Preparation of Phenylthianthrenonium Chloride (2c).[11]—To a solution of 1.97 g of thianthrene 5-oxide in 100 ml of benzene was added 11.2 g of aluminum chloride. The solution turned dark purple immediately. During 24 hr of boiling the color gradually turned dark brown. The solution was cooled and poured onto a mixture of 100 g of ice and 10 ml of concentrated hydrochloric acid, extracted with benzene until the benzene layer was colorless, and then extracted with chloroform to give 963 mg of **2c**, mp 252–253° (benzene–methanol). The ultraviolet spectrum had maxima at 310 nm (ϵ 7.54 × 10^3) and 225 (3.16 × 10^4).

Kinetics of Reaction of 1 with Anisole.—The apparatus in Figure 1 was used. An aliquot of a stock solution of thianthrene was introduced into B, and an aliquot of a stock solution of **1** was introduced into C. A sealed capillary (D) containing a known amount of anisole was placed in B. The chambers B and C were sealed by torch, the solvent was pumped out of B and C, and stopcock E was closed. Dried solvent was distilled into A which contained Linde Molecular Sieve 3A $^1/_{16}$. The solvent was then degassed by the freeze–thaw technique. After opening stopcock E, solvent was distilled into B, the stopcock was closed, and the apparatus was removed from the vacuum line at G. The capillary was then crushed by the magnet F, after which the solution was poured from B into C, and shaken well to dissolve the **1**. The volume was measured and the cell was placed in the spectrophotometer for absorbance measurements at 546 nm.

Kinetic measurements were made with both nitromethane and acetonitrile as solvent. Acetonitrile itself reacts very slowly with **1**, whereas nitromethane solutions are stable indefinitely.

Registry No.—**1**, 21299-20-7; **2a**, 30882-98-5; **2b**, 30882-99-6; **2c**, 30953-02-7.

Basicities of the Individual Amino Groups in ω-Dimethylamino Alkyl Amines[1a]

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The relative basicities of the two different amino groups in the compounds $Me_2N(CH_2)_nNH_2$ where n is 2–5 have been determined by nmr measurements of the chemical shifts of the methyl protons in aqueous solutions containing various amounts of added acid. The primary amino groups were 1.6–3.7 times as basic as the tertiary amino groups. The fact that the chemical shifts of the methyl protons of $Me_2N(CH_2)_2NMe_2$ and $Me_2N(CH_2)_3NMe_2$, which were used as reference compounds, were linear functions of the number of equivalents of protons added was taken as evidence against a cyclic hydrogen-bonded structure for the monoprotonated forms of these diamines. The observed relative basicities were combined with overall basicities determined by potentiometric titration to obtain the absolute basicities of the various individual amino groups in water at 35°.

In several cases polyamines, sometimes acting through their monoprotonated forms, have been found to give internal catalysis of various kinds of reactions.[2-4] For a quantitative understanding of such reactions it is desirable to know the basicities of the individual nitrogen atoms of such polyamines. Potentiometric, conductometric, and other standard methods of determining basicity constants, which yield directly only overall values, may be used for this purpose with symmetrical polyamines and are relatively satisfactory if various amino groups differ enough in basicity. However, with simple ω-dimethylamino alkyl amines, where the amino groups are of comparable basicity, it is not obvious how to partition the observed total basicity into that contributed by each of the two different basic centers. We have therefore made proton magnetic resonance measurements, somewhat like those used by Loewenstein and Roberts to determine the relative acidities of the different carboxy groups in citric acid.[5] The results have also shed light on the question of whether the monoprotonated forms of such diamines are stabilized by internal hydrogen bonding.

Results

When the chemical shifts of the methyl protons of compounds of the type $Me_2N(CH_2)_nNH_2$ (where n is 2, 3, 4, and 5) were measured in aqueous solution in the presence of increasing amounts of acid, the downfield shift that accompanied the addition of the first equivalent of acid was less than that which accompanied the addition of the second equivalent. Figure 1 illustrates this for the case of 3-dimethylaminopropylamine. (The experimental points deviate from the idealized line constructed from the initial and final slopes because of overlapping mono- and diprotonation of the amine.) Since the tertiary amino group is thus more affected by the second protonation, it follows that the first protonation takes place largely at the primary amino group. To treat the data quantitatively, let us define f_m as the fraction of the diamine that is monoprotonated, f_d as the fraction diprotonated, f_t as the fraction of monoprotonated diamine that is protonated at the tertiary position, δ_d as the downfield chemical shift of the methyl protons of the diprotonated diamine, δ_t as the shift of the methyl protons of the diamine monoprotonated at the tertiary position, and δ_p as the shift of the methyl protons of the primary-monoprotonated diamine (all chemical shifts relative to that of the methyl group of the unprotonated diamine). It may be shown that if the various differently protonated forms of the diamine are in rapid equilibrium with each other the observed chemical shift of the methyl protons may be expressed as shown in eq 1. The values of

$$\delta_{obsd} - f_d\delta_d = f_m[f_t(\delta_t - \delta_p) + \delta_p] \qquad (1)$$

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[1] (a) This investigation was supported in part by Public Health Service Grants AM 06829-MCB and AM 10378 from the National Institute of Arthritis and Metabolic Diseases. Abstracted largely from the Ph.D dissertation of F. A. Via, The Ohio State University, 1970. (b) To whom communications should be addressed at The Ohio State University.

[2] J. Hine, F. E. Rogers, and R. E. Notari, *J. Amer. Chem. Soc.*, **90**, 3279 (1968).

[3] W. P. Jencks and K. Salvesen, *Chem. Commun.*, 548 (1970).

[4] J. Hine, M. S. Cholod, and J. H. Jensen, *J. Amer. Chem. Soc.*, **93**, 2321 (1971).

[5] A. Loewenstein and J. D. Roberts, *ibid.*, **82**, 2705 (1960); *cf.* R. B. Martin, *J. Phys. Chem.*, **65**, 2053 (1961).

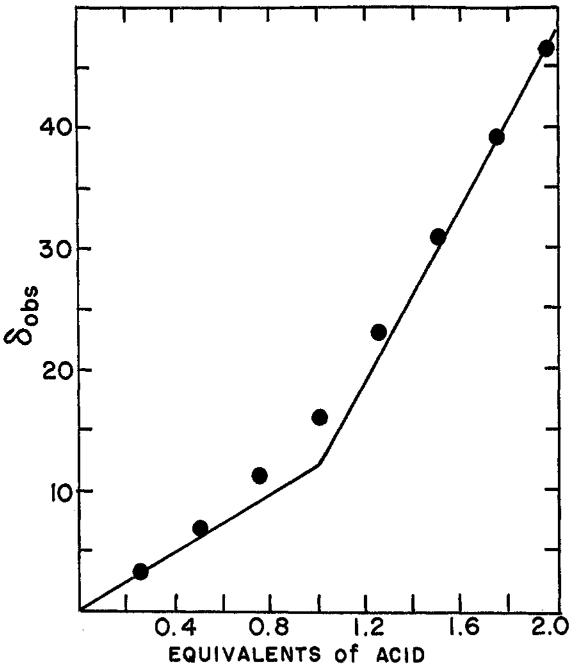


Figure 1.—Plot of the downfield shift of the methyl protons of 3-dimethylaminopropylamine (relative to those of the free base) *vs.* the number of equivalents of added acid.

f_d and f_m may be calculated from the two acidity constants of the diamine, and δ_d may be determined from measurements on solutions of diamine containing 2 equiv of strong acid. A plot of the left side of eq 1 *vs.* f_m should give a straight line, as shown in Figure 2 for the case of 2-dimethylaminoethylamine, of slope $[f_t(\delta_t - \delta_p) + \delta_p]$. These slopes and values of δ_d for the four ω-dimethylamino alkyl amines studied are listed in Table I.

Table I

Proton Magnetic Resonance Determination of the Relative Basicities of the Two Amino Groups in ω-Dimethylamino Alkyl Amines in Aqueous Solution at 35°

Diamine	$f_t(\delta_t - \delta_p) + \delta_p$, Hz	δ_d, Hz	δ_p, Hz	f_t
$Me_2N(CH_2)_2NH_2$	18.4	47.3	2.0	0.38
$Me_2N(CH_2)_3NH_2$	14.7	47.6	0.9	0.30
$Me_2N(CH_2)_4NH_2$	14.0	42.0	0.4	0.33
$Me_2N(CH_2)_5NH_2$	8.9	41.3	0.2	0.21

In order to obtain the desired values of f_t from these slopes, it was necessary to have values for the chemical shifts δ_t and δ_p. These were estimated from data on model compounds. We considered the possibility that the diprotonated diamine might be the best model for a given monoprotonated diamine. If this is true then δ_p, the change in the chemical shift of the methyl protons brought about by protonating the primary amino group of $Me_2N(CH_2)_nNH_2$, will be essentially the same as $\delta_d - \delta_t$, the change brought about by protonating the primary amino group of $Me_2N^+H(CH_2)_nNH_2$. That is, δ_d will be equal to δ_p plus δ_t. The validity of this equation may be tested by using as models symmetrical diamines, such that we know that the two different amino groups are protonated to the same extent. Let us denote the difference in chemical shifts between the boldfaced hydrogen atoms of $(C\mathbf{H}_3)_2N(CH_2)_nN(CH_3)_2$ and $(C\mathbf{H}_3)_2N^+H(CH_2)_nN(CH_3)_2$, that is, the effect of the first protonation on the shift of the methyl group adjacent to the positive charge, as δ_{a1}, and the differences in shift between $(C\mathbf{H}_3)_2N(CH_2)_nN^+H(CH_3)_2$ and $(C\mathbf{H}_3)_2N^+H(CH_2)_nN^+H(CH_3)_2$ as δ_{a2}. Analogously, the differences between $(C\mathbf{H}_3)_2N(CH_2)_nN(CH_3)_2$ and $(C\mathbf{H}_3)_2N(CH_2)_nN^+H(CH_3)_2$ and between $(C\mathbf{H}_3)_2N^+H$-$(CH_2)_nN(CH_3)_2$ and $(C\mathbf{H}_3)_2N^+H(CH_2)_nN^+H(CH_3)_2$, that is, the effects of remote charges, will be denoted δ_{r1} and δ_{r2}, respectively. Obviously $\delta_{a1} + \delta_{r2}$ is equal to $\delta_{a2} + \delta_{r1}$, since either is equal to δ_d. It may be shown that a plot of δ_{obsd} *vs.* the number of equivalents of protons added to such a symmetrical diamine will be a straight line only if δ_{a1} is equal to δ_{a2} (and hence δ_{r1} equal to δ_{r2}). Figure 3 shows that such plots do give satisfactory straight lines for the cases when n is 2 and 3. Hence $\delta_{a1} + \delta_{r1}$, the equivalent in the symmetrical diamine case of $\delta_p + \delta_t$ in the primary–tertiary diamine case, is equal to δ_d in these cases.

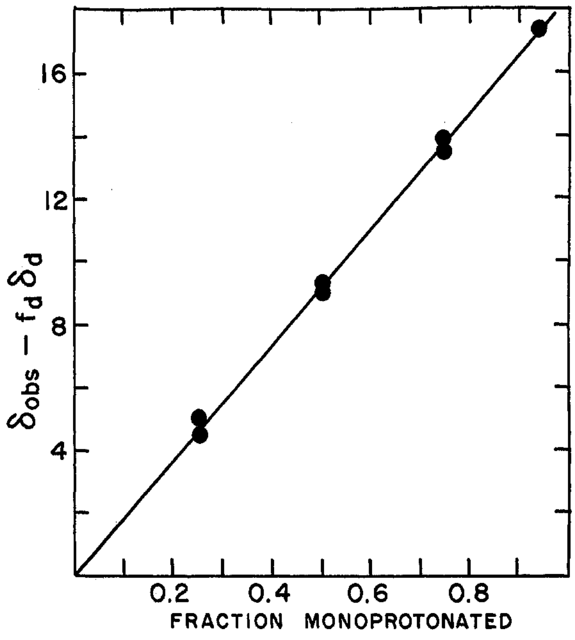


Figure 2.—Plot of chemical shift data for methyl protons of 2-dimethylaminoethylamine using eq 1.

Since the primary amino groups of our ω-dimethylamino alkyl amines are at least three atoms further from the methyl protons than the tertiary amino groups are, δ_p must be much smaller than δ_t. Even if the percentage error in estimating δ_p from data on model compounds is somewhat larger than for δ_t, the absolute error should be much smaller. Therefore, if the equation $\delta_d = \delta_t + \delta_p$ is a good approximation, it is better to estimate δ_p and calculate δ_t than to follow the reverse procedure. Changes in chemical shifts of various protons of several model amines are listed in Table II. The methyl group of 2-methoxyethylamine, separated by an oxygen atom from the $CH_2CH_2NH_2$ group that becomes protonated, provides the best model for δ_p for 2-dimethylaminoethylamine, which relates to a methyl group separated by a nitrogen atom from the $CH_2CH_2NH_2$ group that becomes protonated. Values of δ_p for the other ω-dimethylamino alkyl amines were calculated from this δ_p value by use of a "fall-off factor" of 2.3-fold per additional atom of separation from the primary amino group (an average of the factors ranging from 1.77 to 2.67 that may be

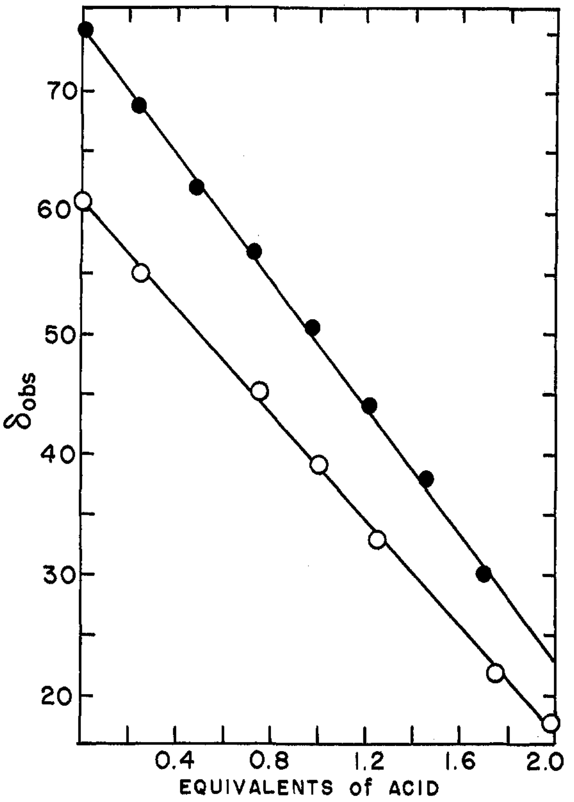


Figure 3.—Plot of chemical shift of methyl protons (upfield from methanol) *vs.* equivalents of added acid: ● for $Me_2N(CH_2)_2NMe_2$; ○ for $Me_2N(CH_2)_3NMe_2$.

calculated from the data in Table II). These values and the resulting values of f_t are listed in Table I. The values of δ_t that may be calculated, ranging from 41.1 to 46.7 Hz, seem plausible in view of the data on reference compounds. If we assume that the equation $\delta_d = \delta_t + \delta_p$ is not necessarily applicable, and that for 2-dimethylaminoethylamine δ_p may be anywhere in the range 0–5 Hz and δ_t anywhere in the range 40–50 Hz, it follows that f_t is in the range 0.30–0.46. The uncertainty in the other f_t values is probably somewhat less because of smaller uncertainties in δ_p.

We shall use the symbol TP for the tertiary–primary diamines studied, HTP^+ for the tertiary monoprotonated and TPH^+ for the primary monoprotonated species, and $HTPH^{2+}$ for the diprotonated species. The value of the acidity constant K_{HTP}, defined by eq 2, may be calculated from the experimentally determined acidity constant of the monoprotonated diamine (K_1) and f_t by use of eq 3, and the value of K_{TPH}, the acidity

$$K_{HTP} = \frac{[H^+][TP]}{[HTP^+]} \qquad (2)$$

$$K_{HTP} = K_1/f_t \qquad (3)$$

constant of TPH^+, may be calculated similarly. The resulting acidity constants (including K_2, the acidity constant of $HTPH^{2+}$) are listed in Table III.

$$K_2 = \frac{[H^+]([HTP^+] + [TPH^+])}{[HTPH^{2+}]} \qquad (4)$$

Discussion

The values of f_t in Table I show that the primary amino groups of our ω-dimethylamino alkyl amines are 1.6–3.7 times as basic as the tertiary amino groups. This is not surprising in view of the fact that, for the seven primary R groups for which the basicity of both RNH_2 and $RNMe_2$ is given in Perrin's table of aliphatic amine basicities,[6] the primary amines are 2–13 times as basic as the corresponding tertiary amines.

TABLE II

CHANGES IN CHEMICAL SHIFTS BROUGHT ABOUT BY COMPLETE PROTONATION OF THE AMINO GROUPS IN WATER AT 35°

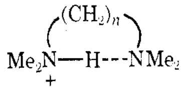
A B C D	δ_A	δ_B	δ_C	δ_D
$N(CH_3)_3$	41.4			
$N(CH_2CH_3)_3$	43.5	17.5		
H_2NCH_3	19.7			
$H_2NCH_2CH_2CH_3$	24.1	13.6	5.1	
$H_2NCH_2CH_2\text{-}O\text{-}CH_3$	23.6	11.1		2.0
$[(CH_3)_2NCH_2]_2$	52.6			
$[(CH_3)_2NCH_2]_2CH_2$	44.2			

TABLE III

ACIDITY CONSTANTS OF ω-DIMETHYLAMINO ALKYL AMINES IN WATER AT 35°

Amine	pK_1	pK_{HTP}	pK_{TPH}	pK_2
$Me_2N(CH_2)_2NH_2$	9.30 ± 0.03	8.88	9.09	5.98 ± 0.01
$Me_2N(CH_2)_3NH_2$	9.91 ± 0.02	9.39	9.75	7.67 ± 0.02
$Me_2N(CH_2)_4NH_2$	10.17 ± 0.01	9.69	10.00	8.44 ± 0.02
$Me_2N(CH_2)_5NH_2$	10.44 ± 0.03	9.77	10.34	9.07 ± 0.02

A cyclic hydrogen-bonded structure such as **1** may be



1

written for the various monoprotonated diamines. If this were the structure of the monoprotonated symmetrical diamines we have studied, then δ_{r1}, the shift produced by a "remote" positive charge, would actually be the result of a rather nearby positive charge and should therefore be larger than δ_{r2}, which should be the result of a truly remote positive charge (since the diprotonated diamine must exist largely in an extended conformation, with the like-charged nitrogen atoms widely separated). The evidence that δ_{r1} is equal to δ_{r2} provided by the plots in Figure 3 is therefore evidence that the monoprotonated amines for which *n* is 2 or 3 do not exist largely in structures like **1**.

Experimental Section

Reagents.—The methylamine and trimethylamine were Matheson products that were not further purified. All the other amines were commercially available products except for *N,N*-dimethyl-1,4-butanediamine and *N,N*-dimethylpentane-1,5-diamine, which were prepared by the lithium aluminum hydride reduction of the corresponding nitriles;[7] all were found by glpc, usually on a Carbowax 20M column, to be more than 99% pure, except for the *N,N*-dimethyl-1,4-butanediamine, which was more than 95% pure.

Proton Magnetic Resonance Spectrum Measurements on Solutions of Amines.—All pmr measurements were made at 35 ± 1° on a Varian Model A-60 spectrometer, using methanol as an internal reference. Total concentrations of amine around 0.08–0.2 *M* were used with perchloric acid added to neutralize various fractions of the amine. In obtaining the chemical shift of the free amine, a small amount of sodium hydroxide was

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(6) D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution," Butterworths, London, 1965, pp 13–52.

(7) *Cf.* W. A. Lott and J. Krapcho, U. S. Patent 2,813,904 (1957); *Chem. Abstr.*, **52**, 9197c (1958).

added to suppress ionization. Sodium chloride was added to keep the concentration of anions constant (at 0.40 *M* for *N*,*N*-dimethylethylene diamine and *N*,*N*-dimethyl-1,3-propanediamine, and at 0.17 *M* for *N*,*N*-dimethyl-1,4-butanediamine and *N*,*N*-dimethyl-1,5-pentanediamine). The chemical shift of 75% neutralized methylamine was found to be unaffected by the addition of 0.5 *M* sodium chloride. All plots of chemical shift *vs.* number of equivalent of acid added for monoamines were linear.

Determinations of pK_a.—Standard aqueous solutions of the diamines were titrated potentiometrically at 35 ± 1° with standard perchloric acid using a Beckman Research pH meter, Model 101900. About 15 pH readings were taken in the range 0.2–0.8 mol of acid per mole of diamine and another 15 in the range 1.2–1.8 mol of acid per mole of diamine. The pH was taken as $-\log a_{H^+}$, and the Davies equation[8] (which becomes eq 5 at 35°) was

$$\log f = -0.52Z^2\left(\frac{\sqrt{\mu}}{1+\sqrt{\mu}} - 0.2\mu\right) \qquad (5)$$

used to calculate ionic activity coefficients. Each of the possible pairs of pH values, one from the first and one from the second part of the titration, was used to calculate a value of pK_1 and pK_2, and the results obtained in a given titration were averaged.[9] Considering that the values of pK_1 depend largely on the pH's measured with around 0.5 mol of acid per mole of diamine, and the values of pK_2 depend largely on pH's measured with about 1.5 mol of acid per mole of diamine, the average ionic strengths at which the values of pK_1 were obtained ranged from about 0.014 to 0.19 *M* and those at which pK_2 were obtained ranged from about 0.023 to 0.23 *M*. For each amine the concentration of amine and titrating acid were varied so that the ionic strength at which each p*K* was determined varied by at least threefold. In no case was any trend noticed in the thermodynamic pK_a values, the overall average values of which are listed with their standard deviations in Table III.

The values of f_m and f_d used in the plots according to eq 1 were calculated from the concentration acidity constants at the appropriate ionics trength which was calculated from the thermodynamic constants and the Davies equation.

Registry No.—$Me_2N(CH_2)_2NH_2$, 108-00-9; $Me_2N(CH_2)_3NH_2$, 109-55-7; $Me_2N(CH_2)_4NH_2$, 3529-10-0; $Me_2N(CH_2)_5NH_2$, 3209-46-9.

Acknowledgment.—We wish to thank Kenneth W. Narducy for the computer calculation of the p*K* values reported here.

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[8] C. W. Davies, *J. Chem. Soc.*, 2093 (1938).

[9] *Cf.* D. J. MacDonald, *J. Org. Chem.*, **33**, 4559 (1968).

Bicyclo[3.1.0]hexane Conformation. The Crystal Structure of *N*-*exo*-6-Bicyclo[3.1.0]hexyl-*p*-bromosulfonamide

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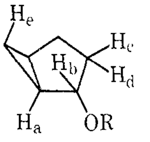
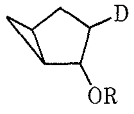
The crystal structure of the *p*-bromosulfonamide of 6-aminobicyclo[3.1.0]hexane has been determined by single-crystal X-ray diffraction. This structure shows the boat conformation as previously indicated by nuclear magnetic resonance studies.

A nuclear magnetic resonance (nmr) study of compounds I and II indicated that the bicyclo[3.1.0]hexane system was in the boat conformation.[1] This conformation explained the unique doublet at τ 6.27 (J = 5.1 cps) in the nmr spectrum of compounds Ia and Ib resulting from the splitting of the absorption of the *cis* C-2 hydrogen (H_b in I) by the *cis* C-3 hydrogen (H_c in I). This was verified by the synthesis of IIb and the presence of a singlet at τ 5.88 in its nmr spectrum. Other nmr studies have also confirmed this boat conformation for the bicyclo[3.1.0]hexane system.[2–6]

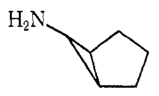


Ia, R = H
b, R = CH_3

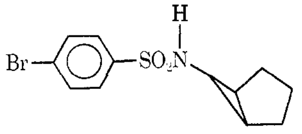


IIa, R = H
b, R = CH_3

The synthesis of 6-aminobicyclo[3.1.0]hexane (III)[7] offered an opportunity to prepare a heavy atom derivative for X-ray crystallographic studies as an independent method of testing the conformation of bicyclo[3.1.0]hexanes. The *p*-bromosulfonamide IV was prepared according to the Hinsberg reaction.[8]



III



IV

Results and Discussion

Crystallographic Measurements.—The structure of the *p*-bromosulfonamide IV was determined by single-crystal X-ray diffraction using the heavy-atom method. Details of the structure analysis, final atomic coordinates (Table I), and thermal parameters (Table I) are given in the Experimental Section.

Figure 1 is a plot of the X-ray data of the molecule with the hydrogens placed in their calculated rather than observed coordinates. As this figure indicates, the bicyclo[3.1.0]hexane system is in the boat conformation. The four ring atoms, C(8), C(9), C(11), and C(12) are all coplanar with the C(7) and C(10) atoms lying

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[1] P. K. Freeman, M. F. Grostic, and F. A. Raymond, *J. Org. Chem.*, **30**, 771 (1965).

[2] M. S. Bergqvist and T. Norin, *Ark. Kemi*, **22**, 137 (1964).

[3] K. Tori, *Chem. Pharm. Bull.*, **12**, 1439 (1964).

[4] H. E. Smith, J. C. D. Brand, E. H. Massay, and L. J. Durham, *J. Org. Chem.*, **31**, 690 (1966).

[5] A. Diefferbacker and W. von Philipsborn, *Helv. Chem. Acta*, **49**, 897 (1966).

[6] S. Winstein, E. C. Friedrich, R. Baker, and Y. Lin, *Tetrahedron*, *Suppl.*, **8**, II, 621 (1966).

[7] The authors wish to thank Dr. Jacob Szmuszkovicz, The Upjohn Co., for this compound.

[8] R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, Wiley, New York, N. Y., 1964, p 119.