Conformational Analysis of Azetidines-Evidence for a Non-planar Ring (1a)

Robert H. Higgins, Norman H. Cromwell, (1b) and William W. Paudler (1b)

Hamilton Laboratory of Chemistry, University of Nebraska, Lincoln, Nebraska 68508

and

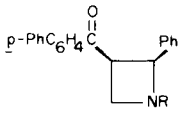
Department of Chemistry, Ohio University, Athens, Ohio 45701

Received June 16, 1971

The proton coupling constants and particularly chemical shifts of a series of 1-alkylazetidines, 1-alkylazetidin-3-ols, 1-alkyl-3-methylazetidin-3-ols, and C-methylazetidines are rationalized in terms of a conformationally mobile, non-planar azetidine ring. Preferred conformations for these compounds are discussed.

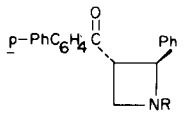
Introduction.

Other papers in this series have dealt with conformational analysis of 1-alkyl-3-(*p*-phenylbenzoyl)azetidines (**1**, **2**, **3**) (2,3). Proton coupling constants obtained from the pmr spectra of 1-alkyl-2-phenyl-3-(*p*-phenylbenzoyl)-azetidines (**1**, **2**) seemed indicative of a non-planar azetidine ring (3). Van der Waals dispersion effects allowed the assignment of a preferentially *anti* relationship (2) between the *N*-alkyl and the 2-phenyl substituents, while the examination of molecular models indicated these substituents are preferentially oriented at the *anti*-pseudoequatorial positions of **1** and **2**.



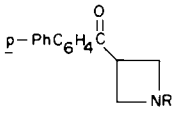
cis

1



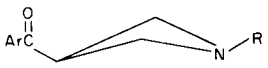
trans

2

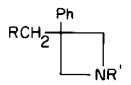


3

The pmr spectra of the 1-alkyl-3-(*p*-phenylbenzoyl)-azetidines (**3**) were rather complex (2), as the C-3 and C-2,4 ring protons had nearly identical chemical shifts. As the *N*-alkyl substituent was varied, variations in the chemical shifts of the C-2,4 protons were observed, which were assigned to intramolecular van der Waals dispersion effects. Examination of molecular models and a comparison of the pmr spectra of these compounds with the corresponding *trans*-azetidines (**2**) allowed the assignment of the preferred conformation to the 1-alkyl-3-(*p*-phenylbenzoyl)azetidines (3). Thus it was suggested (2) that the *N*-alkyl and the 3-aroyl substituents occupy *syn*-pseudoequatorial positions.



Vigevani and co-workers (4) have concluded from temperature effects on the chemical shifts of ring protons that 3,3-disubstituted azetidines (**4**) are non-planar and are undergoing rapid conformer interconversion. Thus it appears as though the above azetidines (**1**, **2**, **3**, and **4**) may be regarded as conformationally analogous to non-planar cyclobutanes (5) rather than planar, or nearly so, oxetanes (6).



4

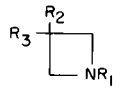
R	R'
n-C_3H_7	H
OH	H, CH_3
$OCOC_2H_5$	CH_3
$OCONH_2$	CH_3, C_2H_5

The reported synthesis (7a) of 2,5-methanopiperidine, where the azetidine ring cannot be planar, is evidence that the azetidine ring need not be planar. Indeed, Carreira and Lord (7b) observed bands in the infrared spectrum of **5a** which were assigned to nitrogen inversion in a non-planar ring.

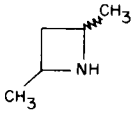
Results.

It became of interest to extend our investigations to

less substituted azetidines (**5a-j**, **6a,b**) in an effort to investigate the generality of non-planarity. It seemed that the most obvious method (2,3,8) would involve comparison of vicinal proton coupling constants obtained from the pmr spectra of the compounds. There are few systematic reports (2,3,9,10) in the literature of the pmr spectra of azetidines, and those (9,10) for simple systems give values of 6.5-7.4 Hz for vicinal coupling constants, regardless of *cis* or *trans* coupling. Significant variation in the coupling constants for the *cis* and *trans* protons of **5a-g** and **6a,b** was likewise absent.



5



6

	R_1	R_2	R_3
a.	H	H	H
b.	t-C_4H_9	H	H
c.	C_6H_{11}	H	H
d.	H	CH_3	H
e.	t-C_4H_9	OH	H
f.	C_6H_{11}	OH	H
g.	$CH(Ph)_2$	OH	H
h.	H	CH_3	CH_3
i.	t-C_4H_9	OH	CH_3
j.	C_6H_{11}	OH	CH_3

a. *cis*
b. *trans*

In view of the sensitivity of proton coupling constants to the presence of nearby heteroatoms (11,12) we are hesitant to suggest magnitudes for dihedral and geminal angles on the basis of coupling constants. Chemical shifts (Table II) seem to give a more definitive insight into the preferred conformation of these systems, however.

The configurations of the *cis* and *trans*-2,4-dimethylazetidines (**6a,b**) are assigned quite easily, and independently from the conformations of these molecules. Regardless of whether the conformation involved is a planar ring or a rapidly inverting puckered one (13), the methylene protons at C-3 of the *trans* isomer are equivalent, whereas the methylene protons at C-3 of the *cis* isomer are not.

Discussion.

The chemical shifts of the ring protons at C-2 and C-4 of the 1-alkylazetidin-3-ols are seen to be sensitive functions of the steric requirement of the *N*-alkyl substituent (2,3). Any shielding or deshielding exerted upon these protons is a combination of the anisotropy of the C-O, C-C, and C-H bonds (15); effect of the nitrogen lone-pair of electrons (16); and intramolecularly induced van der Waals dispersion effects (17,18).

Methyl groups have been shown to shield (15b-c,19) *cis*-vicinal protons more than the corresponding *trans* protons. Thus the C-2 (and C-4) protons of **5d** which are shielded with respect to the corresponding protons of **5a**

TABLE I

Proton Coupling Constants of Some Azetidines (a)

Azetidine	J_{23}	J_{22} (b)	J_{33} (b)	Ref.
5a	7 (c)	(d)	(d)	
1-Et	7.4 (e)	(d)	(d)	9
1-n-C_4H_9	7.4 (e)	(d)	(d)	9
5b	7.65, 6.44 (f)	7.45 (f,g)	10.0 (f,g)	9
5c	7	(d)	(d)	
5d	7 (c)	7	-------	
5e	6.1, 6.2 (h,i)	6.5 (g,h)	-------	
5f	7	7	-------	
5g	6.0	6.0	-------	
1-i-C_3H_7-3-OH	*ca.* 6.5	*ca.* 6.5	-------	10
1-neo-C_5H_{11}-3-OH	*ca.* 7	*ca.* 7	-------	10
6a	7 (c)	------	10	
6b	7 (c)	------	-------	

(a) Unless otherwise indicated spectra were determined in *ca.* 5% (w/v) deuteriochloroform solutions. (b) This coupling is probably negative. (c) Determined in carbon tetrachloride solution. (d) Not determined. (e) Presumably in benzene solution--see reference 9. (f) Values used in computer simulation. (g) This coupling constant is negative. (h) Computer simulation of band positions was exact, however band intensities were not in exact agreement with experimental intensities. (i) Long range coupling constant between non-equivalent H-2 and H-4 is 1.8 Hz.

TABLE II

Chemical Shifts (a) of Ring Protons of Some Azetidines

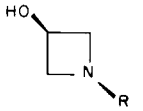
Azetidine	H_2	H_3	Ref.
5a(b)	212	140	
5b	190.7	116.5	
5c	190	120 (c)	
5d(b)	214, 190	160	
1-neo-C_5H_{11}-3-OH	221, 165	265	10
1-*i*-C_3H_7-3-OH	211, 170	261	10
5e	203, 180	262	
5f	215, 170	265	
5g	207, 170	265	
5h(b)	198	---	
5i	191	---	
5j	189	---	
6a(b)	224	140, 90	
6b(b)	230	117	

(a) Unless otherwise indicated spectra were determined in *ca.* 5% (w/v) deuteriochloroform solutions; chemical shifts are reported in Hz downfield from internal standard, tetramethylsilane, with respect to a 60 MHz field. (b) In carbon tetrachloride. (c) Partially obscured by the cyclohexyl resonance.

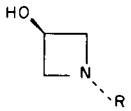
may be assigned as *cis* to the methyl group. Only one of the C-3 protons (the proton *cis* to both methyl groups) of **6a** is shielded with respect to the C-3 protons of **5a**, while both C-3 protons of **6b** are shielded.

Hydroxyl groups have been shown to shield (15c,20) *cis* vicinal protons and to deshield (20,21) *trans* vicinal protons. Thus the C-2 (and C-4) protons of the 1-alkylazetidin-3-ols which are shielded with respect to the corresponding protons of **5b** or **5c** may be assigned as *cis* to the hydroxyl group.

The variation in the chemical shift of the C-2 protons of the 1-alkylazetidin-3-ols, with the variation of the *N*-alkyl substituent, may be ascribed to dispersion effects (*vide supra*). Thus the C-2 (and C-4) proton (the more shielded proton) which is shifted to lower field when bulkier *N*-alkyl substituents are present may be assigned as *syn* (3) to the *N*-alkyl substituent, and those which shift to higher field when bulkier *N*-alkyl substituents are present may be assigned as *anti* to this substituent (3). It should be noted that this assignment places the 1-alkyl and the 3-hydroxy substituents on the same side of the ring in the preferred (but probably not fixed) conformation (**7c**) of the molecule. A similar molecular conformation was found for the 1-alkyl-3-(*p*-phenylbenzoyl)azetidines (**3**) (1).



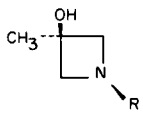
7a



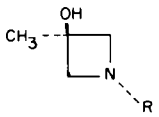
7b

There are two conceivable factors which would tend to orient these substituents in the *syn* conformer (**7a**). Dipole-dipole interaction between the oxygen atom and the *syn* nitrogen lone-pair in the *anti* invertomer (**7b**) would be expected to destabilize **7b** with respect to **7a**. However, if the ring were non-planar one would expect a conformational preference for **7a**, since both 1,2- and 1,3-interactions would be minimal.

In an effort to distinguish between these two factors, **5i** and **5j** were prepared and their spectra recorded. If invertomer **7a** were favored due to dipole-dipole interactions, one would anticipate that **5i** and **5j** would prefer to exist with the *N*-alkyl and the 3-hydroxyl substituents also *syn* (probably even to a greater extent than the 1-alkylazetidin-3-ols prefer **7a**). Thus dispersion induced shielding and deshielding should be observable on the C-2 and C-4 protons of **5i** and **5j**. If, however, **7a** were favored due to non-planarity of the azetidine ring, little or no conformational preference for either **8a** or **8b** should be expected--methyl and hydroxyl substituents have been shown (22) to have nearly the same spacial requirements. Thus by analogy with **5b** and **5c**, dispersion effects should be negligible. Indeed, the data in Table II seems to indicate the latter.



8a



8b

It was suggested in another report (2) that protons which are preferentially pseudoaxial at C-2 and C-4 absorb at higher fields than do corresponding pseudoequatorial protons (20,23). The smaller upfield shift of the resonance frequency for the ring methylene protons of **5h**, compared with that observed for protons *cis* to the methyl substituent of **5d** is evidence for a non-planar conformational preference (24) for **5d**.

It seems unlikely (15b,c) that the shielding effect of a methyl group *trans* to a proton should not cause an upfield shift in the absorbance of that proton as well as, but probably to a lesser extent than, the *cis* proton. Since the vicinal protons *trans* to the methyl groups in **5d** and **6a** would be expected to possess a conformational preference for the pseudoequatorial position, this effect should cause a deshielding of this proton--it would spend

less time as pseudoaxial. The fact that the chemical shift of the proton *trans* to the methyl substituent is rather insensitive to the methyl substituent in these compounds (**5d** and **6a**) can be rationalized in terms of a fortuitous cancelling of these effects.

The fortuitous cancelling of the effects of methyl and hydroxyl substituents observed on the *cis* and *trans* C-2 and C-4 protons of **5i** and **5j** may likewise be attributed in part to the lack of a distinctly preferred conformation (except for possibly a planar ring) for these compounds, since the resonance frequencies are distinctly different for **5d-5h** where a non-planar conformational preference is suggested.

The data for **5a**, **5b**, **5c**, **5h**, **5i**, **5j**, and **6b** are not clearly indicative of a non-planar ring. The proton coupling constants for these compounds are difficult to rationalize in terms of a planar ring, but do not necessarily exclude this possibility. Since the non-planarity of the methylazetidines (**5d** and **6a**) and the 3-hydroxyazetidines seems to stem primarily from 1,2-eclipsing interactions we tentatively suggest that these interactions should likewise result in non-planarity for **5b**, **5c**, **5h**, **5i**, **5j** and **6b**. These compounds would, however, lack a preferred, or at least distinctly preferred, conformation.

EXPERIMENTAL (25)

The syntheses for 1-*t*-butylazetidine (9) (**5b**), 1-cyclohexylazetidine (**5c**), 1-*t*-butylazetidin-3-ol (**5e**), (10) and 1-cyclohexylazetidin-3-ol (**5f**) (10) have been reported elsewhere (2).

General Method for the Preparation of N-H Azetidines **5a**, **5d**, **6a**, **6b**.

To one equivalent of the appropriate propane-1,3-dihalide or propane-1,3-diol ditosylate in *ca.* 10 volumes of 95% ethanol was added a solution prepared from one equivalent of *p*-toluenesulfonamide and one equivalent of either potassium hydroxide or sodium hydroxide in the minimum volume of water. The solution was stirred and brought to reflux. Upon becoming neutral (12-36 hours) an additional equivalent of alkali metal hydroxide was added and reflux continued until neutral (24 hours-one month). The solvent was removed *in vacuo*, the residue made basic with excess 10% aqueous alkali metal hydroxide, and extracted with chloroform. The chloroform was removed *in vacuo*, and the residue was crystallized from aqueous ethanol. The resulting 1-*p*-toluenesulfonylazetidines were reduced by sodium in *n*-pentanol to the free bases as described by Vaughan, *et al.* (26).

The spectra were determined on material collected by preparative gas chromatography.

1-*p*-Toluenesulfonylazetidine (**9**).

From 269.4 g. (1.33 moles) of 1,3-dibromopropane and *p*-toluenesulfonamide was obtained 116.8 g. (41.8%) of **9** as white crystals, m.p. 119-121° (lit. (26) m.p. 119-121.5°).

Azetidine (**5a**).

From 36.5 g. (0.173 mole) of **9** and 73.2 g. (3.19 g.-atom) of sodium in 1000 ml. of refluxing 1-pentanol was obtained 3.30 g. (34%) of **5a**, b.p. 63° (lit. (26) b.p. 61-66°).

1-(*p*-Toluenesulfonyl)-3-methylazetidine (**10**).

A dry stream of air was slowly passed through 181 g. (2.0 moles) of 3-chloro-2-methylpropane at 0-5° for 30 minutes. The cooled, stirred solution was then subjected to a stream of anhydrous hydrogen bromide until hydrogen bromide was no longer absorbed (10 hours). The solution was then washed with an equal volume of water, 10% aqueous potassium carbonate, again with water, and finally dried (sodium sulfate).

Distillation gave 61.5 g. (18%) of 3-chloro-1-bromo-2-methylpropane, b.p. 53-54° at 20 torr.; nmr (neat): 4H (triplet), τ 4.50 (J = 6 Hz); 1H (multiplet), τ 3.83; 3H (doublet), τ 2.20 (J = 7 Hz).

From 61.5 g. (0.36 mole) of the above chlorobromide on reaction with *p*-toluenesulfonamide followed by cyclization with base was obtained 55.0 g. of viscous oil. Alumina chromatography (Grade III, neutral) with petroleum ether-ether as eluant on a small portion gave an analytical sample of **10**, m.p. 50-51°.

Anal. Calcd. for $C_{11}H_{15}NO_2S$: C, 58.67; H, 6.67; N, 6.22; M. W. 225. Found: C, 58.68; H, 6.52; N, 6.07; M. W. 225.5 (osmetric).

3-Methylazetidine (**5d**).

From 16.2 g. (0.072 mole) of **10** in 600 ml. of refluxing 1-pentanol and 32.0 g. (1.39 g.-atom) of sodium was obtained 2.97 g. (58%) of **5d**, b.p. 74-75°.

Anal. Calcd. for C_4H_9N: M. W., 71. Found: M. W. 71 (mass spectrometric).

2,4-Pentanediol Ditosylates (**11**).

To 10.0 g. (0.096 mole) of the *meso* and *d,l*-threo-2,4-pentanediols (27) in 100 ml. of dry pyridine at 0° was added 42.0 g. (0.22 mole) of *p*-toluenesulfonyl chloride. The solution was maintained at 0° for 2 hours and then allowed to warm to room temperature overnight (12 hours). The mixture was then cooled to 0° and 5 ml. of water added. After 5 minutes the solution was carefully added to 100 g. of iced water. Two recrystallizations from 95% ethanol afforded 12.73 g. of **11**, m.p. 130-132°.

Recrystallization of the crude product from benzene gave m.p. 133-135° (lit. (16c) m.p. (*meso*) 135.5-136°; (*threo*) m.p. 91-92°).

cis and *trans*-1-(*p*-Toluenesulfonyl)-2,4-dimethylazetidines (**12**).

These compounds were prepared in 14% yield from 2,4-dichloropentanes (27) and in 17% yield from dibromopentanes (27). The ratio of *cis* **12** to *trans* **12** was 3:2 in either case. Likewise **11**, when recrystallized from benzene, gave a 17% yield of **12**, with a *cis:trans* ratio of 3:2 (as determined by glc). When the ditosylate (**11**) from ethanol crystallizations was used the *cis:trans* ratio was 19:1, yield 17%. 3:2 mixture: m.p. 126-134°; 19:1 mixture: m.p. 140°.

Anal. Calcd. for $C_{12}H_{17}NO_2S$: C, 60.22; H, 7.31; N, 5.85; M. W. 239. Found: C, 60.36; H, 7.07; N, 5.96; M. W. 245 (osmetric).

2,4-Dimethylazetidines (**6a** and **6b**).

From 10.57 g. (0.0442 mole) of **12** in 350 ml. of refluxing 1-pentanol and 18.7 g. (0.813 g.-atom) of sodium was obtained 2.935 g. (78%) of the *cis* and *trans*-2,4-dimethylazetidines (**6a** and **6b**), b.p. 78-81° (750 torr).

Separation of **6a** and **6b**.

These compounds were separated on a 6 ft. column of 10% Silicone Grease on Chromosorb W. Helium flow rate was 43.5 ml. per minute oven temperature was 30°, injector temperature was

79°, and detector temperature was 251°. Relative retention times were 1:1.2 for **6a** and **6b** respectively. Mass spectrometry indicated molecular masses of 85 for both **6a** and **6b** (calcd. M. W. for $C_5H_{11}N$ is 85).

3-Amino-2,2-dimethylpropanol (**13**).

To a stirred solution of 40.5 g. (1.07 moles) of lithium aluminum hydride in 300 ml. of ether was added a solution of 30.0 g. (0.213 mole) of ethyl α,α-dimethylcyanoacetate in 100 ml. of ether at such a rate as to maintain a gentle reflux. Upon completion of the addition of the cyanoacetate the mixture was refluxed for 6 hours. Upon cooling, 77 g. of water (4.85 moles) was added cautiously. The mixture was dried over sodium sulfate and filtered; the residual salts being washed with ether. The combined ether solutions were evaporated to yield 9.65 g. (44.4%) of crude 3-amino-2,2-dimethylpropanol (**13**).

Dimethyl *N*-(3-Hydroxy-2,2-dimethylpropyl)-3,3′-amino-dipropionate (**14**).

This compound was prepared by a modification of the synthesis of Wadsworth (28). The crude **13** (9.65 g., 0.0947 mole) was dissolved in 150 ml. of methyl acrylate containing 0.1 g. of 1,3-dinitrobenzene. After 12 hours of refluxing, the solvent was removed *in vacuo* leaving 18.85 g. (72%) of crude **14**.

Dimethyl *N*-(3-Chloro-2,2-dimethylpropyl)-3,3′-imino-dipropionate (**15**).

The crude **14** was treated with 7.1 g. (0.068 mole) of thionyl chloride (27) in 10 ml. of chloroform and 5 drops of *N,N*-dimethylformamide at 25°. The mixture was stirred for 30 minutes and poured into excess aqueous sodium bicarbonate solution. An additional 50 ml. of chloroform was added; the chloroform layer was separated and dried (sodium carbonate). Evaporation of the solvent *in vacuo* yielded 20.0 g. (99%) of crude **15**.

1-(2-Carbomethoxyethyl)-3,3-dimethylazetidine (**16**).

Crude **15** (20.0 g., 0.0681 mole) was mixed with 40 g. of sodium carbonate and 200 g. of copper shot. The mixture was heated at 165-205° at 20 torr. The crude distillate (**16**) weighed 3.27 g. (28%).

3,3-Dimethylazetidine (**5h**).

The crude **16** (3.27 g., 0.0191 mole) was mixed with powdered potassium hydroxide (2.40 g., 0.043 mole). Upon standing for 5 hours at room temperature a distinct amine odor was observed. The mixture was heated to *ca.* 270° while the 3,3-dimethylazetidine and methanol distilled. From preparative gas chromatography was obtained 1.23 g. (76%) of **5h**, b.p. 91-92° (lit. (29) b.p. 90-92°).

1-Benzhydrylazetidin-3-ol (**5g**).

To a solution of 9.25 g. (0.10 mole) of epichlorohydrin in 50 ml. of methanol was added 18.3 g. (0.10 mole) of benzhydrylamine. The solution was stirred for 3 days at room temperature and then refluxed for 3 days. The methanol was evaporated *in vacuo*, yielding a gummy yellow residue. Ether was added and the mixture extracted with aqueous potassium hydroxide. The ethereal extract was dried over magnesium sulfate. Evaporation of the ether gave a yellow oil which partially crystallized. Recrystallization from Skellysolve B-ether gave 3.02 g. of **5g** as white crystals, m.p. 113-115° (lit (30) m.p. 115°).

1-*t*-Butyl-3-methylazetidin-3-ol (**5i**).

To a stirred solution of 6.13 g. (0.057 mole) of 3-chloro-2-methyl-1,3-epoxypropane (31) in 25 ml. of methanol was added 4.20 g. (0.057 mole) of *t*-butylamine. The solution was stirred for 3 days at room temperature, and then refluxed for 3 days. The methanol was removed *in vacuo*, and the resulting oil taken up in 150 ml. of ether and 100 ml. of 20% sodium hydroxide. The ethereal solution was dried over sodium carbonate and distilled yielding 2.70 g., 32% of **5i**, b.p. 63-64° at 2 torr, which was analyzed as its picrate, m.p. 170-172° (benzene-ethanol).

Anal. Calcd. for $C_{14}H_{20}N_4O_8$: C, 45.16; H, 5.36; N, 15.05. Found: C, 45.27; H, 5.27; N, 14.88.

1-Cyclohexyl-3-methylazetidin-3-ol (**5j**).

To a stirred solution of 10.5 g. (0.099 mole) of 3-chloro-2-methyl-1,2-epoxypropane (31) in 10 ml. of dimethylsulfoxide was added 9.6 g. (0.099 mole) of cyclohexylamine, the temperature being maintained at 20° for 24 hours. The solution was then heated at 50° for four days. Dilution with aqueous sodium hydroxide solution yielded a yellow oil. The mixture was extracted three times with ether, and the combined ether extracts were dried over sodium hydroxide. Distillation gave 5.07 g. of yellow oil. Redistillation gave 4.70 g. (28%) of **5j** as a colorless, liquid; b.p. 75-76° at 0.01 torr.

Anal. Calcd. for $C_{10}H_{19}NO$: M. W., 169. Found: M. W., 169 (mass spectrometric).

Acknowledgment.

This work was supported in part by grant CA-02931 from the National Cancer Institute of the U. S. Public Health Service and grant R10-CAO-7917-03 from the National Institute of Health, by a Dow Fellowship held by R. H. H. during the summer of 1968, and by a grant from the Damon Runyon Memorial Fund for Cancer Research.

REFERENCES

(1a) Abstracted in part from the M. S. thesis of R. H. H., Ohio University, 1967. (b) To whom correspondence should be addressed.

(2) R. H. Higgins, E. Doomes, and N. H. Cromwell, *J. Heterocyclic Chem.*, **8**, 1063 (1971).

(3) E. Doomes and N. H. Cromwell, *J. Org. Chem.*, **34**, 310 (1969).

(4) A. Vigevani, G. G. Gallo, and B. Gioia, *Chim. Ind. (Milan)*, **50**, 1232 (1968).

(5) J. D. Dunitz and V. Schomaker, *J. Chem. Phys.*, **20**, 1703 (1952); A. Almenminger, O. Bastiansen, and P. V. Skanke, *Acta Chem. Scand.*, **15**, 711 (1961).

(6) See S. Searles, Jr. in A. Weissberger (ed), "The Chemistry of Heterocyclic Compounds," Vol. 19, Part II, Interscience, New York, 1964, Chapter 9.

(7a) J. V. Braun, W. Haensel, and F. Zobel, *Ann.*, **462**, 283 (1928); (b) L. A. Carreira and R. C. Lord, *J. Chem. Phys.*, **51**, 2735 (1969).

(8a) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); (b) M. Karplus, *J. Chem. Soc.*, **85**, 2870 (1963).

(9) A. Bottini and J. D. Roberts, *J. Am. Chem. Soc.*, **80**, 5203 (1958).

(10) V. R. Gaertner, *J. Org. Chem.*, **32**, 2972 (1967).

(11a) For a discussion of the effect of heteroatoms on geminal couplings see H. J. Bernstein and N. Sheppard, *J. Chem. Phys.*, **42**, 1339 (1965); (b) M. Anteunis, *Bull. Soc. Chim. Belges*, **75**, 396 (1966) and *Bull. Soc. Chem. Belges*, **75**, 413 (1966).

(12) For a discussion of the effect of heteroatoms on vicinal couplings see: (a) Reference 8b; (b) H. Booth, *Tetrahedron Letters*, 411 (1965); (c) E. L. Eliel and Sr. M. Knoeber, *J. Am.*

Chem. Soc., 90, 3444 (1968); (d) See Reference 11b.

(13) An alternative explanation involving slow ring inversion is eliminated by variable temperature studies. The spectra of **6a** and **6b** are essentially unchanged through a wide range of temperatures (-80° to +80°).

(14) R. M. Rodebaugh, Ph.D. Thesis, University of Nebraska, 1970.

(15a) J. W. ApSimon, W. G. Craig, P. V. DeMarco, D. W. Mathieson, L. Saunders, and W. B. Whally, *Tetrahedron*, 19, 2339 (1967); (b) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill, New York, 1959, pp. 176-180; (c) L. M. Jackman, "Applications of Nuclear Magnetic Resonance in Organic Chemistry," Macmillan, New York, 1959, Chapter 7.

(16) For a discussion of this effect see, (a) J. B. Lambert and R. G. Keska, *Tetrahedron Letters*, 2023 (1970); (b) R. O. Hutchins, L. D. Kopp, and E. L. Eliel, *J. Am. Chem. Soc.*, 90, 7174 (1968); Also see: (c) E. L. Eliel and R. O. Hutchins, *J. Am. Chem. Soc.*, 91, 2703 (1969) for an apparent reversal of this phenomenon. See also: M. G. T. Robinson, *Tetrahedron Letters*, 7153 (1968).

(17) For a discussion of the deshielding mechanism, see A. D. Buckingham, T. Schaefer, and W. G. Schneider, *J. Chem. Phys.*, 32, 1227 (1960); T. Schaefer, W. F. Reynolds, and T. Yonemoto, *Can J. Chem.*, 41, 2969 (1963); and Y. M. S. Gil and W. A. Gibbons, *Mol. Phys.*, 8, 199 (1964).

(18) For a possible explanation of the shielding mechanism, see S. J. Brois, *Tetrahedron*, 26, 227 (1970).

(19) N. L. Allinger and L. A. Tushaus, *J. Org. Chem.*, 30, 1949 (1965).

(20) I. Lillien and R. A. Doughty, *J. Am. Chem. Soc.*, 89, 155 (1967).

(21) N. S. Bhacca and D. H. Williamson, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, California, 1964, p. 183; H. Booth, *Tetrahedron Letters*, 22, 615 (1966).

(22) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, 1966, p. 44.

(23) R. U. Lemieux, R. K. Kullig, H. J. Bernstein, and W. G. Schnedier, *J. Am. Chem. Soc.*, 80, 6098 (1958); E. L. Eliel and M. H. Gianni, *Tetrahedron Letters*, 97 (1962).

(24) It seems unlikely that much contribution to the chemical shift of the C-2 and C-4 protons of the N-H azetidines is due to a conformational preference of the nitrogen pyramid, see N. L. Allinger and J. C. Tau, *J. Am. Chem. Soc.*, 87, 1227 (1965) and N. L. Allinger, J. A. Hirsch, and M. A. Miller, *Tetrahedron Letters*, 3729 (1967) and references cited therein.

(25) The melting points are corrected. Mass spectra were obtained at 80 ev on a Hitachi Perkin-Elmer RMU-6E instrument with an inlet temperature of 180°. The nmr spectra were determined on a Varian A-60 spectrometer equipped with a V-6040 variable temperature probe and controller, the spectra being determined as *ca.* 5% (w/v) deuteriochloroform solutions with tetramethylsilane as internal standard. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.; Micro-Tech Laboratories, Skokie, Ill.; or by Mrs. S. Deboer or Mrs. K. Decker of the Ohio University Microanalysis Laboratories.

(26) W. R. Vaughan, R. S. Klonowski, R. S. McElhinney, and B. B. Millward, *J. Org. Chem.*, 26, 138 (1961).

(27) J. G. Pritchard and R. L. Vollmer, *J. Org. Chem.*, 28, 1545 (1963).

(28) D. H. Wadsworth, *J. Org. Chem.*, 32, 1184 (1967).

(29) T. Testa, L. Fontannella, and G. Cristiani, *Ann. Chem.*, 626, 114 (1959).

(30) S. S. Chatterjee and D. J. Triggle, *Chem. Commun.*, 93, (1968).

(31) C. H. DePuy, G. M. Dappen, K. L. Eilers, and R. A. Klein, *J. Org. Chem.*, 29, 2813 (1964).