Carbon-13 Nuclear Magnetic Resonance Spectra of Phenycyclidine Analogs

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Natural abundance carbon-13 chemical shifts are reported for the hydrochloride salts of phencyclidine (**1a**) and sixteen analogs. The signals are assigned on the basis of chemical shift theory, SFORD multiplicities, signal intensities, and comparisons with model compounds. In addition to its forensic value, the data suggests that the solution conformations of the analogs are similar to that of phencyclidine hydrochloride.

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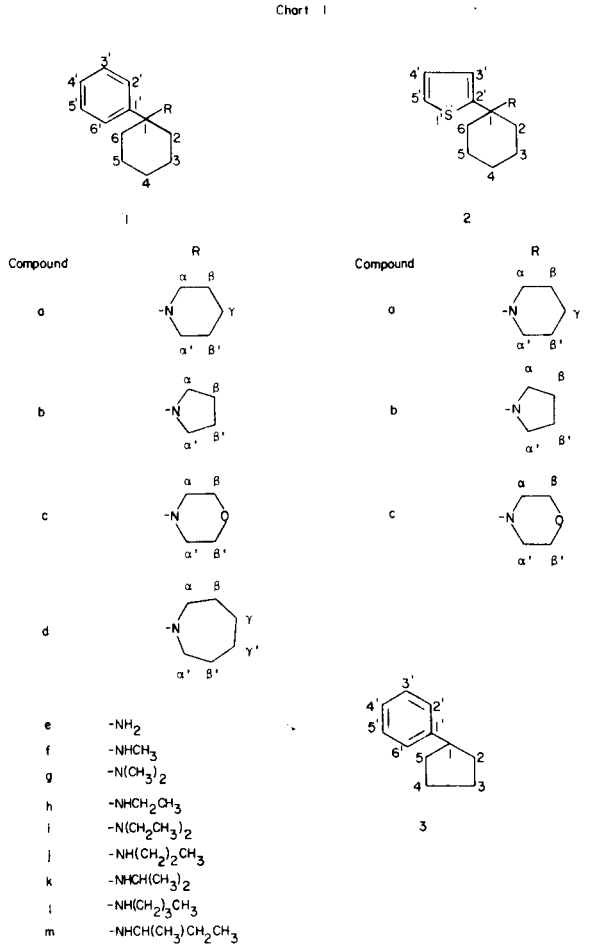
Phencyclidine (**1a**) is a highly potent and widely abused psychotomimetic drug (1). Moreover, numerous phencyclidine analogs have been prepared, several of which have similar biological activities (2). Consequently, the study of the natural abundance ^{13}C nmr spectra of phencyclidine (**1a**) and its analogs is of interest from both a conformational and a forensic viewpoint. A limited study involving the hydrochloride salts of **1a** and the corresponding 4-methyl and 4-*t*-butyl analogs has been described (3). In this paper we report the carbon-13 chemical shifts of sixteen phencyclidine analogs. In addition to its forensic value, our data suggests that the solution conformations of these analogs are similar to that of phencyclidine (**1a**) hydrochloride.

The compounds examined in the present study are summarized in Chart I. They include phencyclidine (**1a**), twelve 1-phenylcyclohexylamine analogs (**1b-m**), three thiophene analogs (**2a-c**), and 1-phenylcyclopentylamine (**3**). The ^{13}C nmr spectra were obtained on the hydrochloride salts under conditions described in the Experimental. Signal assignments were made on the basis of ^{13}C nmr chemical shift theory, multiplicities as obtained by single-frequency off-resonance decoupling (SFORD) experiments, signal intensities, and comparisons to structurally related compounds. The chemical shift assignments are summarized in Table I.

Chart I



Discussion

The phenyl C-1′ resonance was distinguished by its downfield position, its weak intensity, and its appearance as a singlet in the SFORD spectra. With four exceptions, the remaining five phenyl carbons gave rise to three resonances, all doublets (SFORD). Of these, the one having half the intensity of the other two was assigned to C-4′. The C-2′,6′ and C-3′,5′ signals were then differentiated on the basis that the meta carbons (3′,5′) would be least affected by substituent variations and would therefore have a chemical shift value closer to that of benzene (4). The exceptions were compounds **1a**, **1k** and **1m**, in which C-4′ and C-2′,6′ appeared as a three-carbon resonance, and compound **1b**, in which C-2′,6′ and C-3′,5′ had the same chemical shift value (*cf.* Table I).

The phenyl C-1′ chemical shift range varied from 138-139 ppm (primary amine) to 134-135 ppm (secondary amine) to 130-131 ppm (tertiary amine) due mainly to the γ effects resulting from increased substitution on the amine nitrogen (5). In addition, the C-2′,6′ signal shifted downfield *ca.* 1-2 ppm with increased substitution (δ ef-

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Table I

Carbon-13 Nuclear Magnetic Resonance Chemical Shifts of Phencyclidine Hydrochloride and Its Analogs in Deuteriochloroform Solution

Compound Carbon	1a	1b	1c	1d	1e	1f	1g	1h	1i	1j	1k	1l	1m	2a	2b	2c	3
1′ (2′)(a)	130.11	130.16	129.48	130.84	138.50	134.89	129.62	134.89	131.18	134.94	135.23	134.94	134.94	135.96	135.57	135.08	139.76
2′,6′ (b) (3′)	129.18 (c)	128.99 (d)	129.18 (e)	128.99 (e)	126.50	127.82	128.99 (e)	128.06	129.13 (e)	128.16	128.50 (c)	128.11	128.55 (c,e)	129.72	129.82	130.06	126.50
3′,5′ (b) (4′)	128.84	128.99 (d)	129.04 (e)	128.74 (e)	128.55	129.04	128.79 (e)	128.99	128.94 (e)	129.04	128.89	128.99	128.79 (e)	127.52	127.52	127.72	128.35
4′ (5′)	129.18 (c)	129.23	129.57	129.23	128.06	128.70	129.43	128.55	129.28	128.60	128.50 (c)	128.55	128.55 (c)	127.96	128.01	128.40	128.06
1	70.77	67.65	71.11	71.59	58.28	63.31	69.01	63.94	72.03	64.09	65.30	64.04	65.45	69.06	66.52	69.45	66.96
2,6 (b)	30.29	32.00	29.95	31.03	34.44	32.98	30.98	33.07	31.03	33.07	33.41	33.07	33.12	32.73	34.44	32.29	37.41 (f)
3,5 (b)	22.59 (e)	22.30 (e)	22.25	22.30	21.42	21.81	22.20	22.05	22.39	22.10	22.15	22.05	22.11	22.74 (e)	22.78 (e)	22.54	22.64 (g)
4	24.30	24.34	24.34	24.15	24.64	24.83	24.10	24.88	24.25	24.93	24.78	24.88	24.73	23.66	23.76	23.71	
α,α′ (b)	46.82	46.48	45.36	47.60										46.68	46.63	45.12	
β,β′ (b)	22.44 (e)	21.86 (e)	63.31	27.03										22.68 (e)	22.15 (e)	63.31	
γ,(γ′)	22.20			23.17 (b)										22.15			
N-CH_3						25.95	36.93 (b)										
N-CH_2								36.58	43.56 (b)	43.17		41.36					
N-CH											47.26		52.68				
CH_2CH_3										19.37		20.05	28.58				
$CH_2CH_2CH_3$												28.29					
CH_2CH_3								11.76	11.23 (b)	11.18		13.32	10.30				
$CHCH_3$											22.05 (b)		18.35				

(a) The numbers in parentheses are for the thiophene carbons. (b) Unless otherwise indicated, the resonances for these carbons were twice as intense as other similar resonances. (c) These resonances were three times as intense as other similar resonances. (d) These resonances were four times as intense as other similar resonances. (e) Assignments in any one column may be interchanged. (f) This resonance is for C-2 and C-5 (*cf.* Chart I). (g) This resonance is for C-3 and C-4 (*cf.* Chart I).

fects). The remaining phenyl resonances were fairly constant throughout the series. Similar but smaller shifts were observed for the corresponding aromatic carbons of benzylamine hydrochloride upon conversion to the *N*-methyl and *N,N*-dimethyl derivatives (*cf.* Table II) (6). The enhanced magnitude of the γ and δ effects on C-1′ and C-2′,6′ in the present series may reflect an inhibition of deformation in the geminally disubstituted ring system (7). A consequence of this inhibition of deformation would be an increased interaction between the phenyl ring and the amine salt as the steric bulk of the amine increased.

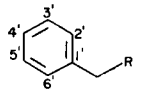
The thiophene C-2′ resonance (compounds **2a-c**) was distinguished by the same characteristics as the phenyl C-1′ resonance. The other easily differentiated thiophene signal was that of C-4′, whose chemical shift was only slightly affected by the substitution at C-2′ (8). The C-3′ and C-5′ signals were assigned on the basis that C-3′ appeared further downfield in the spectrum of thiophene and that alkyl substitution at C-2′ caused similar shifts of the C-3′ and C-5′ resonances (8).

Of the aliphatic carbon resonances, the lone singlet (SFORD) in the 58-72 ppm region was unambiguously assigned to C-1. Likewise, the methine carbons of compounds **1k** and **1m** stood out as SFORD doublets. Finally, the *N*-methyl and *C*-methyl signals were distinguished by their appearance as quartets in the off-resonance spectra. The only compound having two different methyl groups was **1m**, in which the more downfield *C*-methyl resonance was attributed to the group bonded to the more highly substituted carbon (9).

At this point only the methylene carbon resonances (SFORD triplets) remained to be assigned. On the basis of signal intensity, the cyclohexane C-4 signal at 24-25 ppm was unequivocally differentiated from the other methylene resonances in ten analogs (**1b-g, 1i, 1k, 2b-c**). Moreover, the one-carbon signal at 24.30 ppm in the spectrum of **1a** corresponded closely to the resonance previously assigned to the C-4 of phencyclidine hydrochloride in deuteriochloroform solution (3). The observed consistency for the C-4 signal in the above compounds then made feasible its assignment in the spectra of the remaining cyclohexyl derivatives (*cf.* Table I).

Table II

Carbon-13 Nuclear Magnetic Resonance Chemical Shifts of Benzylamine Hydrochloride and Its Analogs (a)



Compound Carbon	R = NH_2 HCl	R = $NHCH_3$ HCl	R = $N(CH_3)_2$ HCl
1′	134.11	132.06	130.55
2′,6′ (b)	128.99	129.96	131.04
3′,5′ (b)	128.50	128.55	128.65
4′	128.31	128.75	129.28
Ar-CH_2	42.14	51.02	59.11
N-CH_3	—	31.81	41.32

(a) The spectra were run in dimethylsulfoxide-d_6 solution. (b) These resonances were twice as intense as other similar resonances.

Signal intensity was also utilized to distinguish the piperidine C-γ resonance in compounds **1a** and **2a** from the other methylene signals. Once the C-4 signal had been differentiated, the assignment of the piperidine C-γ resonance was straightforward. In the case of **1a**, the observed C-γ chemical shift was in excellent agreement with the literature value (3).

In addition to the C-4 resonance, analogs **1h, 1j, 1l** and **1m** also contained other one-carbon signals due to the methylene carbons of the secondary amine substituent. The assignment of the C-4 resonance confirmed that the 36.58 and 28.58 ppm resonances of **1h** and **1m**, respectively, were due to the substituent methylenes. The substituent methylenes of analogs **1j** and **1l** were unambiguously assigned on the basis of chemical shift theory using *n*-propylamine hydrochloride and *n*-butylamine hydrochloride as model compounds (10).

The remaining methylene resonances had a two-carbon intensity. Two such resonances, one at 30-34 ppm and the other at *ca.* 22 ppm, were observed in the spectra of eight compounds (**1e-h, 1j-m**) (*cf.* Table I) and were attributable to the remaining cyclohexane carbons (C-2,6 and C-3,5). Since both phenyl and ammonium substituents were reported to cause a downfield β shift and an upfield γ shift in monosubstituted cyclohexanes (11), the 30-34 and *ca.* 22 ppm resonances were assigned to C-2,6 and C-3,5, respectively. Signals of similar intensity were also observed at the same position in the spectra of the remaining cyclohexyl derivatives (**1a-d, 1i, 2a-c**) and were therefore attributed to the same carbons. These assignments were consistent with those reported previously for phencyclidine (**1a**) hydrochloride (3).

The second group of cyclohexyl derivatives (**1a-d, 1i, 2a-c**) also contained tertiary amine substituents that gave rise to additional two-carbon methylene resonances. Support for the above C-2,6 and C-3,5 assignments was provided by the fact that these latter resonances could be independently differentiated. Thus, the 43.17 ppm signal in the spectrum of **1i** was attributed to the amine methylene by comparison with the spectrum of diethylamine hydrochloride (10). The C-α,α' resonance was distinguished by its downfield position in keeping with chemical shift values reported for piperidine (12), pyrrolidine (12), morpholine (13) and their derivatives. This resonance appeared slightly further downfield in the spectrum of **1d** due to the presence of the seven-membered ring (12a). The C-β,β' resonance of compounds **1c** and **2c** was distinguished by its appearance downfield from the C-α,α' resonance as expected for the methylenes adjacent to the morpholine oxygen (13). For compounds **1a-b** and **2a-b**, the signal ascribed to C-β,β' appeared at *ca.* 22 ppm and was not differentiated from the C-3,5 signal (*cf.* Table I). The presence of the extra ring methylene in compound **1d** caused a downfield shift in the C-β,β' resonance (12a), thereby separating it from the C-3,5 signal. The C-γ,γ' resonance of **1d** (two-carbon intensity) also appeared downfield from the C-3,5 signal.

The resonances due to the remaining cyclopentane carbons (C-2,5 and C-3,4) were differentiated using the same reasoning applied to the cyclohexyl derivatives. Thus, the 37.41 and 22.64 ppm signals were assigned to C-2,5 and C-3,4, respectively, on the basis of the combined effects expected for the phenyl and ammonium substituents (11). This completed the assignment of the carbon resonances.

The position of the C-1 resonance of the 1-phenylcyclohexylamines moved downfield with increased substitution on the amine nitrogen. Thus, the replacement of an amine hydrogen by an *n*-alkyl substituent caused a 5-6 ppm downfield shift due largely to increased β effects (5). Substitution of a methyl group for a substituent α hydrogen (compounds **1k** and **1m**) moved the resonance *ca.* 1 ppm further downfield. The change from a secondary to a tertiary amine was accompanied by a further shift of *ca.* 7 ppm (additional β effects). The observed effect was somewhat smaller in the case of the *N,N*-dimethyl analog **1e** and decidely smaller for the pyrrolidine analog **1b** (14). In the latter case, the effects on the cyclohexane ring were reduced because the nitrogen substituents were part of a five-membered ring. In general, however, the magnitude of the amine substituent effects on the chemical shift of C-1, especially in going from a secondary to a tertiary amine, was somewhat greater than that expected on the basis of data reported for some 1-amino-4-*t*-butylcyclohexanes (15). This may also be a consequence of the geminally disubstituted cyclohexane ring system. In this case, the presence of the aromatic substituent could enhance the steric effects of the amine substituent on the C-1 chemical shift (16).

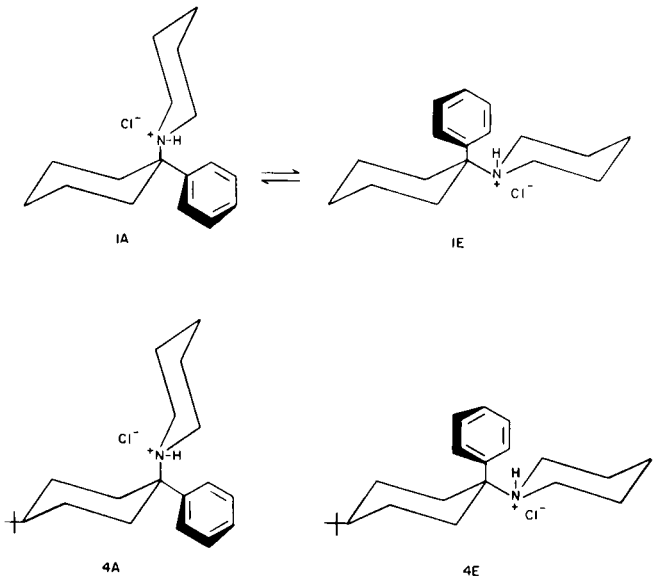
The cyclohexane C-2,6 resonance shifted upfield *ca.* 1.5 ppm as the amine substituent changed from primary to secondary and upfield another 2-3 ppm in the case of tertiary amines (γ effects). The shift again was significantly less for the pyrrolidine analogs. The C-3,5 resonance, on the other hand, appeared reasonably consistent over the entire series of compounds, undergoing only a slight downfield shift with increased substitution on the amine nitrogen. As noted earlier, the C-4 resonance was distinguished by its consistency. For those compounds having a phenyl substituent, the average chemical shift of C-4 was 24.55 $\pm$ 0.45 ppm. This value decreased to 23.71 $\pm$ 0.05 ppm for the thiophene analogs.

The two most probable conformations of phencyclidine (**1a**) hydrochloride are illustrated in Chart II. The solid state conformation was determined by X-ray analysis to be **1A**, in which both the cyclohexane and piperidine rings are in the chair form and the piperidine ring occupies the

axial position (17). That **1A** was the preferred solution conformation was postulated by Kalir and co-workers (18) on the basis of ^1H nmr data. In contrast, the ^{13}C nmr data of Geneste and Kamenka (3) indicated that conformation **1E** with the piperidine ring equatorial is predominant (≥92%) in both deuteriochloroform and aqueous (water/deuterium oxide, 1/1) solution. Part of the evidence presented in the latter study were the ^{13}C nmr chemical shift values, in deuteriochloroform, for the hydrochloride salts of the two 4-*t*-butyl analogs **4A** and **4E** (*cf.* Chart II) (19). The chemical shift values observed for phencyclidine hydrochloride corresponded closely to those found for compound **4E** after correction for the 4-*t*-butyl substituent effect (11).

The present chemical shift data (*cf.* Table I) suggested that the predominant conformation of the phencyclidine analogs in deuteriochloroform solution was similar to **1E**; *i.e.*, the amino substituent occupied the equatorial position. A key observation was the consistency of the cyclohexane C-3,5 chemical shift over the entire series. Larger variations in this chemical shift with increased substitution on nitrogen were expected in the case of conformer **1A** (20). In addition, it was possible to rationalize

Chart II



the observed shifts of the cyclohexane C-1 and C-2,6 resonances in terms of amine substituent variations without invoking conformational changes. Nevertheless, the above suggestion is at best tentative since few carbon-13 substituent parameters are available for cyclohexylamines having a geminal substituent and since effects such as protonation remain to be evaluated. It is noteworthy, however, that p*k* studies on *N,N*-dimethyl-1-phenylcyclohexylamine (**1g**) hydrochloride in 80% methylcellosolve indicated that the conformation analogous to **1E** was the more stable one (21). A possible explanation was that conformer **1E** afforded a more favorable interaction between the phenyl ring and the proton on the nitrogen (22).

It is apparent from the present study that the phencyclidine analogs can easily be differentiated from each other by ^{13}C nmr. A similar differentiation using ^1H nmr is more difficult. Since the phencyclidine analogs are often the targets of illict syntheses (23), methodology for the rapid identification of forensic samples is needed. On the basis of the above chemical shift data, it is anticipated that ^{13}C nmr will become increasingly useful for this purpose.

EXPERIMENTAL

Chemicals.

A sample of phencyclidine (**1a**) hydrochloride was obtained from Philips Roxane, Inc., St. Joseph, Missouri, through the courtesy of the National Institute on Drug Abuse. Analogs **1b-d** and **2a-c** were synthesized from the appropriate carbonitrile intermediates (2b) using the Grignard procedures described by Maddox and co-workers (2a). Compound **1e** was prepared using the procedure devised for 1-(*m*-tolyl)cyclohexylamine (2a). Methylation of the intermediate *N*-benzyl-1-phenylcyclohexylamine followed by hydrogenation afforded **1f**. Methylation of **1e** provided **1g**. Analogs **1h** and **1j-m** were synthesized *via* an imine intermediate as described by Maddox and co-workers (2a). Compound **1i** was obtained from **1h** by acetylation followed by lithium aluminium hydride reduction (2b). Analog **3** was prepared from 1-phenylcyclopentane carbonitrile (Fluka) using the procedures of Kalir and Pelah (24). The analogs were purified as the hydrochloride salts and characterized by melting point and spectral data. The melting point and analytical data on the salts are summarized in Table III.

Spectral Measurements.

The natural abundance ^{13}C nmr spectra were determined at 25.034 MHz on a modified JEOL JNM-PS-100 FT nmr interfaced with a Nicolet 1085 20K Fourier-transform computer system. Interferograms were stored in 8K of computer memory, which allowed 4K output data points in the Fourier-transformed, phase corrected real spectrum. Proton lines were decoupled by a broad band (2500 Hz) irradiation from an incoherent 99.539 MHz source. A flip angle of 72°, fixed pulse repetition time of 0.90 second, and a spectral width of 5000 Hz were used. Typically, 1012 data accumulations were obtained for 24 mg. of sample in 0.3 ml. of solvent; twice as many accumulations were taken for SFORD spectra. Samples were run at the ambient temperature in 5 mm o.d. tubes, using the deterium resoanance of the solvent as an internal lock. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane and are believed to be precise to within ±0.05 ppm. Spectra were recorded in both deuteriochloroform and CMSO-d_6. Since the chemical shift data obtained for DMSO-d_6 solutions agreed closely with that obtained in deuteriochloroform solution, only the deuteriochloroform values were reported in Table I.

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Table III

Melting Point and Analytical Data on the Phencyclidine Analog Hydrochlorides

Compound No.	Molecular Formula	M.p. °C (a)	Literature M.p. °C (Reference)	Analysis % (b) Calculated C	Calculated H	Calculated N	Found C	Found H	Found N
1b	$C_{16}H_{24}ClN$	219-221	229-230 (2b)	72.29	9.10	5.27	72.29	9.04	5.08
1c	$C_{16}H_{24}ClNO\cdot 1/2H_2O$	199-201	187-189 (2a)	66.08	8.66	4.82	66.17	9.03	4.74
1d	$C_{18}H_{26}ClN$	205-206	205-206 (25)						
1e	$C_{12}H_{18}ClN$	248-250	247-248 (2a)						
1f	$C_{13}H_{20}ClN$	180.5-183.5	185-186 (2a)	69.16	8.93	6.20	69.16	8.92	6.35
1g	$C_{14}H_{22}ClN$	166-168	164-165 (2a)						
1h	$C_{14}H_{22}ClN$	232-235	236-237 (2a)	70.12	9.25	5.84	70.04	9.44	5.76
1i	$C_{16}H_{26}ClN$	162-164		71.75	9.78	5.23	71.50	9.93	5.11
1j	$C_{15}H_{24}ClN$	224-226	203-204 (2a)	70.98	9.53	5.52	70.79	9.64	5.38
1k	$C_{15}H_{24}ClN$	241-243	234-235 (2a)	70.98	9.53	5.52	70.89	9.62	5.37
1l	$C_{16}H_{26}ClN$	245-247		71.75	9.79	5.23	71.73	9.78	5.04
1m	$C_{16}H_{26}ClN$	207-208		71.75	9.79	5.23	71.55	9.88	5.15
2a	$C_{15}H_{24}ClNS$	231-235	230-235 (2b)	63.02	8.46	4.90	63.05	8.68	4.84
2b	$C_{14}H_{22}ClNS$	187-189	187-189						
2c	$C_{14}H_{22}ClNOS$	167-169		58.42	7.70	4.87	58.23	7.69	4.78
3	$C_{11}H_{16}ClN$	230-231.5	240-242 (24)	66.80	8.16	7.09	66.59	8.09	7.02

(a) All melting points were obtained on a Hoover capillary apparatus. (b) Elemental analyses were not obtained on those analogs whose melting points corresponded closely to reported values.

REFERENCES AND NOTES

(1) R. E. Garey, L. A. Weisberg and R. G. Heath, *J. Psychedelic Drugs*, **9**, 280 (1977).

(2a) V. H. Maddox, E. F. Godefroi and R. F. Parcell, *J. Med. Chem.*, **8**, 230 (1965); (b) A. Kalir, H. Edery, Z. Pelah, D. Balderman and G. Porath, *ibid.*, **12**, 473 (1969).

(3) P. Geneste and J. M. Kamenka, *Org. Magn. Reson.*, **7**, 579 (1975).

(4) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N. Y., 1972, p. 197.

(5) The occurrence of β, γ, and δ effects across nitrogen was demonstrated in earlier ^{13}C nmr work on amines; *cf.*, J. E. Sarneski, H. L. Surprenant, F. K. Molen and C. N. Reilley, *Anal. Chem.*, **47**, 2116 (1975).

(6) Whether deuteriochloroform or dimethylsulfoxide-d_6 was used had little effect on the chemical shifts of the phencyclidine analogs; *cf.* Experimental. Consequently, solvent effects were not significant in this comparison of the phencyclidine analogs with the benzylamine analogs.

(7) J. P. Mazaleyrat and Z. Welvart, *Chem. Commun.*, 485 (1969).

(8a) T. F. Page, T. Alger and D. M. Grant, *J. Am. Chem. Soc.*, **87**, 5333 (1965); (b) K. Takahashi, T. Sone and K. Fujieda, *J. Phys. Chem.*, **74**, 2765 (1970).

(9) H. Eggert and C. Djerassi, *J. Am. Chem. Soc.*, **95**, 3710 (1973).

(10) The chemical shift data for the model compounds was obtained from reference 5. Good correlation between the phencyclidine analog amine substituents and the model compounds was obtained.

(11) T. Pehk and E. Lippmaa, *Org. Magn. Reson.*, **3**, 679 (1971). The chemical shift parameters reported in this paper were for compounds at conformational equilibrium.

(12a) G. E. Maciel and G. B. Savitsky, *J. Phys. Chem.*, **69**, 3925 (1965); (b) I. Morishima, K. Yoshikawa, K. Okada, T. Yonezawa and K. Goto, *J. Am. Chem. Soc.*, **95**, 165 (1973).

(13a) A. J. Jones, C. P. Beeman, M. U. Hasan, A. F. Casy and M.M.A. Hassan, *Can. J. Chem.*, **54**, 126 (1976); (b) B. Nilsson and S. Hernestam, *Org. Magn. Reson.*, **11**, 116 (1978).

(14) A similar difference between the six- and five-membered ring amine substituents was observed for the thiophene analogs **2a-c** (*cf.* Table I).

(15) H.-J. Schneider and V. Hoppen, *J. Org. Chem.*, **43**, 3866 (1978). In the literature series, the formation of the *N*-methyl derivative caused a larger downfield shift of the C-1 resonance than the subsequent formation of the *N,N*-dimethyl derivative, irrespective of the amine group orientation.

(16) An analogous effect was seen in the 1-methylcyclohexanols; *cf.* reference 4, pp 169-170. Upon acetylation, the C-1 downfield shifts in these compounds were much larger than those for the corresponding cyclohexanols.

(17) P. Argos, R. E. Barr and A. H. Weber, *Acta, Cryst.*, **B26**, 53 (1970).

(18) A. Kalir, S. Sadeh, H. Karoly, E. Shirin, D. Baldeman, H. Edery and G. Porath, *Israel J. Chem.*, **13**, 125 (1975).

(19) M. Mousseron, J. M. Kamenka and M. R. Darvich, *Bull. Soc. Chim. France*, 1435 (1970).

(20) This expectation was based on the equatorial and axial γ substituent effects reported for several 1-substituted-1-methyl-4-*t*-butylcyclohexanes; *cf.* reference 15.

(21) S. Sicsic and Z. Welvart, *Chem. Commun.*, 499 (1966).

(22) S. Sicsic and Z. Welvart, *Bull. Soc. Chim. France*, 575 (1967).

(23) A. T. Shulgin and D. E. MacLean, *Clin. Toxicol.*, **9**, 553 (1976).

(24) A. Kalir and Z. Pelah, *Israel J. Chem.*, **5**, 223 (1967).

(25) U. S. Patent 3,192,219; *cf. Chem. Abstr.*, **63**, 9921e (1965).