Configuration and Conformation Isomerism of Azetidines

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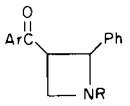
In a previous paper (2) it was concluded that the azetidine ring of 1-alkyl-2-phenyl-3-aroylazetidines (*cis:* **1a-f**, *trans:* **2a-f**) is non-planar. Others (3) have likewise concluded that 3,3-disubstituted azetidines are non-planar and are undergoing rapid ring inversion. Furthermore, the interesting L-azetidine-2-carboxylic acid has been shown to be non-planar by x-ray analysis (4).



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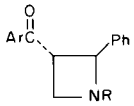


2

Ar = p-$C_6H_5C_6H_4$

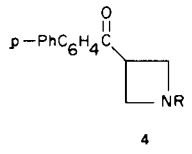
a. R = $C(Et)_3$
b. R = $C(Me)_3$
c. R = $CH(Me)_2$
d. R = C_6H_{11}
e. R = Et
f. R = Me

In our previous article (2), a rather lengthyl discussion, concerning the effect of the *N*-alkyl substituent on the C-2 ring proton was given. The variations in the chemical shift of this proton were rationalized in terms of intramolecular van der Waals dispersion induced deshielding. In an effort to more fully elucidate the origin of factors which effect the chemical shifts of ring protons, the 60 MHz pmr spectra of the *cis* and *trans*-3-aroylazetidines, **1a-f** and **2a-f**, have been reexamined.

The assignment of the C-4 protons of the *cis*-azetidines (**1a-f**) was simplified considerably by consideration of the proton coupling constants--*cf.* Table III in reference 2. The complexity of the spectra of the *trans*-azetidines, **2a-f**, resulted in our adoption of another criterion for the assignment of the C-4 protons in this series. Thus, the C-4 protons in the *trans*-azetidines were initially assigned on the assumption that the proton which is *cis* to the 3-aroyl substituent should have a resonance frequency at lower field than that proton which is *trans* to the aroyl substituent.

However, the results of a recent publication (5), when applied to this system, indicate that the carbonyl substituent should probably shield both the *cis* and the *trans* C-4 protons. In order to clarify the nature of this effect, the spectra of some 1-alkylazetidines (**3a, b**) and some 1-alkyl-3-(*p*-phenylbenzoyl)-azetidines (**4a, b**) were determined--*cf.* Tables I and II.

3



4

a. R = $C(Me)_3$
b. R = C_6H_{11}

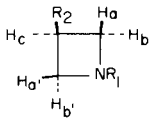
It may be seen from the data in Table I that introduction of the aroyl substituent has caused a deshielding of both of the C-2 (and C-4) protons. It is, however, not immediately obvious as to which proton has been deshielded to a greater extent in **4b**. This assignment will be discussed in detail below.

As was mentioned above, the C-4 protons of the *cis*-azetidines (**1a-f**) were quite easily assigned on the basis of proton coupling constants. A more detailed examination of the data in Table II of reference 2 indicates that the C-4 proton (H_a) which is *cis* to the C-2 proton (H_d) undergoes shifts similar to those which the C-2 proton undergoes when the *N*-alkyl substituent is varied--*cf.* Table III. The origin of this phenomenon is probably largely due to intramolecular van der Waals dispersion induced deshielding (2). An opposite effect is observed with that proton (H_b) which is *trans* to the C-2 proton (H_d)--*cf.* Table II in reference 1. This effect may likewise be attributed to van der Waals dispersion effects (6).

Thus since dispersion effects seem to be operative on the C-2 and the C-4 protons of the *cis*-azetidines and upon the C-2 protons of the *trans*-azetidines, it seems likely that these effects should also be operative upon the C-4 protons of the *trans*-azetidines. As the *N*-alkyl substituent is varied, not only would one anticipate the trends in the chemical shift of the C-2 and the *cis* C-4 proton to be in the same direction, but also of essentially the same magnitude if there exists no appreciable deformation of the angles formed by C-2 (or C-4), the nitrogen

TABLE I

Ring Proton Chemical Shifts (a) for Some 1-Alkylazetidines



3: $R_2 = H_c'$ 4: $R_2 = p\text{-}C_6H_5C_6H_4CO$

Compound	R_1	νH_a (= $\nu H_a'$)	νH_b (= $\nu H_b'$)	νH_c
3a	$C(Me)_3$	190.7 (b)	190.7 (b)	116.5 (b)
4a	$C(Me)_3$	213 (c)	213 (c)	(d)
3b	C_6H_{11}	190	190	120 (e)
4b	C_6H_{11}	201.5 (c,f)	223.5 (c,f)	(d)

(a) Spectra were recorded on *ca.* 5% solutions in deuteriochloroform. Chemical shifts are reported in Hz downfield from internal standard, tetramethylsilane, with respect to a 60 MHz field. (b) Chemical shifts used in exact computer simulation of this compound. (c) From spectrum of 3-deuterio derivative. (d) Some overlapping of the resonance frequency for this proton and those of H_a and/or H_b was observed. (e) Partially obscured by the resonance of the cyclohexyl ring protons. (f) By analysis of the AB spectrum of the 3-deuterio compound.

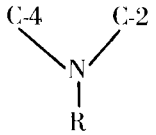
TABLE II

Ring Proton Coupling Constants for Some 1-Alkylazetidines

Compound	R_1	R_2	$[J_{ab}]$ (a)	J_{ac}	J_{bc}	$[J_{cc'}]$ (a)
3a (b)	$C(Me)_3$	H_c'	7.45 (c)	6.45	7.65	10.0 (c)
4a	$C(Me)_3$	*p*-PhC_6H_4CO	(d)	*ca.* 7	*ca.* 7	------
3b	C_6H_{11}	H_c'	(d)	*ca.* 7	*ca.* 7	(d)
4b	C_6H_{11}	*p*-PhC_6H_4CO	7.2 (e)	*ca.* 7	*ca.* 7	------

(a) The vicinal proton coupling constants are presumably negative. (b) From a computer simulation of the spectrum of this compound. (c) Computerized spectra were rather insensitive to this parameter. (d) Not determined. (e) Determined by analysis of the AB spectrum of the 3-deuterio compound.

atom, and the *N*-alkyl substituent. Thus by analogy with the *cis*-azetidines, it seems that one may assign the C-4 protons (H_a' and H_b') of the *trans*-azetidines by use of



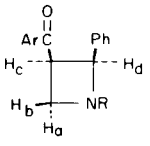
expected dispersion effects. It should be noted that the configuration assigned to these protons (H_a' and H_b') is opposite to our initial assignment (2).

If the new assignments of the C-4 protons (H_a' and H_b') are correct and if the variation observed in chemical shifts of these protons is correctly attributed to intramolecularly induced dispersion effects, it may be surmised for both the *cis* and *trans*-azetidines that, on the average, the *N*-alkyl substituent spends more time *anti* to the 2-phenyl substituent that *syn* to this substituent. This result seems quite reasonable as one would anticipate 1-2 interactions in compounds of this nature to be more important than 1-3 interactions.

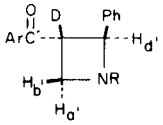
It was suggested previously (2) that vicinal (and long range) proton coupling constants are indicative of a nonplanar azetidine ring. In view of the sensitivity of proton coupling constants to heteroatoms (7,8a-d) we are hesitant to suggest magnitudes for dihedral or geminal angles. However, major deviations from the Karplus relationship (9) are anticipated only when the β-proton (H_c or H_c') assumes a conformation *anti* (8b,c) to or fully eclipsed (8b-d) with the heteroatom. Neither of these extreme cases is possible with 4-membered ring heterocycles. Consequently, the vicinal proton coupling constants for the

TABLE III

Chemical Shift Differences (a) in Ring Protons



1 (*cis*) Ar = *p*-PhC$_6$H$_4$



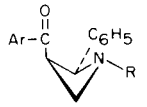
2 (*trans*)

R	Compound	(ν H$_d$-ν H$_a$)	Compound	(ν H$_d$'-ν H$_a$') (b)
C(Et)$_3$	**1a**	105	**2a**	72
C(Me)$_3$	**1b**	96	**2b**	69
CH(Me)$_2$	**1c**	93	**2c**	72.5
C$_6$H$_{11}$	**1d**	94	**2d**	72.5
Et	**1e**	94	**2e**	69
Me	**1f**	90	**2f**	65.5

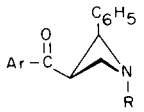
(a) Chemical shift differences are in Hz with respect to 60 MHz field. See Tables II and IV in reference 2 for the chemical shifts of the *cis* and *trans*-azetidines, respectively. (b) Notice that the assignment of the C-4 protons (H$_a$' and H$_b$') in **2** above is opposite to that suggested in the previous paper (2).

cis and the *trans*-azetidines are probably inconsistant with a planar azetidine ring and suggest at least a modest "puckering" of the azetidine ring in the preferred conformation.

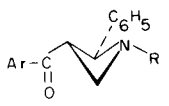
If, indeed, our suggestions that the ring is non-planar and that the *N*-alkyl substituent is preferentially *anti* to the 2-phenyl substituent are valid, only two of the possible conformations need be considered for each series of compounds.



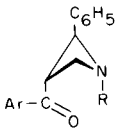
5a



5b



6a



6b

In the *trans* series we suggest that the preferred (although not fixed) conformation is most accurately represented by **6a**, since all three substituents are placed in pseudoequatorial positions. Furthermore, molecular models indicate larger steric interactions between the *N*-alkyl substituent and the *syn* protons (H$_a$' and H$_d$') in conformer **6b** than in **6a**.

The preferred conformation of the *cis*-azetidines is assigned by similar arguments. Again models indicate larger interactions between protons H$_a$ and H$_d$ and the *N*-alkyl substituent in **5b** than in **5a**. Furthermore, there are fewer pseudoaxial substituents in **5a** than in **5b**. Consequently we suggest that, for both the *cis* and *trans*-azetidines, the preferred conformation is that conformer in which the *N*-alkyl and the 2-phenyl substituents occupy pseudoequatorial positions (**5a** and **6a**, respectively).

In view of the rather small differences in the vicinal coupling constants as the *N*-alkyl substituent is varied, it seems unlikely that a major conformational change has occurred. These data may simply reflect a somewhat greater population of conformers such as **5b** or **6b** and

TABLE IV

A Comparison of Chemical Shifts (a) of Corresponding Protons in *cis* and *trans*-Azetidines (**1a-f** and **2a-f**).

R	(ν H$_a$-ν H$_a$')	(ν H$_b$-ν H$_b$')	(ν H$_d$-ν H$_d$')
C(Et)$_3$	-15	25	-18
C(Me)$_3$	-12	24	-15
CH(Me)$_2$	- 8.5	23	-12
C$_6$H$_{11}$	- 8	25	-13.5
Et	-12	19	-13
Me	-10.5	18.5	-14

(a) Chemical shift differences are in Hz with respect to a 60 MHz field.

the conformers in which the *N*-alkyl substituent and the 2-phenyl substituent are *syn*. These data may also be interpreted as previously suggested (2). The ring may be somewhat more flattened when larger *N*-alkyl substituents are present. Further evidence for the lack of a large change in conformation as the *N*-alkyl substituent is varied may be obtained from a comparison of the chemical shifts for corresponding protons. These data are presented in Table IV as differences in chemical shifts of corresponding protons. Thus if a large change in conformation had occurred in either the *cis* or the *trans*-azetidines, but not in the other, one would anticipate a rather abrupt difference in the chemical shift differences as the *N*-alkyl substituent is varied.

If our interpretation of the data is correct (*i.e.*, **5a** and **6a** are the preferred conformations), the differences in chemical shifts of corresponding protons should be primarily the result of the aroyl substituent, since other factors should tend to cancel. Thus it is seen (Table IV) that the aroyl substituent does indeed exert a larger *deshielding* influence on the *cis* protons than on the *trans* protons. This effect is, however, rather small (8-25 Hz) and may be of lesser importance than other factors, such as dispersion effects or orientation of the protons within the molecule.

Another interesting observation concerning the C-4 protons can be made. In the *cis*-azetidines (**1a-f**) and in those *trans*-azetidines (**2c-f**), in which the dispersion effects are not too large, the pseudoaxial proton (H_a or H_a') absorbs at higher field (10,11) than the corresponding pseudoequatorial proton (H_b or H_b'). While it is likely that at least a portion of the shielding of the pseudoaxial proton, with respect to the pseudoequatorial proton, is of similar origin as observed in carbocycles (10,11), we feel that the major portion of this shielding is probably due to the effect of the nitrogen long-pair (12). Regardless of the origin of this phenomenon, the effect seems to be general (13).

By comparing the chemical shifts of the C-2 (and C-4) protons of 1-cyclohexyl-3-(*p*-phenylbenzoyl)-azetidine, **4b**, with those of the *t*-butyl analog, **4a**, one sees that the difference in chemical shifts of corresponding protons may be attributed to dispersion effects. The proton assigned as H_a is apparently preferentially *syn* to the *N*-alkyl substituent, since the resonance frequency of this proton is at lower field in **4a** than in **4b**, and the resonance frequency of H_b is at higher field in **4a** than in **4b**.

The similarity in the chemical shifts of the C-2 and C-4 protons (H_a and H_b) of **4a** and **4b** with the C-4 protons (H_a' and H_b') of **2b** and **2d**, respectively, suggest that the preferred orientation of substituents and the preferred conformation of the azetidine ring are identical, or nearly so, in **4a** and **4b** as in the *trans*-azetidines. This assignment is also consistant with that which has been made for other 1,3-disubstituted azetidines (13).

EXPERIMENTAL (14)

1-*t*-Butylazetidine (**3a**).

This compound was prepared from 3-(*N*-*t*-butylamino)-1-propanol in 92% yield by the method of Bottini and Roberts (15).

1-Cyclohexylazetidine (**3b**).

To a stirred solution of 28.35 g. (0.181 mole) of 3-(*N*-cyclohexylamino)-1-propanol (16) in 350 ml. of carbon tetrachloride maintained at 0° was carefully added 21.07 g. (0.181 mole) of chlorosulfonic acid. After warming to room temperature overnight, the white crystals were removed by filtration and dissolved in 200 ml. of 20% aqueous sodium hydroxide. The mixture was refluxed for 3 hours and allowed to cool to room temperature. The resulting mixture was extracted with ether and dried (calcium chloride); the ether was then removed *in vacuo*. The resulting oil was distilled yielding 6.60 g. (26%) of **3b** as colorless liquid, b.p. 66-73° at 22 torr (lit. (17) b.p. 30-45° at 10 torr).

1-*t*-Butylazetidin-3-ol (**7**).

This compound was prepared by the procedure of Gaertner (18).

1-*t*-Butyl-3-azetidinyl tosylate (**8**).

To a stirred solution of 0.064 g. (0.040 mole) of sodium hydride in 60 ml. of ether was added 5.16 g. (0.040 mole) of **7**. After stirring at room temperature for 15 hours, a solution of 7.62 g. (0.040 mole) of freshly crystallized *p*-toluenesulfonyl chloride in 60 ml. of ether was added at a rate just sufficient to maintain a gentle reflux. After an additional 8 hours, the mixture was filtered and evaporated *in vacuo*. Recrystallization of the resulting solid from hexane afforded 8.79 g. (78%) of **8**, m.p. 70-71° (lit. (17), m.p. 70-71°).

1-*t*-Butyl-3-cyanoazetidine (**9**).

This compound was prepared from 5.7 g. (0.020 mole) of **8** and 4.0 g. (0.06 mole) of potassium cyanide as described by Chen and co-workers (17), and was used in the synthesis of **4a** without purification (19).

1-*t*-Butyl-3-(*p*-phenylbenzoyl)azetidine (**4a**).

To a mixture of 0.49 g. (0.020 g.-atom) of magnesium in 50 ml. of tetrahydrofuran (THF) was added a solution of 4.66 g. (0.020 mole) of *p*-phenylbromobenzene in 100 ml. of THF. The mixture was refluxed for one hour and a solution of **9** in 50 ml. of ether added dropwise. The solution was then refluxed an additional 7 hours and decomposed by addition of 30 ml. of saturated aqueous ammonium chloride. The resulting solution was evaporated to dryness *in vacuo* to a viscous yellow oil. The oil was dissolved in hexane (total volume 48 ml.) and 13 ml. of the hexane solution placed on a column of grade 4 neutral alumina. The column was eluted with a 10% ether in petroleum ether (b.p. 60-70°) solution, yielding a small amount of *p*-phenylbromobenzene. Further elution gave **4a**. Recrystallization from hexane afforded 0.56 g. (35% based on sampling) of **4a**, as white crystals, m.p. 87.5-88.5°; ir ν co 1679 cm^{-1} (chloroform); uv λ max 279 mμ (ϵ = 26,700) in isooctane.

Anal. Calcd. for $C_{20}H_{23}NO$: C, 81.87; H, 7.90; N, 4.77.

Found: C, 81.86; H, 7.97; N, 4.93.

After standing for *ca.* 6 months, the remainder of the crude hexane solution deposited an additional 2.52 g. (59% when corrected for sampling) of **4a** as yellow needles, m.p. 86-88°.

1-Cyclohexylazetidin-3-ol (**10**).

This compound was prepared in 20% yield by ring closure in methanol. The conditions were exactly the same as for the preparation of **7**.

1-Cyclohexyl-3-cyanoazetidine (**11**).

To a stirred solution of 1.42 g. (0.059 mole) of sodium hydride in 500 ml. of ether was added 9.18 g. (0.059 mole) of **10**. After stirring for 2 hours, 11.30 g. (0.059 mole) of freshly crystallized *p*-toluenesulfonyl chloride in 200 ml. of ether was carefully added to the mixture which was maintained at 0°. After stirring at 0° for an additional 2 hours, the mixture was filtered and the ether removed *in vacuo* using no heat. Efforts to induce crystallization of the light yellow oily residue were unsuccessful.

Consequently the crude tosylate was dissolved in a mixture of 12.0 g. (0.185 mole) of potassium cyanide in 200 ml. of methanol. The mixture was stirred at room temperature for 4 days. The methanol was then removed *in vacuo* and replaced with an equal volume of ether. The mixture was filtered, and the ether removed *in vacuo* yielding a yellow oil. Distillation afforded 3.98 g. (41% from **10**) of **11**, b.p. 116-120° at 5 torr.

Anal. Calcd. for $C_{16}H_{19}N_5O_7$, (picrate, hygroscopic, m.p. 144-146° dec.): C, 48.84; H, 4.87; N, 17.82. Found: C, 48.56; H, 4.81; N, 17.38.

1-Cyclohexyl-3-(*p*-phenylbenzoyl)azetidine (**4b**).

To a solution of 0.05 mole of *p*-phenylphenylmagnesium bromide prepared from 1.20 g. (0.050 g.-atom) of magnesium and 11.65 g. (0.050 mole) of *p*-phenylbromobenzene (see preparation for **4a**) in 100 ml. of THF, was added 3.47 g. (0.0214 mole) of **11** in 100 ml. of ether. After stirring for one hour, the solution was decomposed with excess saturated aqueous ammonium chloride. The ethereal layer was separated and dried (calcium chloride). The basic products were separated as their hydrobromides by subjecting the ethereal solution to a stream of dry hydrogen bromide. The hydrobromides were filtered, and the free amines liberated in ether with a 2-3 fold excess of *t*-butylamine. The suspended *t*-butylamine hydrobromide was removed by filtration, and the filtrate evaporated to a yellow oil *in vacuo*. Crystallization from hexane afforded 3.54 g. (52%) of **4b**, m.p. 108-110°. Recrystallization from methanol gave an analytical sample, m.p. 112-114°; ir ν co 1670 cm^{-1} (chloroform); uv λ max 270 mμ (ϵ = 24,800) in isooctane.

Anal. Calcd. for $C_{22}H_{25}NO$: C, 82.72; H, 7.83; N, 4.39. Found: C, 82.60; H, 7.82; N, 4.58.

Deuteration at C-3 of **4a** and **4b**.

The 3-deuterio derivatives of **4a** and **4b** were prepared from **4a** and **4b**, respectively, by dissolving about one g. of the aroylazetidine (**4a** or **4b**) in 5 ml. of methanol-d_1. A catalytic quantity (2) of sodium methoxide was added and the solution stirred for 3 hours at room temperature. The solvent was removed *in vacuo*, and the residue extracted with ether. Filtration to remove the suspended sodium methoxide and evaporation of the ether *in vacuo* gave pure **4a** (deuterated); however, **4b** underwent partial decomposition under these conditions.

Acknowledgment.

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(14) Melting points are uncorrected. Microanalyses were determined by Micro-Tech Laboratories, Skokie, Illinois or by Alfred Bernhardt Mikroanalytisches Laboratorium, Hohenweg, West Germany. Pmr spectra were determined on a Varian A-60-D spectrometer, infrared spectra were determined on a Perkin-Elmer Model 237 instrument, and ultraviolet spectra were determined on a Cary Model 14 spectrophotometer.

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