Configurational Analysis of 1-Alkyl-2-Methylazetidin-3-ols

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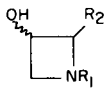
Recently Gaertner (2) obtained a mixture of diastereomeric 1-*t*-butyl-2-methylazetidin-3-ols (**1** and **2**) by allowing *t*-butylamine to react with 3-bromo-1,2-epoxybutane in DMSO, and was successful in obtaining one isomer in pure form. More recently, Okutani and coworkers (3) reported that tris (dipivalomethanato) europium coordinates at the hydroxyl group of 1-cyclohexyl-2-phenyl-azetidin-3-ols (**3** and **4**) and that the configurations of **3** and **4** could be assigned in an unambiguous manner by the pmr spectra of the resulting complexes.



	cis	*trans*
$R_1 = t$-Bu; $R_2 = CH_3$:	1	2
$R_1 = C_6H_{11}$; $R_2 = C_6H_5$:	3	4
$R_1 = C_6H_{11}$; $R_2 = CH_3$:	5	6

Since azetidin-3-ols have been shown (4,5) to be potentially useful for the preparation of 3-aroylazetidines, we have repeated the preparation of **1** and **2**. A satisfactory separation of these diastereomers was achieved by fractional distillation followed by fractional crystallizations. Interestingly, when cyclohexylamine was allowed to condense with 3-bromo-1,2-epoxybutane only one of the two possible diastereomeric azetidinols, **5** and **6**, was isolated.

In previous reports from this laboratory concerning the configurational analysis of 1,2-disubstituted 3-aroylazetidines (5,6,7), the C-2-C-3 proton coupling constants, from their pmr spectra, were sufficiently different to allow configurational assignments. These parameters are not sufficiently different in **1** and **2** to allow an unequivocal configurational assignment (see Table I).

For other *cis* and *trans* 1,2,3-trisubstituted azetidines it was suggested (5) that the preferred conformation is that conformer in which the *N*-alkyl and the C-2 substituents occupy pseudoequatorial positions in a nonplanar ring. It has also been suggested that vicinal protons which are *cis* to methyl or to hydroxyl substituents are somewhat shielded by these substituents (8), and that pseudoaxial protons absorb at higher fields than do the corresponding pseudoequatorial protons (when other factors are equal).

We suggest that the preferred conformations of the *cis* and *trans*-1-alkyl-2-methylazetidin-3-ols are analogous to those reported for other 1,2,3-trisubstituted azetidines (5,6,7), *i.e* **7** and **8** are the preferred conformations of the 1,2-disubstituted azetidin-3-ols. If this suggestion has any merit and the C-2 and the C-3 protons (H_2 and H_3) of the *trans* isomers (**2**, **6**) should absorb at higher field than the corresponding protons of the *cis* azetidinols (**1**, **5**), since these protons are shielded, relative to those of the *cis* isomers, by being *cis* to hydroxyl or to methyl and by being preferentially pseudoaxial. Consequently, it is suggested that the lower melting 1-*t*-butyl-2-methylazetidin-3-ol (m.p. 65-66°) is the *trans*-azetidin-3-ol, **2**. Indeed, examination of the reported chemical shifts (3) for the ring protons of **3** and **4** reveals the same phenomenon.

TABLE I

The Partial Pmr Spectra (a) of 1-Alkyl-2-methylazetidin-3-ols

No.	R	M.p. °C	H_2	H_3	H_4	H_4'	J_{2Me}	J_{23}	J_{34}	$J_{34'}$	J_{24}	$J_{24'}$	$J_{44'}$
1	t-C_4H_9 (b)	86-87	215.0	249.1	180.9	203.2	6.6	6.2	1.75	6.6	1.2	0.0	-9.1
2	t-C_4H_9 (b)	65-66	193.9	233.0	201.3	171.65	6.2	6.0	6.4	6.65	0.0	0.0	-7.2
4	C_6H_{11}	80-81.5	176.6	228.2	216.8	153.5	6.2	5.8	6.4	6.6	-9.95	0.0	-7.2

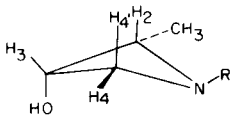
(a) Chemical shifts are reported in Hertz downfield from tetramethylsilane, internal standard, and are with respect to a 60 MHz field.
(b) The pmr spectrum of this compound was simulated by computer with the parameters given.

TABLE II

An Infrared Examination of Hydrogen Bonding in **1** and **2**

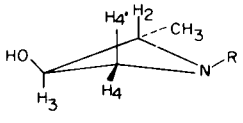
1			**2**		
Concentration	Frequency (cm^{-1})	Relative Intensity	Concentration	Frequency (cm^{-1})	Relative Intensity
1.00 *M*	3585 (a)	1.00	1.01 *M*	3625 (a)	1.00
	3415 (b)	2.80		3610 (a,c)	.8
	3190 (b)	2.94		3350	4.05
				3100 (b)	4.53
1.00×10^{-1} *M*	3585 (a)	1.00	9.63×10^{-2} *M*	3625 (a)	1.00
	3415 (b)	.97		36.0 (a,c)	.8
	3215 (b)	1.00		3350 (b)	.85
				3125 (b)	1.06
9.75×10^{-3} *M*	3580 (a)	1.00	9.75×10^{-3} *M*	3625	1.00
	3415 (b)	d		3610	0.8
	3215 (b)	d			

(a) Sharp. (b) Broad. (c) Shoulder. (d) Too weak for measurement.



cis

7



trans

8

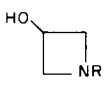
These same principles may be applied to the C-4 protons (H_4 and H_4') of **2** in an unambiguous manner. The pseudoaxial proton (H_4') is *cis* to the hydroxyl substituent and should absorb at higher field than the pseudoequatorial proton (H_4), which is *trans* to the hydroxyl substituent.

The configurational assignment by chemical shift arguments of the C-4 protons of **1** is more complex, as each of these protons is being influenced by opposing effects. This assignment is fortunately simplified by the magnitudes of the coupling constants between H_3 and the C-4 protons. Thus the C-4 proton exhibiting the smaller coupling (1.75 Hz) is assigned as *trans* to H_3. Thus it appears as though the anisotropy of the pseudoaxial hydroxyl substituent is, at least in this case, more important than the "axial effect".

The configurations and the assignment of the C-4 protons of **3** and **4** derived by application of this method of configurational analysis are identical in every respect with those derived by use of the shift reagent (3).

The configurational assignment of the 1-cyclohexyl-2-methylazetidin-3-ols is based upon the similarity observed in its spectrum with that of **2**. One would expect the resonance frequency of H-2 to be increased, by the application of van der Waals dispersion effects (4,5) in changing the *N*-alkyl substituent from *t*-butyl to cyclohexyl for either the *cis* or the *trans*-azetidinols, if the preferred conformations remain the same. A similar effect (both in direction and in magnitude) should be observed for the pseudoaxial C-4 proton (H_4'); the pseudoequatorial proton (H_4) should undergo a shift of similar magnitude but to lower field (5). Consequently these data fit slightly better if the isolated 1-cyclohexyl-2-methylazetidin-3-ol is assigned the *trans* configuration, **6**.

The chemical shift of the C-3 proton of this 1-cyclohexylazetidine is clearly much nearer that observed in **2** than in **1**--the chemical shifts of the C-3 protons of 1-alkylazetidin-3-ols (**9**) are nearly independent of the *N*-alkyl substituent (2,8). The magnitude of the dispersion effects observed in the spectra of 1-alkylazetidin-3-ols (**9**) is clearly much nearer to that observed in the 1-alkyl-2-methylazetidin-3-ols if the 1-cyclohexyl-2-methylazetidin-3-ol is **6**. Likewise the resonance frequencies of the C-4 protons are much nearer to the frequencies reported (3) for the C-4 protons of **4** than of **3** (when corrected for the different field strengths used). For the above reasons it is suggested that the isolated 1-cyclohexyl-2-methylazetidin-3-ol is the *trans* isomer, **6**.



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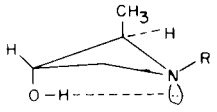
Structures **7** and **8** suggest that intramolecular hydrogen bonding might be very important in **7** and of little or no importance in **8**. Thus a detailed examination of hydrogen bonding by infrared spectroscopy might be of value in supporting our configurational and conformational assignments. Consequently dilution studies on each of the

diastereometic 1-*t*-butyl-2-methylazetidin-3-ols (**1** and **2**) in carbon tetrachloride were conducted (see Table II).

Clearly the two lower frequency bands in each of the diastereomers are associated with intermolecular hydrogen bonding. The highest frequency band in the spectra of **1** can safely be attributed to intramolecular hydrogen bonding since the frequency of this band is well below that generally observed for "free OH" stretching (9).

The absorption frequency for the two high frequency bands in the spectrum of **2** is concentration independent; the ratio of the intensities of these bands is also independent of concentration. Three possibilities exist for assigning these bands:

Both may be due to intramolecular hydrogen bonding. This seems extremely unlikely as the two conformers (**10** and **11**) from which this could occur are unlikely--particularly so in **11** where serious deformation of the C-O-H bond angle would be necessary, even in a planar ring.



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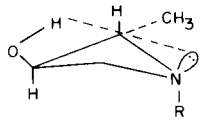
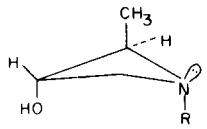


11

One of these bands might be due to intramolecular hydrogen bonding and the other due to "free OH" stretching. While this possibility cannot be entirely elimnated from consideration it seems unlikely that either **10** or **11** could be of enough importance with respect to **8** to account for the observed ratio of intensities.

Both bands may be due to "free OH" stretching, presumably in different conformations. This proposal seems to be the most attractive of the three since molecular models indicate relatively little difference in the nonbonded interactions present in **8** and in **12**.



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Regardless of the nature of the two high frequency bands in **2**, it seems clear that intramolecular hydrogen bonding in **1** is of considerably greater importance than in **2**, in agreement with what could be predicted from the configurations and conformations which have been suggested.

EXPERIMENTAL (10)

3-Bromo-1,2-epoxybutane.

To a stirred solution of 204.5 g. (2.84 moles) of crotyl alcohol in 600 ml. of chloroform, maintained at 0°, was slowly added 454 g. (2.84 moles) of bromine in 150 ml. of chloroform. Upon dissipation of the red color the chloroform was removed *in vacuo* to yield the crude 2,3-dibromo-1-butanol (11).

The crude 2,3-dibromo-1-butanol was dissolved in 1400 ml. of ether and added to a vigorously stirred solution of 160 g. (2.86 moles) of potassium hydroxide in 1700 ml. of water. After stirring for two hours, the mixture had become neutral to litmus. The ethereal layer was removed, washed twice with water and dried over magnesium sulfate. The solvent was removed *in vacuo* and the 3-bromo-1,2-epoxybutane distilled, yielding 257 g. (60%), b.p. 80-85°, at 70 torr (lit. (12) b.p. 80-82° at 70 mm).

1-*t*-Butyl-2-methylazetidin-3-ols (**1** and **2**).

The mixture of isomers was prepared by the method of Gaertner (2).

3-Bromo-1,2-epoxybutane (83.91 g., 0.555 mole) and 40.5 g. (0.555 mole) of *t*-butylamine were condensed in 100 ml. of dimethylsulfoxide at room temperature for three days. The solution was heated at 60-70° for an additional three days, then made strongly basic with aqueous sodium hydroxide after cooling to room temperature. The mixture was extracted three times with ether; the combined ether layer being extracted twice with 5% aqueous sodium hydroxide and dried over sodium carbonate. The ether was removed *in vacuo*; and the products were distilled yielding 26.87 g. (34%) of the crude mixture of azetidinols, b.p. 73-84° at 0.8 torr (lit. (2) b.p. 65-68° at 0.7 torr).

Fractional distillation of the above distillate through a 24″ column packed with glass helices with glycerol as a chaser at 5 torr gave a satisfactory separation of the isomers. Fractions of b.p. 83-91.5° at 5 torr solidified, yielding 13.28 g. The fraction (0.67 g.) of b.p. 91.5-93° was a clear, viscous liquid. The remaining fractions were collected at one mm. b.p. 78.5-84° and yielded 11.15 g. of solid material. The combined distillates of b.p. 83-91.5° (at 5 torr) were recrystallized from ether yielding 2.41 g. of **1** m.p. 86-87° (lit. (2) m.p. 83-84°). The combined distillates of b.p. 78.5-84° (at 1 torr) were recrystallized from ether yielding 5.50 g. of **2**, m.p. 65-66°.

Anal. Calcd. for $C_8H_{17}NO$: C, 67.08; H, 11.96; N, 9.78. Found: C, 66.85; H, 11.80; N, 9.75.

trans-1-Cyclohexyl-2-methylazetidin-3-ol (**4**).

To a solution of 42.13 g. (0.279 mole) of 3-bromo-1,2-epoxybutane in 50 ml. of DMSO was added 27.60 g. (0.279 mole) of cyclohexylamine. The solution was maintained at 30° for 6 days and then heated at 60-70° for 24 hours. After cooling to room temperature the dark mixture was made basic with aqueous potassium hydroxide and extracted with ether. The ethereal extract was washed with aqueous potassium hydroxide and dried (potassium hydroxide). The ether was removed *in vacuo* yielding a black oil. Distillation at 0.5 torr gave 12.70 g. of viscous yellow oil, b.p. 103-138°, which crystallized on standing and a fraction of b.p. 138-153° (at 0.5 torr) which did not solidify. The solid was successively recrystallized from ether, petroleum ether (b.p. 60-70°), and finally ether, yielding 2.29 g. of **4** as white crystals, m.p. 80-81.5°.

Anal. Calcd. for $C_{10}H_{19}NO$: C, 70.95; H, 11.32; N, 8.27. Found: C, 70.87; H, 11.53; N, 8.12.

The filtrates from the recrystallizations were combined with the distillate of b.p. 138-153° (at 0.5 torr) and redistilled, b.p. 81-158° at 0.25 torr. The distillate (10.72 g.) was collected in 5 fractions; the pmr spectrum of each fraction seemed to indicate that **4** was predominate. The distillates were combined and recrystallized from ether yielding an additional 1.82 g. of **4**, m.p. 78-80°. The total isolated yield of **4** was 4.11 g. (9%).

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