to $\mu = 0$. The ΔpD value of 0.40 is in good agreement with data in the literature.[25,26]

The pD values, used for the calculation of the second-order rate constants of eq. 3, were actually obtained by using the correction ΔpD = 0.40 with the pH meter readings of the D_2O solutions, the meter having been standardized with a standard buffer in H_2O.

The rate measurements of the hydrolysis of I were carried out at 2170 Å. by means of a cell with a path length of 3 cm. through which the solution from a reactor of approximately 200 ml. circulated.[27] The enamines II and III are only sparingly soluble in water. The reactor could not be used for the hydrolysis measurements of II and III because too much time was needed to dissolve them. Therefore, silica cells were used with path lengths of 1 cm. and the enamines were dissolved by vigorous shaking of the buffer with 1 drop of a dilute solution of I or II in absolute ethanol during a few seconds. A constant temperature of the solutions during the experiments was obtained by storing the silica cells in small iron vessels containing mercury, which were placed in a constant-temperature bath. The heat transfer is rapid and the silica cells remain clean.

The hydrolysis experiments of III at 0.03° were carried out in a room with a constant temperature of approximately 3°, in order to avoid condensation of water vapor on the cooled silica cells. The absorbances were measured with a Zeiss spectrophotometer, type PMQ II.

Analysis of the Products.—To an aqueous phosphate buffer solution of pH 6.30 (0.320 g. of $Na_2HPO_4 \cdot 12H_2O$, 0.380 g. of KH_2PO_4, and 0.600 g. of NaCl) 500 mg. of I was added. After 2, 8, and 120 min., 100 ml. of this solution was extracted with 2 ml. of carbon tetrachloride. These carbon tetrachloride solutions were dried with magnesium sulfate and their infrared spectra were recorded in 1-mm. cells. The spectra demonstrate the disappearance of the >C=C< absorption peak of I at 1665 cm.$^{-1}$, whereas a strong band at 1730 cm.$^{-1}$, which has to be ascribed to the carbonyl absorption of isobutyraldehyde, appeared already in the first infrared spectrum.

Gas chromatographic analysis of the solution of carbon tetrachloride, obtained after 120 min., showed the presence of isobutyraldehyde (checked with pure isobutyraldehyde).

In a few rate experiments the increase in absorbance at 2800 Å. (λ_{max} of isobutyraldehyde) was measured as a function of the time. Although these rates could not be determined in an accurate manner (log ϵ 1.19),[28] they show that the rate of increase in absorbance at 2800 Å. equals the rate of decrease in absorbance at 2170 (I) and 1960 Å. (IV) within the experimental error.

The formation of the secondary amines could be checked by means of their pK values, which were obtained from potentiometric titration curves of aqueous solutions of I, II, and III, after complete hydrolysis had occurred.[29]

Calculations.—All first-order rate constants were obtained by least-squares calculations. The standard deviation in k is approximately 0.2%. The second-order rate constants were calculated by an iterative procedure from the first-order rate constants (eq. 3 and 4). The standard deviation in the values of $k_{H_3O^+}$ and K is 10 to 15%, whereas that in k_{HA} is 5%.

Acknowledgment.—The authors are indebted to Professor Dr. H. Wynberg and Dr. M. J. Janssen for their interest and helpful comments, and to Professor Dr. M. Gruber for the loan of the cold-storage chamber of the Laboratory of Biochemistry of The University. They also wish to thank Dr. H. G. Kaper and Miss N. Schmidt, who designed a computor program for the calculation of the second-order rate constants. These calculations were performed on the ZEBRA electronic computor of this university under the direction of Dr. D. W. Smits.

(25) K. Mikkelsen and S. O. Nielsen, *J. Phys. Chem.*, **64**, 632 (1960).
(26) P. Salomaa, L. L. Schaleger, and F. A. Long, *J. Am. Chem. Soc.* **86**, 1 (1964).
(27) H. Arnoldy, Thesis, Amsterdam, 1961.
(28) Reference 10a, Vol. II, p. 21.
(29) These experiments will be published in a subsequent paper.

Mechanism of Enamine Reactions. III.[1] The Basicity of Tertiary Enamines

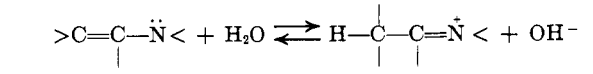
E. J. STAMHUIS, W. MAAS, AND HANS WYNBERG

Department of Organic Chemistry, The University, Bloemsingel 10, Groningen, the Netherlands

Received February 8, 1965

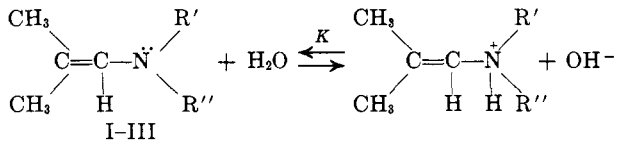
The base strengths of 1-N-morpholino-1-isobutene, 1-N-piperidino-1-isobutene, and 1-N-pyrrolidino-1-isobutene have been determined in aqueous solution by kinetic, potentiometric, and spectroscopic methods at 25°. In addition the basicity of the corresponding saturated amines has been determined by potentiometric titration. The results clearly show that in contrast with current opinion tertiary enamines are much weaker bases than the corresponding saturated compounds. The difference, approximately 2 pK units, can be equally attributed to an inductive and a resonance effect. The basicity of these compounds in order of decreasing base strength is secondary amine > saturated tertiary amine > tertiary enamine.

During the last 10 years tertiary enamines have become an extremely important group of intermediates in numerous organic syntheses.[2] As is well known, simple enamines are very unstable in water and hydrolysis, resulting in the formation of a carbonyl compound and an amine, occurs rapidly.[3] Direct measurement of the basicity of enamines in aqueous solution is therefore a difficult problem. In spite of the high reactivity toward water some papers deal with the base strength of α,β-unsaturated tertiary amines, especially those of cyclic enamines, in pure or partly aqueous solution.[4-7] The results of these measurements have led these authors[4-7] to conclude that tertiary enamines are stronger bases than the corresponding saturated amines. The explanation for this unexpected increase in basicity is sought in the existence of an equilibrium between the enamine and the quaternary hydroxide in aqueous solutions.[4]



During our investigations on the mechanism of the hydrolysis of enamines we succeeded in measuring the basicity of 1-N-morpholino-1-isobutene (I), 1-N-piperidino-1-isobutene (II), and 1-N-pyrrolidino-1-isobutene (III) from the kinetics of this reaction.[1] It was also explained that, in contrast with the equilibrium mentioned above, the protonation of these enamines in aqueous solutions occurs at the nitrogen atom.

(1) Part II: E. J. Stamhuis and W. Maas, *J. Org. Chem.*, **30**, 2156 (1965).
(2) J. Szmuszkovicz, *Advan. Org. Chem.*, **4**, 1 (1963).
(3) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).
(4) R. Adams and J. E. Mahan, *ibid.*, **64**, 2588 (1942).
(5) N. J. Leonard, A. S. Hay, R. W. Fulmer, and V. W. Gash, *ibid.*, **77**, 439 (1955).
(6) N. J. Leonard, P. D. Thomas, and V. W. Gash, *ibid.*, **77**, 1552 (1955).
(7) N. J. Leonard and A. G. Cook, *ibid.*, **81**, 5627 (1959).



I–III

Because the pK values of the conjugate acids of I–III are much smaller than may be expected on account of several data in the literature,[2,4] the base strengths of these enamines were also determined potentiometrically. Besides, the basicity of I was calculated from spectrophotometric measurements.

The values obtained have been compared with the pK values of the corresponding staturated amines.

Results

In the previous paper of this series[1] it was explained that the hydrolysis of 1-N-morpholino-1-isobutene (I), 1-N-piperidino-1-isobutene (II), and 1-N-pyrrolidino-1-isobutene (III) in aqueous solutions can be described by the kinetic equation

$$k = \frac{K}{K + a_{H_3O^+}} \sum_i k_{HA_i} c_{HA_i} \qquad (1)$$

where k is the first-order rate constant, K the dissociation constant of the N-protonated conjugate acid of the enamine, $a_{H_3O^+}$ the activity of the hydronium ions, k_{HA_i} the catalytic constant of the acid HA_i, and c_{HA_i} the concentration of the acid HA_i.

Values of K for I–III were calculated from the first-order rate constants, which were obtained from a large number of rate measurements in aqueous phosphate, acetate, and borax buffers at 25° (Table I).

TABLE I

pK VALUES AT 25°

	Kinetic[a]	Spectroscopic	Titrametric	ΔpK
1-N-Morpholino-1-isobutene	5.47 ± 0.04	5.45 ± 0.05	5.45 ± 0.1	2.4
N-Isobutylmorpholine			7.82 ± 0.02	
Morpholine			8.51 ± 0.02	
1-N-Piperidino-1-isobutene	8.35 ± 0.1		8.35 ± 0.1	2.1
N-Isobutylpiperidine			10.44 ± 0.01	
Piperidine			10.7 ± 0.02	
1-N-Pyrrolidino-1-isobutene	8.84 ± 0.09		8.7 ± 0.1	1.6
N-Isobutylpyrrolidine			10.38 ± 0.01	
Pyrrolidine			11.13[b]	

[a] Reference 1. [b] Reference 17.

The experiments showed that I is much less reactive than II and III and therefore rapid potentiometric titrations of I were performed in aqueous solution with a dilute solution of hydrochloric acid at 25°. An example is shown in Figure 1.

From the titration curve A of Figure 1 a pK value of 5.5 can be calculated. After the solution was stored at pH 3.5 for about an hour, it was titrated with a solution of 0.1110 N sodium hydroxide resulting in curve B. This indicates that during the hydrolysis a stronger base has been formed. From curve B a pK value of 8.47 can be derived. This value equals the pK of morpholine, as was checked by a potentiometric titration of pure morpholine.

In consequence of the instability of II and III toward water, potentiometric titrations of these enamines were impossible. Therefore, a solution of I or II in absolute ethanol was dissolved rapidly in water, which already

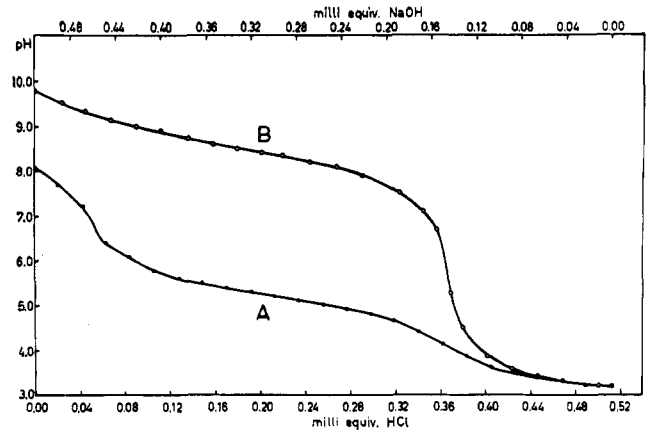


Figure 1.—Potentiometric titration of I with a dilute solution of hydrochloric acid (curve A), and after that with a dilute solution of sodium hydroxide (curve B).

contained an amount of hydrochloric acid, just sufficient for half neutralization of the enamine.[8] The pH of the solution after addition of II or III remained at a constant value for a few seconds. This value of the pH equals the pK of the conjugate acid of II or III. After a few seconds, a rise of the pH was observed. This must be attributed to the formation of the secondary amines piperidine and pyrrolidine, respectively. The pH values, which were measured after complete hydrolysis of II and III had occurred, were in good agreement with those of piperidine and pyrrolidine, respectively. The pK values are given in Table I.

A spectrophotometric determination of the dissociation constant of the conjugate acid of I (IV) could be accomplished in the following way. The molar absorptions of I at 2170 (λ_{max} of I) and at 1960 Å. (λ_{max} of IV) were derived from the absorbances of dilute solutions of I in 0.001 N sodium hydroxide. In this solution the hydrolysis proceeds at a very low rate[1] ($k < 10^{-5}$ sec.$^{-1}$). The following values were obtained for I: ϵ_I^{2170} 6600, ϵ_I^{1960} 4100. The rate of hydrolysis of a known quantity of I in a 0.01 N hydrochloric acid solution was measured spectrophotometrically at 1960 Å. at 25° and the absorbance at zero time was calculated from a plot of log $(E_t - E_\infty)$ *vs.* time by extrapolation, giving a value for ϵ_{IV}^{1960} of 2650. The absorbance of this solution at 2170 Å. appeared to be negligible.

The absorbances of I and IV were measured during an hydrolysis reaction in an aqueous acetate buffer at 2170 and 1960 Å., respectively. From the absorbance, measured immediately after the reaction had begun, the concentrations of I and IV were calculated (see Experimental). The pK, derived from these concentrations and the pH of the buffer solution, is given in Table I.

In consequence of the high reactivity toward water, the pK values of the conjugate acids of I–III, determined from the experiments described in this paper, are not very accurate. For this reason no corrections for the ionic strength on these data were performed. In the kinetic measurements the ionic strength was always kept constant at 0.100 M. In the potentiometric and spectroscopic measurements the ionic

(8) L. C. Craig and R. M. Hixon, *J. Am. Chem. Soc.*, **53**, 4367 (1931).

strength had a lower value. Nevertheless these pK values are in good agreement with those obtained from the kinetic measurements.[1]

The saturated amines, N-isobutylmorpholine, N-isobutylpiperidine, and N-isobutylpyrrolidine, were obtained from the corresponding enamines by reduction with concentrated formic acid. These compounds are stable toward water and their pK values were derived from potentiometric titration curves (Table I).

Discussion

The values of the pK, summarized in Table I, clearly show that the enamines I–III are not stronger, but 30 to 200 times *weaker* bases than the corresponding saturated tertiary amines. This result can be explained by two effects. operating in the same direction: (i) the electron-withdrawing effect of the double bond, and (ii) the delocalization of the lone pair on the nitrogen atom owing to its conjugation with the π electrons of the double bond.

The low basic strength of aromatic amines due to effects, i and ii, compared with aliphatic amines has been investigated extensively by Wepster.[9] He found that each of these effects is responsible for a decrease in basicity of about 3 pK units.

The question arises whether it will be possible to establish the extent of the decrease in basic strength in the enamines studied, as caused by each of the two effects i and ii separately. This can be done, because the base-weakening inductive effect in α,β-unsaturated amines has been evaluated by Grob, *et al.*[10] These workers measured the basicity of quinuclidine and dehydroquinuclidine in aqueous solution at 25°. The result, 1.13 pK units, can only be attributed to the inductive effect, since in the dehydroquinuclidine molecule the overlap of the olefinic π-orbital and the lone-pair orbital on the nitrogen atom is at a minimum. From this value of 1.13 pK units and the data of Table I it can be seen that the resonance effect (ii) results in a decrease in basicity of approximately 1 pK unit. Although this is a rough estimation, it demonstrates that in these enamines the influence of both effects is approximately equal in magnitude. It is very likely that the resonance effect can become more important, because models of the enamines I–III show some steric hindrance between one of the methyl groups and the ring methylene groups, by which a maximum overlap of the orbitals is hampered.

It can be calculated[9] that the average value of the resonance stabilization in the enamines I–III amounts to 1.2 kcal./mole.

Our observations contradict the current opinion, which states that enamines are stronger bases than the corresponding saturated compounds.[2,4,11,12] As a result, several workers[2,5,11] have proposed that the marked difference between the effect of a double bond α,β and β,γ (base-weakening effect[4]) to the amine nitrogen in comparison with the basicity of the saturated compound provides a diagnostic tool for the determination of an α,β double bond. It is evident, in the light of our findings, that this method can lead to incorrect conclusions.

From Table I it may be concluded that the enamines I–III are 200 to 1000 times weaker bases than the secondary amines from which they are formed. It is well known that in aqueous solution tertiary amines are weaker bases than secondary amines.[13] We now find an order of decreasing base strength as follows: secondary amine > tertiary amine > tertiary enamine. This result is therefore compatible with expectations.

Experimental

Materials.—The enamines I–III were prepared as described previously.[1]

N-Isobutylmorpholine was synthesized from 1-N-morpholino-1-isobutene as described by Opitz and Griesinger[14]: b.p. 62–64° (17 mm.), n^{20}D 1.4421 after repeated distillation, equiv. wt.[15] 142.6 (calcd. 143.2); lit.[14] b.p. 65° (19 mm.), n^{20}D 1.4391.

N-Isobutylpiperidine was prepared from 1-N-piperidino-1-isobutene by reduction with concentrated formic acid according to de Benneville and Macartney[16]: b.p. 43.0–43.5° (10 mm.), n^{20}D 1.4418, yield 72%.

Anal. Calcd. for $C_9H_{19}N$: C, 76.52; H, 13.56; N, 9.92; equiv. wt., 141.2. Found: C, 76.48; H, 13.43; N, 9.88; equiv. wt., 143.7.

N-Isobutylpyrrolidine was synthesized from 1-N-pyrrolidino-1-isobutene as described by Opitz and Griesinger[14]: b.p. 40–41° (13 mm.), n^{20}D 1.4348, equiv. wt. 128.3 (calcd. 127.2); lit.[14] b.p. 66° (55 mm.), n^{20}D 1.4343.

The chemicals used for the potentiometric titrations and the spectroscopic measurements were pro analyse grade. The solvent water was purified as described earlier.[1]

Potentiometric Titration Measurements.—N-Morpholino-1-isobutene (I), 0.0898 g., was dissolved in absolute ethanol up to 10 ml.; 5 ml. of this solution in 195 ml. of conductivity water was titrated at 25° with an aqueous solution of 0.1064 N hydrochloric acid to pH 3.5 within 5 min. After 1 hr. this solution was titrated with an aqueous solution of 0.1110 N sodium hydroxide (Figure 1). The pH at semineutralization of curve A (in duplicate) was 5.5, 5.4; the pH at semineutralization of curve B (in duplicate) was 8.47, 8.50. The pK of morpholine was determined potentiometrically. Values of 8.50 and 8.52 were obtained at 25°.

N-Piperidino-1-isobutene (II), 0.1139 g., was dissolved in absolute ethanol up to 10 ml.; 5 ml. of this solution was rapidly dissolved in 200 ml. of conductivity water, to which 1.914 ml. of of 0.1070 N hydrochloric acid solution had been added. After a few seconds the pH of the solution had a value of 8.3 (in duplicate 8.4). After that the pH rose slowly as a result of hydrolysis to isobutyraldehyde and piperidine to 10.7 (in duplicate 10.7). The pK of piperidine was derived from a potentiometric titration curve. A value of 10.7 was obtained.

N-Pyrrolidino-1-isobutene (III), 0.1000 g., was dissolved in absolute ethanol up to 10 ml.; 5 ml. of this solution was rapidly dissolved in 200 ml. of conductivity water, to which 1.869 ml. of 0.1070 N hydrochloric acid had been added. Immediately the pH rose to a value of 8.7 (in duplicate 8.7). Hydrolysis resulted in a rise of the pH to 10.8 (in duplicate 10.7). The pK of pyrrolidine is 11.3.[17]

The saturated tertiary amines were titrated potentiometrically in aqueous solution with a dilute solution of hydrochloric acid at 25° in the usual way.[18] The following results were obtained:

(9) B. M. Wepster, *Rec. trav. chim.*, **71**, 1171 (1952).

(10) C. A. Grob, A. Kaiser, and E. Renk, *Chem. Ind.* (London), 598 (1957).

(11) H. C. Brown, D. H. McDaniel, and O. Häfliger, in "Determination of Organic Structures by Physical Methods," E. A. Braude and F. C. Nachod. Ed., Academic Press Inc., New York, N. Y., 1955, pp. 582, 649, 650.

(12) A. Albert, Ionization constants, in "Physical Methods in Heterocyclic Chemistry," Vol. I, A. R. Katritzky, Ed., Academic Press Inc., New York, N. Y., 1963, p. 53.

(13) R. P. Bell, "The Proton in Chemistry," Methuen and Co., Ltd., London, 1959, p. 176.

(14) G. Opitz and A. Griesinger, *Ann.*, **665**, 101 (1963).

(15) The equivalent weights of the amines were obtained from potentiometric titration curves.

(16) P. L. de Benneville and J. H. Macartney, *J. Am. Chem. Soc.*, **72**, 3073 (1950).

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

(18) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases, a Laboratory Manual," John Wiley and Sons, Inc., New York, N. Y., 1962, p. 16.

N-isobutylmorpholine, pK = 7.82, 7.80, and 7.83; N-isobutylpiperidine, pK = 10.44, 10.43, and 10.45; N-isobutylpyrrolidine, pK = 10.37, 10.39, and 10.37.

Spectroscopic Determination of the pK of I.—A kinetic run of I in an aqueous acetate buffer (c_{HOAc} 0.0020 M, c_{NaOAc} 0.0013 M, pH 4.51) was carried out at 25°. Immediately after the addition of I to the buffer solution the absorbances at 1960 and 2170 Å. were measured, to prevent errors due to the absorbances of the hydrolysis products. The following values were obtained: E_{1960} 1.130 and E_{2170} 0.278. Since the values of ϵ_I^{1960}, ϵ_I^{2170}, ϵ_{IV}^{1960}, and ϵ_{IV}^{2170} are 4100, 6600, 2650, and 0, respectively (see Results), the concentrations of I and its conjugate acid IV were evaluated, using the equations: $4100c_I + 2650c_{IV} = 1.130$, and $6600c_I = 0.278$. Thus, c_I is 4.2×10^{-5} M and c_{IV} is 3.6×10^{-4} M. Since $K = c_I c_{H_3O^+}/c_{IV}$, K has a value of 3.6×10^{-6} M and pK = 5.4[5] (±0.05).

Acknowledgment.—The authors are indebted to Dr. M. J. Janssen for his interest and helpful comments and to Miss T. Rozema for the preparation of N-isobutylpiperidine. They wish to thank Mr. W. M. Hazenberg for the microanalysis of N-isobutylpiperidine.

Cyclization in the Course of Clarke–Eschweiler Methylation[1]

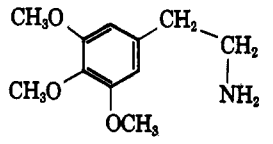
ARTHUR C. COPE AND W. DICKINSON BURROWS

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

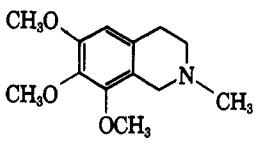
Received December 28, 1964

On treatment with formic acid and formaldehyde, 1,5-dimethyl-4-hexenylamine undergoes cyclization to *cis*- and *trans*-α,α,1,6-tetramethyl-3-piperidinemethanol.

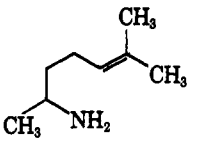
Cyclization during Clarke–Eschweiler methylation is well documented for certain ring-substituted β-phenylethylamines, being a special case of the Pictet–Spengler synthesis of tetrahydroisoquinolines.[2,3] Mescaline (1), for example, is reported by Castrillón to give on treatment with formaldehyde and formic acid only the tetrahydroisoquinoline 2. In the course of preparation of some amino alcohols we have found that 1,5-dimethyl-4-hexenylamine (3) when treated with formaldehyde and formic acid undergoes cyclization to form the piperidinemethanol 4 rather than the expected dimethylamine.



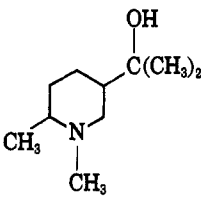
1



2

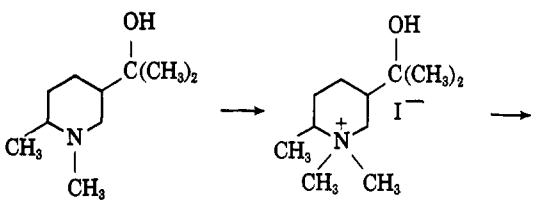


3

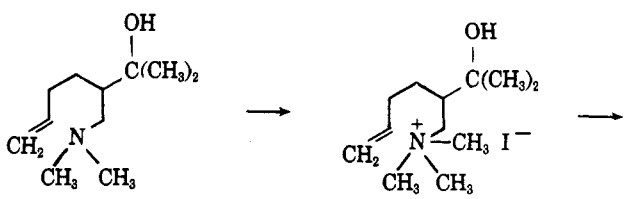


4

The Clarke–Eschweiler product from 1,5-dimethyl-4-hexenylamine was obtained in 75% yield as a semicrystalline mass, shown by vapor phase chromatography to comprise two components in 2:1 ratio. The major component is a crystalline solid of empirical formula, $C_{10}H_{21}NO$. The n.m.r. spectrum in carbon tetrachloride displays a 1-proton singlet (τ 6.62) due to tertiary hydroxyl, a 3-proton singlet due to nitrogen-bonded methyl (τ 7.80), and what appears to be a 3-proton doublet (τ 8.93, J = 4.5 c.p.s.) superimposed on two 3-proton singlets (τ 8.97, 8.87), resulting from the 6-methyl and nonequivalent α-methyl groups. In the n.m.r. spectrum of the methiodide (5) in deuterium oxide, the 6-methyl doublet (τ 8.66, J = 6.0 c.p.s.) is shifted downfield relative to the α-methyl singlets (τ 8.81, 8.77), and two 3-proton singlets appear due to N-methyl (τ 7.04, 6.84). The Hofmann product of 5 is the terminally unsaturated amino alcohol 6. Principal features of the n.m.r. spectrum of 6 in carbon tetrachloride are the two C-methyl singlets (τ 8.98, 8.88), a 6-proton N-methyl singlet (τ 7.70), two partially resolved multiplets (τ 5.08, 4.83) due to the terminal vinyl protons, and a broad, complex multiplet (τ 3.8–4.5) due to the other vinyl proton. The methiodide (7) of 6 undergoes fragmentation in the Hofmann reaction, yielding trimethylamine, acetone, and 1,5-hexadiene, the last being identified by comparison of its infrared, n.m.r. and mass spectra with those of authentic material. These results establish the structure of the major Clarke–Eschweiler product as 4. The minor, liquid product is the stereoisomer, since it has the same formula and gives the same Hofmann product. In the n.m.r. spectrum of the minor methiodide in deuterium oxide the 6-methyl doublet (τ 8.54, J = 7.5 c.p.s.) and N-methyl singlets (τ 6.88, 6.75) appear farther downfield than in the spectrum of the major meth-



4 5



6 7

$$CH_2{=}CHCH_2CH_2CH{=}CH_2 + CH_3COCH_3 + (CH_3)_3N$$

(1) Supported by Merck Sharp and Dohme Research Laboratories; presented at the 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965.

(2) J. A. Castrillón, *J. Am. Chem. Soc.*, **74**, 558 (1952).

(3) R. Baltzly, *ibid.*, **75**, 6038 (1953).