, 23.2, 25.8, 29.7, 39.7, 45.5, 47.2, 53.0, 56.7; IR (film) 3281, 2931 cm^{-1}; HRMS (ES) calcd for $C_{10}H_{21}N_2$ (MH^+) 169.1705, found 169.1706. **2c**: oil, ^1H NMR (500 MHz, $CDCl_3$) δ 1.22–1.25 (m, 1H), 1.41–1.46 (m, 3H), 1.58–1.73 (m, 3H), 2.03 (br., 1H), 2.23–2.34 (m, 3H), 2.50–2.55 (m, 1H), 2.61–2.66 (m, 1H), 2.77–2.84 (m, 3H), 2.99–3.01 (m, 1H), 3.31 (s, 3H), 3.41–3.50 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, rt) δ 22.2, 26.5, 29.1, 29.6, 46.4, 52.2, 54.6, 58.8, 70.1; ^{13}C NMR (125 MHz, $CDCl_3$, 250 K) *N*-in: 20.2, 21.0, 27.7, 30.6, 46.7, 51.3, 53.4, 54.5, 57.8, 58.9, 68.7; *N*-out: 15.4, 23.0, 24.2, 26.1, 29.6, 39.6, 45.6, 52.5, 53.2, 58.5, 70.2; IR (film) 2946, 1357 cm^{-1}; HRMS (ES) calcd for $C_{11}H_{23}N_2O$ (MH^+) 199.1810, found 199.1809. **2d**: oil, ^1H NMR (500 MHz, $CDCl_3$) δ 0.81 (s, 9H), 1.19–1.40 (m, 2H), 1.49–1.56 (m, 3H), 1.70–1.87 (m, 3H), 2.08–2.15 (m, 2H), 2.28–2.31 (m, 1H), 2.39 (br., 1H), 2.57–2.66 (m, 3H), 2.77 (m, 1H), 3.01 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, rt) δ 19.3, 23.1, 24.9, 27.7, 33.5, 41.2, 49.0, 53.4, 61.3, 65.9; ^{13}C NMR (125 MHz, $CDCl_3$, 250 K) 17.1, 22.6, 24.7, 26.1, 27.2, 33.6, 39.5, 47.1, 52.6, 60.7, 65.4; IR (film) 2931, 1118 cm^{-1}; HRMS (ES) calcd for $C_{13}H_{27}N_2$ (MH^+) 211.2174, found 211.2179.

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7. For examples of this phenomenon, see: Reference 6, p. 219 and: (a) Binsch, G.; Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 4511–428; (b) Drankenberg, T.; Forsen, S. *J. Phys. Chem.* **1970**, *74*, 1–7.
8. With the exception of slight broadening of the C2 signal of **10** in the ^{13}C NMR spectrum.
9. The ^{13}C NMR shift of C8 was particularly diagnostic, occurring at ~21 ppm for the *N*-in form and at ~16 ppm for the *N*-out form.
10. For **2a** and **2d**, peaks for the minor isomer were observed but with low intensity corresponding to <10%.
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