The Effect of Solvent upon the N.m.r. Spectra of N-Methylamides. I. Solvent–Solute Complex Formation between Amides and Aromatic Solvents

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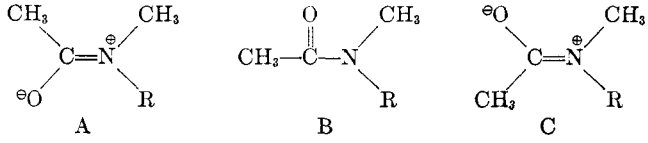
The effect of aromatic solvents such as pyridine, collidine, and benzene upon the chemical shift of protons in systems possessing internal hindered rotation has been studied. It was found that progressive dilution of a carbon tetrachloride solution of N-methylcyclohexylacetamide with pyridine shifted the two N-methyl peaks unequally with respect to each other leading to gradual coalescence and crossover with a change in sign of their chemical shifts. This behavior is discussed in terms of specific complex formation between the amide and pyridine. Similar solvent dependency studies using N-methylsulfonamido, N-methylsulfinamido, and N-methylnitrosoamino derivatives also are described.

Nuclear magnetic resonance has proved to be a very valuable method for the study of hindered internal rotation in systems in which the rate of interconversion between two rotational conformers is sufficiently slow to allow a chemical shift difference between signals arising from the two rotamers.[1] Several N-methylamides[2,3] show a doublet methyl resonance attributable to such a chemical shift difference between the methyl groups at each rotational site.[3] Gutowsky and Holm[3] have determined the barrier height *Ea* for rotation about the CO—N bond for a number of amides. This measurement is based upon the variation with temperature of the signals arising from the resonance absorption due to each rotational isomer. Typical values of *Ea* are 7 ± 3 kcal. for N,N-dimethylformamide and 12 ± 2 kcal. for N,N-dimethylacetamide. The origin of the potential energy barrier is due to resonance conjugation between the p-orbital on nitrogen and the p-orbital of the carbonyl π-electron system resulting in the two planar dipolar forms A and C.

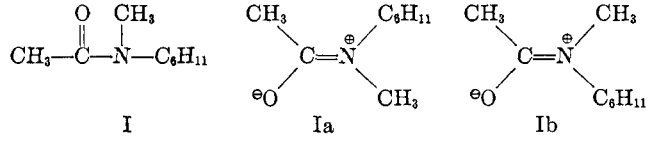


A B C

The effect of solvent on this process may be separated into a direct effect on the barrier height changing its value and leading to a different rate of interconversion or, secondly, a molecular association between solvent and solute leading to an alteration of the proton chemical shifts of the rotamers. One would predict a solvent effect upon the barrier height since the ground state A is polar relative to the nonpolar transition state for rotation B. Such solvent dependency has been demonstrated by Rogers and Woodbrey.[4] The second type of solvent effect is due to the specific contribution of aromatic solvents to the reaction field of the solute, $\delta\epsilon$,[5] and possible solute solvent complex formation δc.[6-8] These latter solvent effects lead to a difference in the chemical shift from the pure substance due to the secondary magnetic field generated by the ring current of the solvent.[5]

Results and Discussion

Solvent Effects on the Amide Group.—N-Methylcyclohexylacetamide (I) was chosen as a model compound for these studies because both N-methyl and C-methyl groups appear as sharply resolved doublets at room temperature when measured as a pure liquid (Fig. 1) and in 20% carbon tetrachloride solution. At elevated temperatures (55°) both methyl groups are singlets in agreement with the concept of a relatively large barrier to internal rotation about the N—C—O bond.[9] Cooling to room temperature leads to a restoration of the doublet pattern. The spectrum at room temperature is a superposition of the bands due to rotamers Ia and Ib. In contrast to a symmetrical case such as N,N-dimethylformamide, Ia and Ib correspond to different structures. Each has a different energy and the composition at room temperature should contain unequal amounts of each isomer depending upon



I Ia Ib

their relative stabilities. The high and low field component of each doublet may be distinguished by the dissimilar shapes but assignment of their actual position in A or B cannot be made. For this discussion the taller peak in each doublet is designated as α and the shorter as β. The band position of the methylenes and methine of the cyclohexane ring and the N-methyl and C-methyl are based upon abundant analogy and supported by the integrated ratios. Dilution of a 30% carbon tetrachloride solution with pyridine to solutions of mole fraction of 83.50, 67.23, and 53.10 (in amide and pyridine) causes a progressive downfield shift of the α C—CH_3 by $\Delta\delta$ = 0.08, the β C—CH_3 by $\Delta\delta$ = 0.09, and the α N—CH_3 by $\Delta\delta$ = 0.04, and the β N—CH_3 by $\Delta\delta$ = 0.13 (Table I). The spectra of the amide–pyridine–carbon tetrachloride solution N_1, 83.50, 67.23, and 53.10 are shown in Fig. 1, 2, 3, and 4, respectively. At the concentrations of amide mole fraction of 53.10 and 45.90 the α- and β-N-methyl bonds coalesce to a sharp singlet absorption at δ = 2.80. As dilution with pyridine is continued the β N-methyl peak moves from

(1) J. A. Pople, W. G. Schneider, and H. J. Berstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill, New York, N. Y., 1958, p. 365.

(2) W. D. Phillips, *J. Chem. Phys.*, **23**, 1363 (1955).

(3) H. S. Gutowsky and C. H. Holm, *J. Am. Chem. Soc.*, **25**, 1228 (1956). In this discussion the terms singlet and doublet refer to multiplicity resulting from hindered internal rotation and not spin–spin coupling.

(4) J. C. Woodbrey and M. T. Rogers, *J. Am. Chem. Soc.*, **84**, 13 (1962).

(5) A. D. Buckingham, T. P. Schaefer, and W. G. Schneider, *J. Chem. Phys.*, **32**, 1227 (1960).

(6) J. V. Hatton and R. E. Richards, *Mol. Phys.*, **3**, 253 (1960).

(7) (a) J. V. Hatton and R. E. Richards, *ibid.*, **5**, 139 (1960); (b) C. E. Johnson, Jr., and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958).

(8) J. V. Hatton and W. G. Schneider, *Can. J. Chem.*, **40**, 1285 (1962).

(9) The temperature required for averaging the N-methyl shifts in N,N-dimethylformamide in dilute methylcyclohexane is 99° (ref. 8).

TABLE I

PROTON SHIFTS (δ) FOR N-METHYLCYCLOHEXYLACETAMIDE (I) IN VARIOUS SOLUTIONS[a-d]

Spectrum	Mole fraction I in 30% carbon tetrachloride solution	Solvent	N—CH$_3$ α	N—CH$_3$ $\Delta\alpha$	N—CH$_3$ β	N—CH$_3$ $\Delta\beta$	C—CH$_3$ α	C—CH$_3$ $\Delta\alpha$	C—CH$_3$ β	C—CH$_3$ $\Delta\beta$	—CH$_2$—
1	100		2.79		2.66		1.94		1.99		1.50
2	83.50	Pyridine	2.83	0.04	2.77	0.11	2.01	0.07	2.06	0.07	1.55
3	67.23	Pyridine	2.83	.04	2.79(sh)	.13	2.02	.08	2.08	.09	1.55
4	53.10	Pyridine	2.80	.01	2.80	.14	2.02	.08	2.08	.09	1.55
5	45.90	Pyridine	2.80	.01	2.80	.14	2.02	.08	2.08	.09	1.55
6	33.75	Pyridine	2.73	− .06	2.81	.15	2.04	.10	2.10	.11	1.55
7	19.61	Pyridine	2.70	− .09	2.81	.15	1.99	.05	2.08	.09	1.55
8	6.95	Pyridine	2.67	− .13	2.79	.13	2.00	.06	2.09	.10	1.55
9	34.10	Benzene	2.41	− .38	2.68	.02	1.80	− .14	1.90	− .09	1.40
10	61.10	*s*-Collidine	2.80	.01	2.78	.12	2.04	.10	2.00	.01	1.55
11	19.00	Piperidine	2.80	.01	2.80	.14	2.00	.06	2.00	.01	1.50
12	10.00	Ethanol	2.82	.03	2.73	.07	2.00	.06	2.05	.06	1.60
13	30.00	Piperidine	2.81	.02	2.81	.15	2.00	.06	2.00	.01	1.49

[a] Chemical shifts $\delta = 10^6 \frac{H - H_{ref}}{H_{ref}}$ are relative to tetramethylsilane as internal standard at $\nu = 60.0$ Mc. [b] $\Delta\alpha$ and $\Delta\beta$ refer to the shifts of the α and β components of the N-methyl and C-methyl doublets relative to their positions in the N-methylcyclohexylacetamide in 30% carbon tetrachloride solution. [c] All spectra were determined at room temperature. [d] The methine proton and solvent bands are not included in this table.

under the singlet peak and appears at a new downfield position with a concomitant high field shift of the α N—CH$_3$ peak. This reversed order of appearance persists as additional pyridine is added. Although the α- and β-C-methyl peaks are shifted to lower field upon dilution with pyridine, no coalescence and crossover is observed. Benzene as solvent leads to uniform shifts of all bands to higher fields with the α N—CH$_3$ being shifted past the β-peak by $\Delta\delta = -0.38$. The spectrum of the amide in ethanol is similar to the spectrum of the pure amide in carbon tetrachloride. In 30% carbon tetrachloride solution of I in collidine, the doublet character of the methyl groups is retained but the spacings between the doublet peaks are decreased. Using piperidine as solvent the C-methyl peak appears as a sharp singlet. These results are summarized in Table I. Fig. 5 represents the spectrum of I in 30% carbon tetrachloride solution with benzene and corresponds to spectrum 9 in Table I.

A complete explanation of these solvent effects must account for (a) the direction of the line shifts observed in adding pyridine to a dilute solution of the amide in carbon tetrachloride, (b) the fact that the α and β components of the methyl doublets are shifted unequally relative to one another and in the case of the N-methyl groups, the observed coalescence and crossover pattern, and finally (c) the concentration dependency of the chemical shifts. These three points may be considered in terms of an amide–pyridine complex present according to the following equilibrium.[10]

$$\text{amide} + \text{pyridine} \rightleftharpoons \text{amide–pyridine}$$

It is proposed that the complex formed in this system has a definite structure based upon electrostatic attraction between the amide group and the pyridine. It has been suggested that "disk-shaped" aromatic solvents such as benzene solvate polar molecules by occupying a plane parallel to the plane of the solute.[6,7a] The effect of this arrangement is quite generally highfield shifts due to the secondary magnetic field of the benzene. Johnson and Bovey[7b] have derived a method for calculation of the diamagnetic or paramagnetic shift δ for a proton in any position relative to the benzene ring,

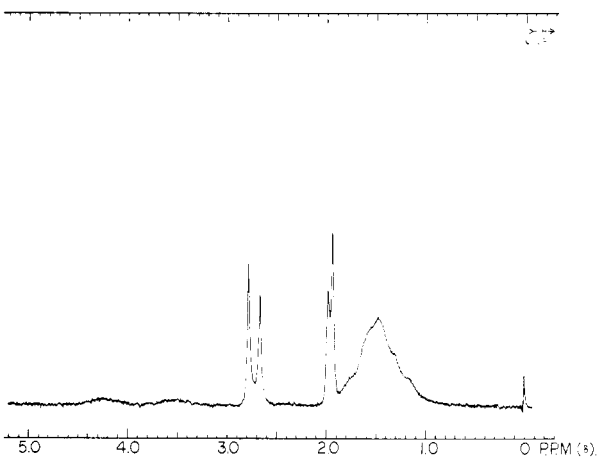


Fig. 1.—N-Methylcyclohexylacetamide (I) in 30% carbon tetrachloride solution measured relative to tetramethylsilane.

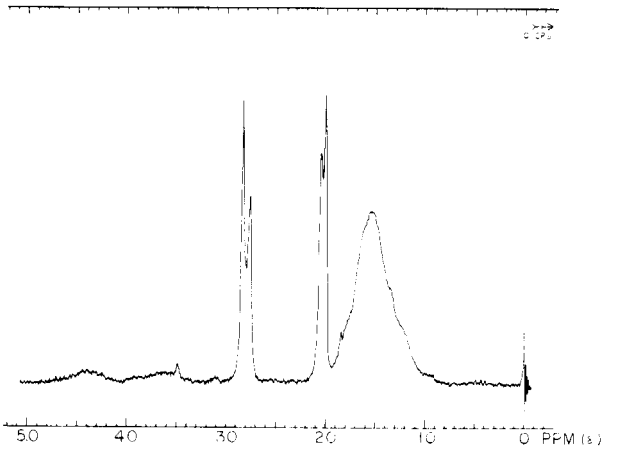
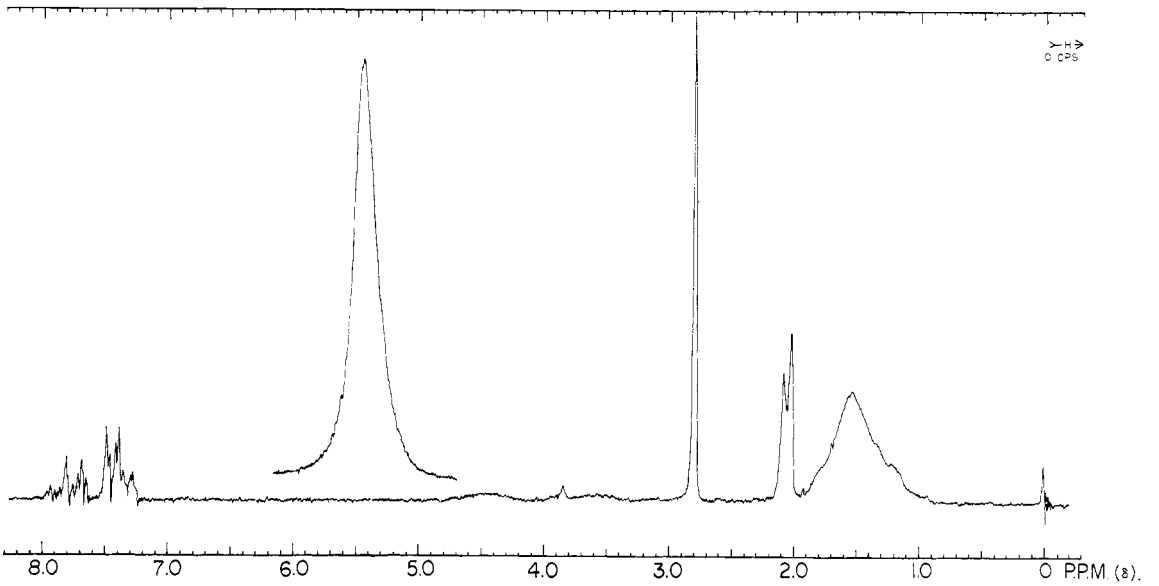


Fig. 2.—N-Methylcyclohexylacetamide (I) and pyridine of mole fraction N_I 83.50 in 30% carbon tetrachloride solution relative to tetramethylsilane.

(10) In dilute carbon tetrachloride solution the amide is considered to be non-associated relative to the dimeric dipolar form proposed for the pure amide (ref. 4).



3.—N-Methylcyclohexylacetamide (I) and pyridine of mole fraction N_I 53.10 in 30% carbon tetrachloride solution relative to tetramethylsilane. The N-methyl peak is repeated at a sweep width of 50 c.p.s.

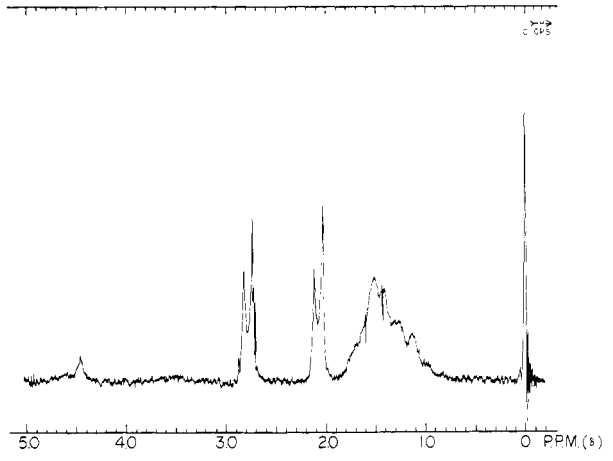


Fig. 4.—N-Methylcyclohexylacetamide (I) and pyridine of mole fraction N_I 33.75 in 30% carbon tetrachloride solution relative to tetramethylsilane.

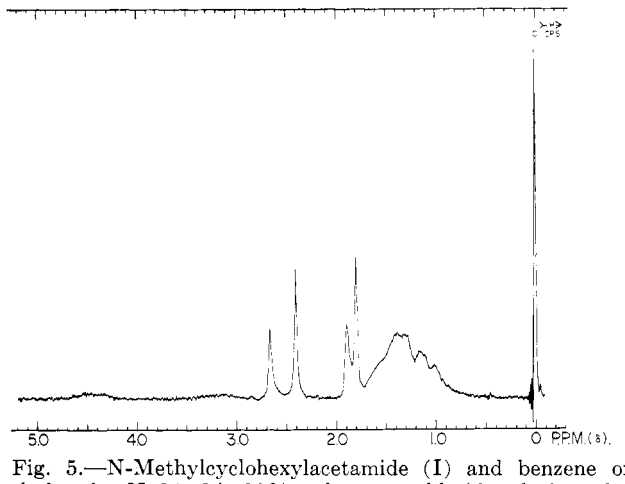
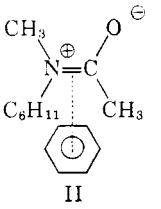


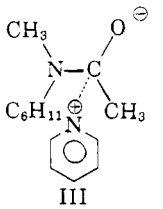
Fig. 5.—N-Methylcyclohexylacetamide (I) and benzene of mole fraction N_I 34.10 in 30% carbon tetrachloride solution relative to tetramethylsilane.

if a free electron model is assumed for the aromatic. The effect is maximal when the aromatic solvent and solute are close; the diagmagnetic shifts decrease inversely with the third power of the separation R of the solute and center of the aromatic ring. This is the behavior observed in the present study with benzene namely, highfield shifts (Table I).

Pyridine, unlike benzene, does not have a symmetrical electronic structure and probably is attracted to a specific site in the amide group. The lone pair on the nitrogen of the pyridine might be partially bonded to the carbonyl group of the amide in the complex structure. This could result in an approximately perpendicular orientation of the pyridine with respect to the average plane of the amide group. Contrasted with the parallel planes model for a symmetrical aromatic, the result of the perpendicular arrangement would be the observed lowfield shifts. This is due to the greatest magnetic susceptibility being direct along the axis of the pyridine ring and the amide carbonyl resulting in enhancement of the external field. These two structural models for the amide–benzene (II) and amide–pyridine (II) are shown below.



II

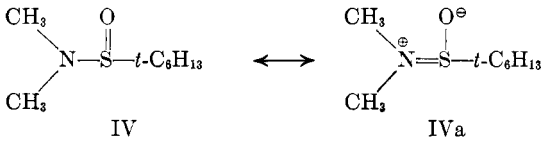


III

Also, it is clear that since α and β conformations of the N-methyl group occupy different positions relative to the pyridine molecule, they would experience different shielding. It is reasonable that in changing the concentration and, therefore, the proportion of the complex, the resonance line due to one rotational state (α N—CH_3) might be shifted by a larger amount relative to the other (β N—CH_3). Since the relative shifts of the resonance lines is dependent upon the equilibrium concentration of the amide–pyridine complex, by decreasing the mole fraction of amide we favor complex formation and observe a constant variation of the spectrum with concentration.

Solvent Effects upon the Sulfonamido, Sulfinamido, and Nitrosamino Groups.—Similarly hindered internal rotation in the related sulfinamides would require

delocalization of the electron pair on nitrogen into the 3d orbital of the sulfinyl group (IV and IVa).



IV IVa

This system bears a formal relationship to the α-sulfinyl carbanion in which some question exists concerning stabilization of the anion by doubly bonded structures implying p-3d delocalization.[11]

The appearance of a doublet N-methyl resonance in the spectrum of N,N-dimethyl-*tert*-hexylsulfinamide (IV) at room temperature indicates the existence of IVa. In dilute carbon tetrachloride solution the spacing of the N-methyl decreases to a broad singlet peak. N,N-Dimethyl-*p*-toluenesulfinamide (V) shows a sharp singlet N-methyl peak presumably due to resonance conjugation of the sulfur atom with the aromatic ring resulting in a decrease of the S—N double bond character. N-Methylcyclohexylmethanesulfonamide (VI) possesses two different methyl groups, namely, the N-methyl and S-methyl. Since rotation about the N—S bond leads to two equivalent rotational isomers, the N-methyl groups should appear as singlets. In dilute carbon tetrachloride solution both the N-methyl group and S-methyl group occur at δ = 2.69. In pyridine solution, however, they are resolved appearing at δ = 2.71 and δ = 2.87. This result may be interpreted in terms of amide–pyridine complex formation leading to an unequal change in their chemical shifts. N-Methylcyclohexylnitrosamine (VII) might be expected to exhibit hindered rotation about the N—N bond leading to a doubling of the N-methyl resonance. In dilute carbon tetrachloride solution the N-methyl resonance appears as a sharp singlet at δ = 2.82. In dilute pyridine this band, occurring at δ = 2.93, is broadened and less symmetrical than in carbon tetrachloride solution. The change in the chemical shift of the N-methyl group in VII from δ = 2.92 in the pure liquid to δ = 2.82 in 20% carbon tetrachloride is probably due to dissociation of the polar nitrosamine by dilution. These results are summarized in Table II.

It may be concluded that pyridine forms a unique complex with polar molecules based upon electrostatic attraction. The effect of the complex formation is very specific changes in the chemical shifts of groups within the polar molecule. The magnitude and direction of the change in chemical shifts from a suitable model may be explained satisfactorily in terms of the preferred orientation of the pyridine with respect to the polar molecule. Future work is aimed at a quantitative study of complex formation in the amide–pyridine system.

Experimental

A Varian Associate high-resolution A-60 instrument operating at 60.0 Mc. was employed. A sweep width of 500 c.p.s. was used, and spectra were repeated to assure constancy of the band positions which are considered accurate to within 0.01 p.p.m. The symmetry of singlet peaks was checked by using an expanded scale of 50 c.p.s. The resonance absorption positions were checked also by using a sweep width of 50 c.p.s. Precision drawn tubes (8 in. × 0.20 in.) were used. All solvents were reagent grade quality and were dried and doubly distilled prior to use. Solutions were prepared by weighing solvent and solute to the nearest milligram.

(11) F. G. Bordwell and P. J. Bouton, *J. Am. Chem. Soc.*, **79**, 717 (1957).

TABLE II

CHEMICAL SHIFTS (δ) OF N,N-DIMETHYL-*t*-HEXYLSULFINAMIDE (VI), N,N-DIMETHYL-*p*-TOLUENESULFINAMIDE (VIII), N-METHYLCYCLOHEXYLMETHANESULFONAMIDE, (IX) AND N-METHYLCYCLOHEXYLNITROSAMINE (X) IN VARIOUS SOLVENTS[a]

Spectrum	Compound	Solvent	Concn., %	NCH_3	$S—CH_3$
14	IV	...	..	2.64[b]	..
15	IV	Carbon tetrachloride	20	2.65	..
16	V	Carbon tetrachloride	20	2.60	..
17	VI	Carbon tetrachloride	20	2.69	2.69
18	VI	Pyridine	30	2.71	2.87
19	VII	...		2.92	
20	VII	Carbon tetrachloride	20	2.82	
21	VII	Pyridine	30	2.93	

[a] Chemical shifts δ are measured relative to tetramethylsilane. [b] Broad doublet.

N-Methylcyclohexylacetamide (I) was prepared by treatment of N-methylcyclohexylamine with acetic anhydride according to the method of Skita,[11] b.p. 140° (13 mm.). It was shown to be a pure substance by v.p.c. and had an infrared and n.m.r. spectrum consonant with the expected structure. N-Methylcyclohexylnitrosamine (X) was prepared according to Skita[11] and had b.p. 121° (12 mm.). The infrared and n.m.r. spectra were consistent with the expected structure.

N,N-Dimethyl-*p*-tolenesulfinamide (VIII).—Dimethylamine, 4.5 g. (0.10 mole), was dissolved in 50 ml. of ether. To this solution cooled to 0° was added *p*-toluenesulfinyl chloride[12] (3.49 g., 0.02 mole) in 50 ml. of ether. The dimethylamine hydrochloride which formed immediately was filtered and the ether solution concentrated to dryness yielding a crystalline residue. Recrystallization from hexane yielded 5.2 g., m.p. 54–55°.

Anal. Calcd. for $C_9H_{13}NSO$: C, 58.87; H, 7.16; N, 7.64. Found: C, 59.07; H, 7.15; N, 7.47.

N-Methylcyclohexylmethanesulfonamide (IX).—N-Methylcyclohexylamine, 5 g. (0.0443 mole), was dissolved in 20 ml. of pyridine, and 10 g. (0.114 mole) of methanesulfonyl chloride was added. After standing at room temperature overnight, ice was added and the resulting crystalline produce was collected, washed with water, and recrystallized from ethanol yielding 1.8 g., m.p. 65–66°.

Anal. Calcd. for $C_8H_{17}NSO_2$: C, 50.23; H, 8.94; N, 7.32. Found: C, 50.20; H, 8.90; N, 7.58.

N,N-Dimethyl-*t*-hexanesulfinamide (VI), b.p. 69–70° (0.35 mm.), $n^{20}D$ 1.4724, was supplied by Phillips Petroleum Co.[13] It was distilled prior to examination and v.p.c. analysis revealed impurities to the extent of 5%.

Acknowledgment.—We wish to thank Professor Paul von R. Schleyer of Princeton University for determining many of the spectra and also for fruitful suggestions and interest in these studies. We wish also to acknowledge helpful information received from Dr. Edwin Becker of the National Institutes of Health, Bethesda, Md.

(12) F. Kurzer, *Org. Syn.*, **34**, 93 (1954).

(13) We wish to thank Dr. J. E. Mahan for supplying us with a sample of this material.