TABLE II

EQUATIONS CORRELATING pK_a WITH $\Sigma\sigma^*$

Class of amine	Equation
Primary	(a) $pK_a = -3.14\Sigma\sigma^* + 13.23$
Secondary	(b) $pK_a = -3.23\Sigma\sigma^* + 12.13$
Tertiary	(c) $pK_a = -3.30\Sigma\sigma^* + 9.61$

Steric Effect of the Solvent.—As we have seen, the hydration of the primary or secondary ammonium ion decreases as the bulkiness of the alkyl groups increases. One might expect that increasing steric requirements of the solvent might prevent solvation of a secondary ammonium ion. This effect has been demonstrated by conductimetric studies in N-methylacetamide,[7] in which solvent the limiting ionic conductances are

$$NH_4^+ < CH_3NH_3^+ < (CH_3)_2NH_2^+ > (CH_3)_3NH^+ > (CH_3)_4N^+ \text{ and } NH_4^+ \lessapprox C_4H_9NH_3^+ \gtrsim (C_4H_9)_2NH_2^+ > (C_4H_9)_4N^+$$

A preliminary potentiometric study of the base strengths of amines in organic solvents[8] gave an order of base strengths in agreement with that in water. It therefore appears that solvation plays an important role in these solvents as well.

Hydration of the Amine.—In the above discussion, the hydration of the ammonium ions has been emphasized at the expense of the hydration of the amine. The latter is by no means negligible. However, Briegleb[9] has calculated that, while the heat of hydration of typical amines is in the range 10–12 kcal. per mole, those of the ammonium ions are in the range 83–85 kcal. per mole. Moreover, the former quantities are similar for primary, secondary and tertiary amines. They are therefore taken to be constant in our comparisons.

(7) L. R. Dawson, E. D. Wilhoit and P. G. Sears, THIS JOURNAL, **78**, 1571 (1956).

(8) H. K. Hall, Jr., *J. Phys. Chem.*, **60**, 63 (1956).

(9) G. Briegleb, *Z. Elektrochem.*, **53**, 350 (1949). See also D. Pressman and M. Siegel, THIS JOURNAL, **79**, 994 (1957).

Dipole Moments.—One other circumstantial bit of evidence in favor of the hydration theory may be mentioned. Taft[2] found that the dipole moments of amines in benzene, in which no solvation occurs, were correlated very well by his equation. Moreover, primary, secondary and tertiary amines all fell on the same straight line. This circumstance again indicates that the division into three lines noted above is concerned in some way with interaction with the solvent.

B-Strain.—Our interpretation has favored the solvation theory at the expense of the B-strain theory. However, it must not be thought that the latter effect will not be found in very highly branched tertiary amines. Indeed, the present investigation will give a useful method for determining the presence of B-strain, inasmuch as the observed pK_a value of a new tertiary amine can now be compared with a predicted value.

Conclusions.—The base strengths of primary, secondary and tertiary amines have been examined with the aid of the Taft equation. A marked base strengthening effect, which is identified with hydration of N^+–H groups, occurs in the following order: ammonia > primary amines > secondary amines > tertiary amines. A high degree of steric hindrance in the primary or secondary amines depresses their base strengths toward those of the tertiary amines.

The correlation equations derived in the course of this work can be used to predict the pK_a value of any tertiary amine or of secondary and primary amines of low steric size. Conversely, deviations from the equations for primary or secondary amines can be used as a gauge of steric requirement.

Acknowledgments.—I am indebted to Professor R. W. Taft for informing me of his unpublished work on this topic, and to Dr. P. W. Morgan for his continued interest and encouragement.

WILMINGTON, DEL.

[CONTRIBUTION FROM THE PIONEERING RESEARCH DIVISION, TEXTILE FIBERS DEPARTMENT, E. I. DU PONT DE NEMOURS & CO., INC.]

Steric Effects on the Base Strengths of Cyclic Amines[1]

BY H. K. HALL, JR.

RECEIVED MAY 31, 1957

A series of 1- and 2-methyl derivatives of piperidine exhibiting a wide variation in degree of steric hindrance was prepared. Their base strengths in water and in acetonitrile were measured. Those of the tertiary amines rose markedly as the degree of substitution increased, but those of the secondary amines rose only slightly. Our interpretation is that the methyl groups interfere with hydration of the secondary ammonium ions, thus offsetting the polar effects of the former.

In an earlier article of this series, polar effects on the base strengths of cyclic amines were studied.[2] In the present article steric effects on the base strengths of such amines have been examined and interpreted in light of a recent theory of base strength.[1]

Preparation of Secondary Amines.—Piperidine (I) and 2-methylpiperidine (III) were commercially available.

cis-2,6-Dimethylpiperidine was prepared readily by the hydrogenation of 2,6-lutidine,[3] but attempts to obtain the pure *trans*-isomer were unavailing by this reaction. The electrolytic[4] and sodium[5] reductions of 2,6-lutidine also

(1) This is the fourth paper of a series on amine base strengths. For the third paper, see THIS JOURNAL, **79**, 5441 (1957).

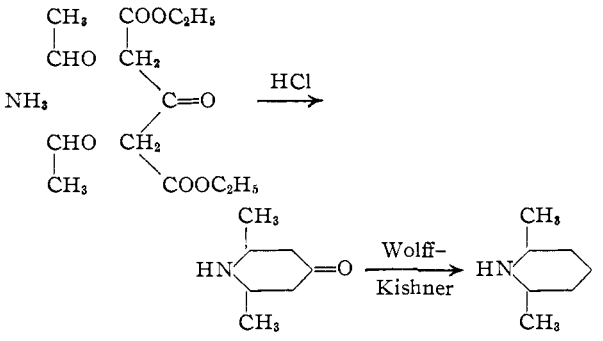
(2) H. K. Hall, Jr., *ibid.*, **78**, 2570 (1956).

(3) C. G. Overberger, L. C. Palmer, B. S. Marks and N. R. Byrd, *ibid.*, **77**, 4101 (1955).

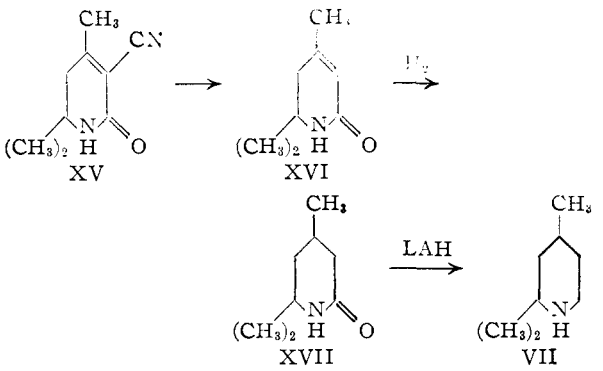
(4) E. V. Zappi, *Anal. Soc. Quim. Argentina*, **3**, 433 (1915); *C. A.*, **10**, 1523 (1916).

(5) A. Marcuse and R. Wolffenstein, *Ber.*, **32**, 2525 (1899). Other investigators have shown that sodium often fails to reduce completely pyridine rings. See S. Wawzonek, M. F. Nelson, Jr., and P. J. Thelen, THIS JOURNAL, **74**, 2894 (1952); R. F. Feldkamp, U. S. Patent 2,657,211.

failed to give pure *trans*-2,6-dimethylpiperidine. Finally, the reaction sequence indicated below also led only to the isolation of the *cis*-isomer.[6]



2,2-Dimethylpiperidine is not available[7] but 2,2,4-trimethylpiperidine could be prepared by an improvement of published procedures. 2,2,4-Trimethyl-4-piperidone is available *via* the condensation of ethyl cyanoacetate with ammonia and mesityl oxide.[8] Issoglio reduced the nitrile XV[8a] with aluminum amalgam to obtain 2,2,4-trimethylpiperidine (VII) in very low yield. In the present work the cyanopiperidone (XV) was hydrolyzed and decarboxylated to the unsaturated piperidone (XVI). Hydrogenation of the double bond over palladium on charcoal, followed by lithium aluminum hydride reduction of the amide link, provided VI in 82.1% yield, based on XVI



2,2,6-Trimethylpiperidone was prepared by Wolff–Kishner reduction of 2,2,6-trimethyl-4-piperidone, available in turn from the reaction of mesityl oxide, ammonia and acetaldehyde.[7,9] Similarly, the condensation of acetone with ammonia provided 2,2,6,6-tetramethyl-4-piperidone,[10] which upon Wolff–Kishner reduction provided 2,2,6,6-tetramethylpiperidine.[11]

Preparation of Tertiary Amines.—The less hindered amines IV and VII were methylated with formaldehyde and formic acid. The more hindered bases X and XII reacted with methyl tosylate to give fair yields of tertiary amine.

Base Strengths.—The base strengths of the amines described above were determined by potentiometric titration of the free bases in water at 30.0 and 59.6° and in acetonitrile at room temperature. The pK_a and $E_{1/2}$ values[12] are given in Table I. The values for the methyl- and ethylamines are included for comparison.

(6) *Cf.* P. Petrenko-Kritschenko, *J. Russ. Chem. Soc.*, **47**, 1126 (1915); *Chem. Zentr.*, **87**, **I**, 1055 (1916).

(7) (a) W. Heintz, *Ann.*, **189**, 222 (1877); (b) L. Orthner, *ibid.*, **456**, 245 (1927); (c) C. Harries, *Ber.*, **29**, 522 (1896); (d) G. A. C. Gough and H. King, *J. Chem. Soc.*, 2444 (1928).

(8) (a) I. Guareschi, *Atti R. Acc. delle Scienze Torino*, 28 (1893); *Ber.*, **26R**, 450 (1893); (b) Piccinini, *ibid.*, **42**, 1013 (1906); (c) G. Issoglio, *ibid.*, **43**, 14/16 (May); *Chem. Zentr.*, **89**, II, 1444 (1908).

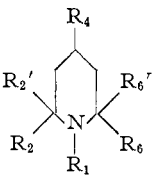
(9) Since this work was completed, 2,2,4,6-tetramethylpiperidine, IX, a compound of similar steric requirements, has become available from the Aldrich Chemical Co.

(10) F. Francis, *J. Chem. Soc.*, 2897 (1927).

(11) N. J. Leonard and E. W. Nommensen, THIS JOURNAL, **71**, 2808 (1949); E. Matter, *Helv. Chim. Acta*, **48**, 612 (1948).

(12) H. K. Hall, Jr., *J. Phys. Chem.*, **60**, 63 (1956).

TABLE I



Compound	R_1	R_2'	R_2	R_4	R_6'	R_6
I	H	H	H	H	H	H
II	CH_3	H	H	H	H	H
III	H	CH_3	H	H	H	H
IV (*cis*)	H	CH_3	H	H	CH_3	H
V (*cis*)	CH_3	CH_3	H	H	CH_3	H
VI (*trans*)	H	CH_3	H	H	H	CH_3
VII	H	CH_3	CH_3	CH_3	H	H
VIII	CH_3	CH_3	CH_2	CH_2	H	H
IX	H	CH_3	CH_3	CH_3	CH_3	H
X	H	CH_3	CH_2	H	CH_3	H
XI	CH_3	CH_3	CH_3	H	CH_3	H
XII	H	CH_3	CH_3	H	CH_3	CH_3
XIII	CH_3	CH_2	CH_3	H	CH_3	CH_3
XIV	C_2H_5	CH_3	CH_3	H	CH_3	CH_3

TABLE II

Compound	pK_a (30.0°)	pK_a (59.6°)	ΔH^a	$\Delta S_{30}{}^a$	$E_{1/2}$	$E_{1/2}$ (av.)
Secondary amines						
I	11.05	10.26	+12.3[c]	−10[c]	32, 36, 47	38
III	10.99	10.16	+12.9	− 8	42	42
IV (*cis*)	10.99	10.17	+12.8	− 9	56, 71	64
VII	11.10	10.32	+12.2	−10	51	51
X	11.27	10.42, 10.39	+13.2	− 8	49	49
XII	11.24	10.48, 10.45	+12.0	−12	56	56
Dimethylamine[d]	10.61[e]		+11.9	−10[e]		73
Diethylamine[d]	11.50[e]		+10.3	−16[e]		..
Tertiary amines						
II	10.13	9.48	+10.1	−13	95	95
V (*cis*)	10.21					
VIII	10.24					
XI	10.76					
XIII	11.25	10.63, 10.63	+ 9.7	−20	58, 63, 51	57
XIV	...[b]	...[b]	..	..		
Trimethylamine[d]	9.72[e]		+ 8.8	−15[e]		88
Triethylamine[d]	10.74[e]		+ 9.7	−16[e]		..

[a] For the reaction: RNH_3^+ (aq.) ⇄ H^+(aq.) + RNH_2(aq.). [b] Insoluble in water. [c] S. Searles, M. Tamres, F. Block and L. A. Quarterman, THIS JOURNAL, **78**, 4920 (1956), give 12.6 kcal. and −9 e.u. for ΔH and ΔS, respectively. [d] W. S. Fyfe, *J. Chem. Soc.*, 1347 (1955). [e] At 25°.

Discussion

The base strengths of the tertiary amines show a marked increase with increasing degree of substitution. Thus the base strength rises from 10.13 for N-methylpiperidine to 11.25 for 1,2,2,6,6-pentamethylpiperidine. This increase of 1.12 pK_a units is strictly a polar effect, since steric effects are not significant for tertiary amines.[1,13]

In the absence of steric effects, the same increase should be observed in passing from piperidine to

(13) The comment of the Referee is pertinent: "Replacing hydrogen by methyl normally reduces σ^* by 0.1 unit. Using $\rho^* = 3.3$ from paper III, $\Sigma\sigma^* = -0.58$ for 1,2,2,6,6-pentamethylpiperidine and $\Sigma\sigma^* = -0.18$ for 1-methylpiperidine, one may estimate that the former amine will be 1.32 log units more basic because of the polar effect. This figure is in satisfactory agreement with the value observed, giving further quantitative support to the conclusions of paper III."

2,2,6,6-tetramethylpiperidine. Yet the increase is only 0.19 unit. Clearly the expected polar effect is being offset by an adverse steric effect on solvation.

It is most interesting that 1,2,2,6,6-pentamethylpiperidine, which possesses an extreme degree of hindrance, is the most basic tertiary amine ever encountered. This is in conflict with expectations based on the B-strain hypotheses[14] but in agreement with the solvation viewpoint outlined earlier.[1]

In accord with an earlier study,[12] the base strengths of the present amines in acetonitrile parallel those in water. This is further evidence for the occurrence of solvation of the ammonium ions in other solvents than water.

Conformational Aspects.—Methyl groups on the ring carbons and on the nitrogen atom will be in the equatorial positions as far as possible, both in the amine and in the ammonium ion. If the rings in the amine and in the ammonium ion are of comparable rigidity, the energy differences arising from this source will be roughly constant.[15]

Acknowledgments.—I am indebted to Dr. P. W. Morgan for helpful suggestions, to Mr. D. G. Preis and Mr. J. Sease for excellent technical assistance, to Dr. Caryl Sly for the hydrogenations, to Dr. C. R. Stine and Mr. H. Thielke for vapor phase chromatograms, and to Miss Margaret Spitznogle, Miss Ann Sheridan and Miss Margaret Lennon for the microanalyses

Experimental

cis-2,6-Dimethylpiperidine.—2,6-Lutidine, 450 g., was hydrogenated over 4 g. of ruthenium dioxide at 130° and 2000 lb. pressure. There was obtained 354 g. (74.5%) of *cis*-2,6-dimethylpiperidine, b.p. 127.8–128.1°, $n^{25}D$ 1.4372. A picrate, prepared in ethyl acetate solution in 97.1% yield, melted at 164–165°. A *p*-toluenesulfonic acid salt, prepared in 79% yield, m.p. 182–183°, was recrystallized from ethanol–ethyl acetate to give an analytical sample, m.p. 185–186°.

Anal. Calcd. for $C_{14}H_{23}O_3NS$: C, 58.91; H, 8.12. Found: C, 58.67, 58.85; H, 8.01, 8.01.

cis-2,6-Dimethyl-4-piperidone.—Into a mixture of 101 g. of diethyl acetonedicarboxylate and 44 g. of acetaldehyde maintained at −25 ± 5° was bubbled ammonia until tests showed that the liquid was saturated. The solution was stored at 0° for 20 hours, by which time it was a white sludge. To this was added 250 ml. of 3 *N* hydrochloric acid and the solution was heated on the steam-bath. Carbon dioxide began to evolve soon, but after 24 hours was still evolving very slowly. The solution was evaporated almost to dryness. To the tan heavy precipitate was added 25 ml. of water and the solution was again evaporated. To the residue was added a solution of 100 g. of sodium carbonate in 450 ml. of water and 200 ml. of chloroform. The layers were shaken and separated. The water layer was extracted six times with 200-ml. portions of methylene chloride until ethereal picric acid showed no yellow color. The organic layers were dried over magnesium sulfate and distilled to give 32.9 g. (51.7%) of white liquid, b.p. 99–105° (25 mm.). Redistillation gave the analytical sample, $n^{20}D$ 1.4648.

Anal. Calcd. for $C_7H_{13}ON$: C, 66.10; H, 10.30. Found: C, 66.45, 66.62; H, 9.90, 10.08.

A picrate was prepared in 80.0% yield by the use of ethereal picric acid. The crystalline precipitate was recrystallized from ethyl acetate, m.p. 182–183°.

Anal. Calcd. for $C_{13}H_{16}O_8N_4$: C, 43.82; H, 4.52; N, 15.72. Found: C, 43.95, 44.15; H, 4.36, 4.44; N, 15.54, 15.32.

To a solution of 157.6 g. (0.829 mole) of *p*-toluenesulfonic acid monohydrate in 415 ml. of warm ethyl acetate was added 102.0 g. (0.801 mole) of the piperidone. Cooling was required because of the heat evolved. The precipitate was drained on a sintered glass funnel and rinsed with 150 ml. of anhydrous ether. There was obtained 256.3 g. of crystalline material. This was recrystallized from 9 liters of Niacet acetonitrile. The pure material crystallized in needles on slow cooling, 102.8 g., m.p. 195.0–198.3°, sl. dec., when inserted in a preheated bath at 180°.

Anal. Calcd. for $C_{14}H_{21}O_4NS$: C, 56.1; H, 7.1; N, 4.7. Found: C, 56.1; H, 6.7; N, 4.6.

The *p*-toluenesulfonic acid salt was submitted directly to a modified Wolff–Kishner reduction,[11] using 35.0 g. of the salt, 13.6 ml. of hydrazine hydrate, 18.0 g. of potassium hydroxide, and 200 ml. of triethylene glycol. The crude product was distilled directly from the reaction mixture. There was obtained, after drying and redistilling, 10.41 g. of *cis*-2,6-dimethylpiperidine, b.p. 126.5–129.0°, $n^{25}D$ 1.4378, identical with authentic material as shown by vapor-phase chromatography.

2,2,4-Trimethylpiperidine.—Mesityl oxide (500 g., 5.10 moles) was rotated overnight with an equal volume of 15 *N* aqueous ammonium hydroxide. Nitrogen was bubbled through the homogeneous solution for 2 hours to remove excess ammonia and the solution was chilled in ice. Ethyl cyanoacetate (500 g., 4.42 moles) was added. A heavy white precipitate formed over a 2-hour period with ice cooling. The precipitate was filtered and dried *in vacuo* to give 447.7 g. (61.6% yield) of XV, m.p. 194–196° (lit.[10a] m.p. 194°).

The unsaturated cyanopiperidone (XV) (246.0 g., 1.50 moles) was refluxed overnight with 1 l. of 12 *N* hydrochloric acid. A portion of the clear dark liquid deposited crystals, m.p. 194° on cooling. A mixed melting point with the starting material was undepressed. Therefore, to the solution was added 250 ml. of 18 *N* sulfuric acid and the mixture was refluxed for 48 hours. It was then chilled and poured cautiously into an iced solution of 2.25 kg. of potassium hydroxide in 6 l. of water. Ammonia was evolved and a white crystalline precipitate appeared. Filtration and air-drying gave an (absurd) weight of 500 g. The precipitate was extracted successively with 1.5 and 1 l. of warm methylene chloride. Evaporation of the combined organic layers gave 135.5 g. (64.9%) pale tan granular crystals of XVI, m.p. 116.5–118° (lit. 8b m.p. 120–121°). They had a faint camphor odor, due to the *gem*-dimethyl group.

The unsaturated piperidone (XVI), 133 g. (0.956 mole) was dissolved in 500 ml. of tetrahydrofuran and hydrogenated, using palladium on charcoal at 50° and 1500 lb. pressure. The saturated piperidone (XVII) was not isolated but was reduced directly with lithium aluminum hydride. The hydrogenation product in tetrahydrofuran was added over two hours to a refluxing, stirred solution of 55 g. (1.45 moles) of lithium aluminum hydride in 500 ml. of tetrahydrofuran. After stirring and refluxing for 48 hours, the mixture was worked up. Fractionation of the product in a spinning band column gave 102.4 g. (82.1%) of 2,2,4-trimethylpiperidine (VII), b.p. 148.7–149.8° (lit.[8c] b.p. 148°), $n^{20}D$ 1.4458–1.4459; picrate m.p. 148–149°.

2,2,6-Trimethylpiperidine.—4-Amino-4-methyl-2-pentanone was prepared from 2 kg. (20.4 moles) of mesityl oxide and 2 l. of 15 *N* NH_4OH by rotating them gently for 6 hours. Nitrogen was then bubbled through the homogeneous solution to remove excess ammonia. The solution was chilled and to it was added over 1 hour with stirring 650 g. (14.78 moles) of acetaldehyde (carrying out the reaction at higher temperature caused mesityl oxide to separate). The solution was stored in the ice-box for 4 days. It was poured into 2150 ml. of 50% NaOH and the upper layer was separated. The lower layer was extracted repeatedly with methylene chloride until the extracts gave a negative picric acid test. The organic extracts were dried over K_2CO_3 and distilled at 20 mm. A large forerun was followed by 918 g. of material boiling up to 110°. Fractionation through a spinning band column at a reflux ratio of 50–1 gave a minimum of 525 g. (25.2%) of 2,2,6-trimethyl-4-piperidone, b.p. 92–94° (16 mm.), $n^{25}D$ 1.4599–1.4612, m.p. 24–26° (lit.[7a] m.p. 26°). An oxime melted at 146–147° (lit.[9a] m.p. 150–151°).

A modified Wolff–Kishner reduction[11] of 2,2,6-trimethylpiperidone, using 475 g. (3.36 moles) of ketone, 460 ml. of 85% hydrazine solution, 420 g. of KOH and 3.1 l. of tri-

(14) H. C. Brown, *Rec. Chem. Progr.*, **14**, 83 (1953).

(15) *Cf.* D. H. R. Barton and R. C. Cookson, *Quarterly Reviews*, **10**, 72 (1956).

ethylene glycol gave 350 g. (81.8%) of 2,2,6-trimethylpiperidine, b.p. 139.5–141.5° (lit.[9d] b.p. 138°).

2,2,6,6-Tetramethylpiperidine.—Into a mixture of 2.5 kg. (43.0 moles) of acetone and 800 g. of 12-mesh $CaCl_2$ was passed ammonia for 30 minutes.[10] More ammonia was introduced for 15-minute periods at intervals of 3 hours for 5 days. The mixture was allowed to stand at room temperature an additional 4 days. At this time it was sirupy and dark, but the calcium chloride had not liquefied. It was poured into 1250 ml. of 50% NaOH (when the liquid was merely decanted from the solids the yield was much lower). The upper layer was decanted from the heavy white sludge of calcium hydroxide, which was then rinsed with ether until tests with ethereal picric acid indicated the absence of amines in the extract. The combined ether layers were dried over K_2CO_3 and distilled to give 1.02 kg. yellow liquid, boiling *ca.* 100° (20 mm.). Careful fractionation of this material through a spinning band column gave 666 g. (20.0%) triacetonamine, b.p. 102–105° (18 mm.), m.p. 34–36° (lit.[10] m.p. 36°). Wolff–Kishner reduction[11] of this material gave a minimum yield of 59.7% of 2,2,6,6-tetramethylpiperidine, b.p. 151–159°. A salt, m.p. 218–219°, was prepared in 91.2% yield by the reaction of this amine with an equivalent of *p*-toluenesulfonic acid monohydrate in ethyl acetate solution.

Anal. Calcd. for $C_{16}H_{27}O_3NS$: C, 61.30; H, 8.68; N, 4.46. Found: C, 61.47, 61.35; H, 8.40, 8.54; N, 5.06, 4.98.

1,2,2,6,6-Pentamethylpiperidine.—A solution of 56.3 g. (0.40 mole) of 2,2,6,6-tetramethylpiperidine and 37.2 g. (0.20 mole) of methyl *p*-toluenesulfonate was heated on the steam-bath. Crystals appeared soon and after 20 minutes a spontaneous exothermic reaction developed. The mixture set to a solid, partly browned, cake. The mixture was cooled. The precipitated tetramethylpiperidine *p*-toluenesulfonate after rinsing with 700 ml. of ether weighed 63.0 g. (100%), m.p. 219–221°, mixed with authentic material 220–223°.

The filtrate was dried over magnesium sulfate and distilled in a spinning band column. Secondary amine, 3.03 g., was recovered and a fraction, b.p. 182.1–185.9°, 20.64 g., $n^{20}D$ 1.4572–1.4600, was obtained. This was combined with identical material, 4.8 g., from a previous experiment, dissolved in 25 ml. of ethyl acetate, and treated with 31.6 g. of *p*-toluenesulfonic acid monohydrate in 200 ml. of ethyl acetate. Evaporation overnight at room temperature caused the mixture to crystallize. The precipitate was filtered and washed with 50 ml. of fresh ethyl acetate to give 51.1 g. (63.5%) white crystals of the salt of XIII, m.p. 160–161°. An analytical sample was crystallized from ethyl acetate:ethanol (5:1), m.p. 162–163°.

Anal. Calcd. for $C_{17}H_{29}O_3NS$: C, 62.34; H, 8.92; N, 4.27. Found: C, 62.11, 62.18; H, 8.49, 8.55; N, 4.68, 4.84.

Regeneration of the free base from 51.1 g. of the salt gave 19.44 g. (80.2%) of IX, b.p. 182°, $n^{20}D$ 1.4583–1.4599.

Anal. Calcd. for $C_{10}H_{21}N$: C, 77.34; H, 13.63. Found: C, 77.56, 77.62; H, 13.28, 13.49.

A small quantity of white crystals appeared in this liquid on standing for several weeks. The crystals were rinsed with ether. They did not liberate iodine from potassium iodide solution. The analytical data were inconclusive.

Anal. Found: C, 64.43, 64.29; H, 11.16, 11.08.

1-Ethyl-2,2,6,6-tetramethylpiperidine.—This was prepared as above by heating a solution of 92.5 g. (0.462 mole) of ethyl *p*-toluenesulfonate and 131.0 g. (0.925 mole) of 2,2,6,6-tetramethylpiperidine on the steam-bath for 19 hours. Fractionation of the product in a spinning band column gave 56.0 g. of recovered tetramethylpiperidine and 10.27 g. of crude 1-ethyl-2,2,6,6-tetramethylpiperidine, b.p. 80° (13 mm.), $n^{20}D$ 1.4578–1.4600. This was dissolved in 25 ml. of ethyl acetate and treated with 11.8 g. of *p*-toluenesulfonic acid monohydrate in 100 ml. of ethyl acetate. The solution darkened and no crystals appeared. Evaporation at room temperature overnight caused crystallization to occur. Filtration and rinsing the precipitate with 20 ml. of ethyl acetate gave 10.3 g. of white crystals, m.p. 151–152°. Evaporation of the filtrate gave 3.55 g., m.p. 148–149°, combined yield 8.9%. An analytical sample was recrystallized from an ethyl acetate:ethanol (9:1) mixture, m.p. 150–151°.

Anal. Calcd. for $C_{18}H_{31}O_3NS$: C, 63.30; H, 9.15; N, 4.10. Found: C, 63.43, 63.54; H, 9.00, 9.18; N, 4.05, 4.36.

Regeneration of the free base by treating 10.3 g. of this salt with alkali gave 0.84 g. (16.4%) of X, b.p. 197.0°, $n^{20}D$ 1.4601–1.4610.

Anal. Calcd. for $C_{11}H_{23}N$: C, 78.03; H, 13.69. Found: C, 78.31, 78.42; H, 13.22, 13.48.

***cis*-1,2,6-Trimethylpiperidine.**—Methylation of IV[16] gave the product in 73.4% yield, b.p. 149°, $n^{25}D$ 1.4459.

Anal. Calcd. for $C_8H_{17}N$: C, 75.5; H, 13.5; N, 11.0. Found: C, 75.4; H, 13.2; N, 10.9.

1,2,2,4-Tetramethylpiperidine.—The same procedure gave a 70.5% yield, b.p. 167°, $n^{25}D$ 1.4480.

Anal. Calcd. for $C_9H_{19}N$: C, 76.5; H, 13.6; N, 9.9. Found: C, 76.2; H, 13.1; N, 9.9.

1,2,2,6-Tetramethylpiperidine.—Methyl tosylate, 37.2 g., was added in portions to 50.2 g. of 2,2,6-trimethylpiperidine. The mixture was kept at room temperature with an ice-bath. After several hours the solid cake was dissolved in alkali and the amine was extracted. Distillation gave 15.59 g. of material, b.p. 169–170°. This was purified by way of the toluenesulfonic acid salt, 9.4 g. (recrystallized) m.p. 134.0–135.0°.

Anal. Calcd. for $C_{16}H_{27}NO_3S$: C, 61.3; H, 8.7. Found: C, 61.3; H, 8.5.

Basification, extraction and distillation gave 2.94 g. (5.3% over-all yield) of tertiary amine, b.p. 167°, $n^{25}D$ 1.4529.

Anal. Calcd. for $C_9H_{19}N$: C, 76.5; H, 13.6; N, 9.9. Found: C, 76.5; H, 13.5; N, 9.8.

All the amines were >99% pure as established by vapor phase chromatography.

Determination of Base Strengths.—The method for water was essentially that of Britton and Williams,[17] using 0.05 *N* HCl instead of nitric acid. The pK_a values were calculated from the expression

$$pK_a = pH + \log \frac{b + \text{meq}_{OH^-}}{a - b - \text{meq}_{OH^-}}$$

where a is the total meq. of amine and b is the meq. of acid added.

For acetonitrile the method was identical to that described earlier.[12] Beckman #1190-42 and #1190-80 glass electrodes gave equally satisfactory results.

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