[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

# ACETYLENIC AMINES. I. PREPARATION AND BASE STRENGTHS OF CERTAIN TERTIARY ACETYLENIC AMINES[1]

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Acetylenic amines have not been investigated in detail, and little is known about their general properties. Most of the acetylenic amines reported hitherto have been prepared by the Mannich reaction (1) and hence are 1-dialkylamino-2-alkynes. A few branched chain 2-amino-1-butynes have been made from acetylene or phenylacetylene by treatment with primary or secondary amines in the presence of cuprous chloride (2) and recently Parcell and Pollard (3) prepared several acetylenic amines from secondary aliphatic amines and 1,2-dibromo-2-propene, using sodamide to dehydrobrominate the intermediate 1-dialkylamino-2-bromo-2-propenes.

$$R_2NH + BrCH_2\underset{Br}{\underset{|}{C}}{=}CH_2 \rightarrow R_2NCH_2\underset{Br}{\underset{|}{C}}{=}CH_2 \rightarrow R_2NCH_2C{\equiv}CH$$

It seemed worthwhile to prepare a series of acetylenic amines in which the two functional groups would be successively farther apart; these substances would be of interest for determining the influence of each functional group on the properties of the other.

In this paper we are reporting the synthesis of two series of acetylenic amines, of the general formulae I and II, and the base strengths of these amines.

$$\underset{\substack{\text{I} \\ n\,=\,1,2,3,4}}{HC{\equiv}C(CH_2)_nN(CH_3)_2} \qquad \underset{\substack{\text{II} \\ n\,=\,1,2,3}}{n\text{-}C_4H_9C{\equiv}C(CH_2)_nN(CH_3)_2}$$

In series I, the first member (n = 1), was prepared from dimethylamine and 1,2-dibromo-2-propene by a method similar to that described recently by Parcell and Pollard (3) for the diethylamino analog. The second amine in the series (I, n = 2) was made in two ways; (a) from $\beta$-ethynylethanol *via* the bromide, and (b) from sodium acetylide and N,N-dimethyl-$\beta$-bromoethylamine; the latter method was found to be the better. The third and fourth amines (I, n = 3, 4) were obtained in satisfactory yield from sodium acetylide and the polymethylene halide, followed by reaction of the acetylenic halide with dimethylamine.

$$HC{\equiv}CNa + Br(CH_2)_nCl \rightarrow HC{\equiv}C(CH_2)_nCl \xrightarrow{HN(CH_3)_2} HC{\equiv}C(CH_2)_nN(CH_3)_2$$

In general, the amines of series II were more easily prepared, and were obtained in better yields than those of series I. The Mannich reaction proved to be satisfactory for the first member of the series (n = 1), and the other two were

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[2] Abstracted from the Ph.D. dissertation of Frank C. Fatora, Jr., University of Notre Dame, June, 1951.

made by the methods outlined above for the corresponding amines of the first series.

Some of the acetylenic amines were hydrogenated to the corresponding ethylenic amines over Raney nickel or palladium. The acetylenes with a terminal triple bond hydrogenated more rapidly, and there was less change in rate of hydrogenation when one mole of hydrogen had been absorbed, than was the case with the non-terminal acetylenes. These results are in good agreement with those obtained by Campbell and O'Connor (4) with acetylenic hydrocarbons. The reduction of 1-dimethyl-amino-2-propyne with sodium in liquid ammonia, however, gives a purer olefin than can be obtained by catalytic hydrogenation.

TABLE I

PHYSICAL CONSTANTS OF ACETYLENIC AMINES

| COMPOUND | B.P., °C. | MM. | $n_D^{20}$ | $d_4^{20}$ | MR$_D$ obs. | MR$_D$ calc'd |
|---|---|---|---|---|---|---|
| 1-$Me_2N$-2-propyne | 82 | | 1.4180 | 0.7792 | 26.90 | 27.27 |
| 1-$Me_2N$-3-butyne | 107 | | 1.4290 | .7896 | 31.67 | 31.89 |
| 1-$Me_2N$-4-pentyne | 129 | | 1.4319 | .7985 | 36.07 | 36.37 |
| 1-$Me_2N$-5-hexyne | 90 | 110 | 1.4369 | .8066 | 41.02 | 41.26 |
| 1-$Me_2N$-2-heptyne | 110 | 90 | 1.4420 | .7995 | 46.01 | 46.24 |
| 1-$Me_2N$-3-octyne | 117 | 55 | 1.4448 | .7985 | 50.62 | 50.87 |
| 1-$Me_2N$-4-nonyne | 118 | 33 | 1.4488 | .8102 | 55.38 | 55.48 |
| 1-$Me_2N$-2-propene | 62 | 745 | 1.3995 | .7172 | 28.93 | 28.79 |
| *cis*-1-$Me_2N$-2-heptene | 58 | 18 | 1.4330 | .7747 | 47.37 | 47.41 |
| *trans*-1-$Me_2N$-2-heptene | 103 | 90 | 1.4311 | .7683 | 47.66 | 47.41 |
| 1-$Me_2N$-propane | 66 | 745 | 1.3860 | .7006 | 29.22 | 29.40 |
| 1-$Me_2N$-heptane | 62 | 18 | 1.4193 | .7580 | 47.74 | 47.88 |

TABLE II

SALTS OF ACETYLENIC AMINES

| AMINE | SALT | M.P., °C. | ANALYSES | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Calc'd | | | Found | | |
| | | | C | H | N | C | H | N |
| 1-$Me_2N$-2-propyne | Oxalate | 122–123 | 48.6 | 6.43 | 8.09 | 48.3 | 6.26 | 7.76 |
| 1-$Me_2N$-3-butyne | HCl | 147–148 | 53.9 | 9.06 | 10.5 | 53.6 | 8.96 | 10.2 |
| 1-$Me_2N$-4-pentyne | HCl | 133–134 | 56.9 | 9.55 | 9.5 | 56.8 | 9.50 | 9.5 |
| 1-$Me_2N$-5-hexyne | Oxalate | 118–119 | 55.8 | 7.96 | 6.51 | 55.5 | 7.71 | 6.9 |
| 1-$Me_2N$-2-heptyne | Oxalate | 108–109 | 57.6 | 8.35 | 6.11 | 57.8 | 8.37 | 6.0 |
| 1-$Me_2N$-3-octyne | Oxalate | 134–135 | 59.2 | 8.69 | 5.76 | 59.5 | 8.78 | 5.52 |
| 1-$Me_2N$-4-nonyne | Oxalate | 130–131 | 60.7 | 9.01 | 5.44 | 60.6 | 8.98 | 5.09 |

The physical constants of the amines prepared in this work are shown in Table I, and their derivatives in Table II.

The base strengths of the acetylenic amines were determined potentiometrically, using a Beckman glass electrode, by the general procedure of Bennett, Brooks, and Glasstone (5) which consists of measuring the *p*H of the solution when exactly one-half of the amine has been neutralized with hydrochloric acid. Where possible, the measurements were made in pure water, but for the higher amines it was necessary to use dilute methanol as solvent. The $pK_H$ values of the acetylenic amines are given in Table III, together with those of some olefinic and saturated amines. From the data given in Table III it will be seen that the presence of a triple bond adjacent to the carbon atom carrying the amino group diminishes the base strength of the amine by 1.5–2.1 $pK_H$ units. The effect of the triple bond on the base strength of the amino group diminishes as the distance between them increases, and when they are separated by four carbon atoms, there is no longer an appreciable decrease in base strength. An olefinic group near the amino function has a similar, but much less marked effect. It would appear that the *cis* configuration of the double bond has more influence than does the *trans*, but no generalizations can be made from the limited data available.

TABLE III

$pK_H$ VALUES OF ACETYLENIC AMINES

| AMINE | SOLVENT | $pK_H$ |
|---|---|---|
| 1-$Me_2N$-2-propyne | $H_2O$ | 7.05 |
| 1-$Me_2N$-3-butyne | $H_2O$ | 8.33 |
| 1-$Me_2N$-4-pentyne | $H_2O$ | 8.88 |
| 1-$Me_2N$-5-hexyne | $H_2O$ | 9.24 |
| 1-$Me_2N$-2-propene | $H_2O$ | 8.72 |
| 1-$Me_2N$-propane | $H_2O$ | 9.25 |
| 1-$Me_2N$-2-heptyne | 30% MeOH | 7.70 |
| 1-$Me_2N$-3-octyne | 30% MeOH | 7.70 |
| 1-$Me_2N$-4-nonyne | 30% MeOH | 8.66 |
| *cis*-1-$Me_2N$-2-heptene | 30% MeOH | 8.83 |
| *trans*-1-$Me_2N$-2-heptene | 30% MeOH | 9.10 |
| 1-$Me_2N$-heptane | 30% MeOH | 9.16 |

The direction of influence of the triple bond on the base strength of an amine is in agreement with the results obtained by Hixon and Jones (6) for acetylenic acids. It would be predicted that the electron-attracting effect of the triple bond would render the unshared electron pair of the nitrogen atom less available for salt-formation, but would promote ionization of the carboxyl hydrogen in the acids. A similar effect should be found in the ethylene series, but since in general the olefinic linkage appears to be less strongly electron-attracting its influence should be less. Hixon and Jones found $K_1$ for propiolic acid to be $3 \times 10^{-3}$, in comparison to $6 \times 10^{-5}$ for acrylic acid and $1 \times 10^{-5}$ for propionic acid, and Craig and Hixon (7) observed that ethylenic amines in general were weaker bases than their saturated analogs.

In most cases the base strength of the acetylenic amines decreased when they were allowed to stand in aqueous solution, due to absorption of carbon dioxide from the air. In two cases, however, 1-dimethylamino-4-pentyne and 1-dimethylamino-5-hexyne, the aged aqueous solutions showed a marked increase in basicity (from $p$H 10 to about $p$H 13) (Figure 1) and the curves obtained on titration resembled those encountered in the titration of a strong base by a strong acid. Back-titration of the acidified solutions, however, gave curves that resembled those obtained when a weak base is liberated from its salt by sodium hydroxide.

The results indicated that a reversible cyclization to a quaternary ammonium hydroxide occurred on standing.

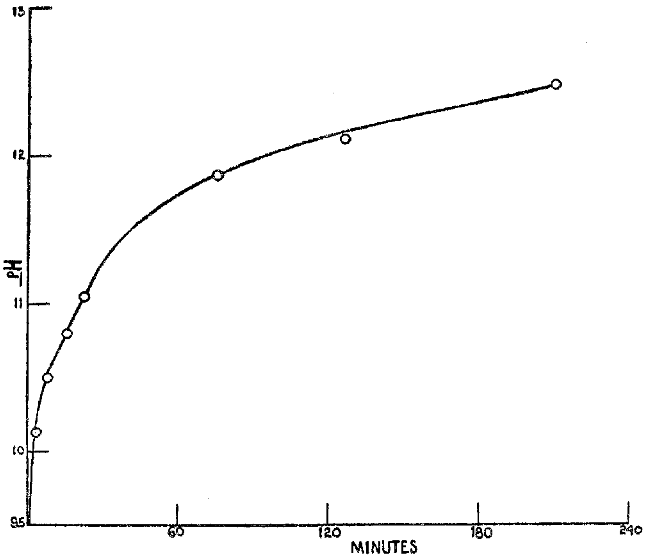
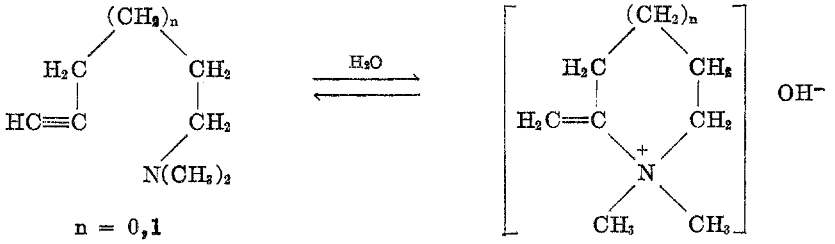


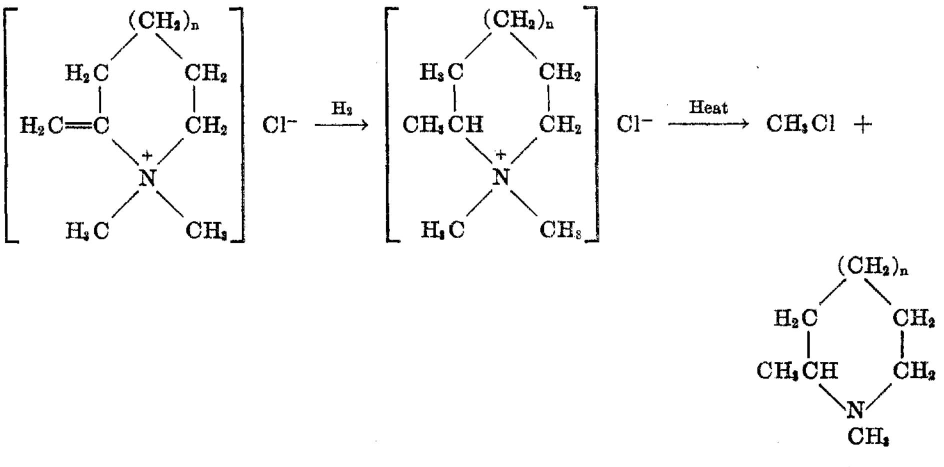
FIGURE 1. EFFECTS OF TIME ON $p$H OF AQUEOUS SOLUTIONS OF 1-DIMETHYLAMINO-4-PENTYNE



Those acetylenic amines which cannot cyclize to a five- or six-membered ring did not show this abnormal increase in basicity on standing in aqueous solution.

Evidence for this cyclization was obtained in the following way: Solutions of the two amines were allowed to age, and then were titrated with hydrochloric acid and immediately hydrogenated over palladium-charcoal. Only one molar equivalent of hydrogen was absorbed in each case. The resulting solutions were evaporated to dryness and the residues dry-distilled. Merling (8) has shown that dry distillation of dimethyl-piperidinium and -pyrrolidinium salts results in the loss of methyl chloride and the formation of the corresponding N-methyl-piperidine or -pyrrolidine. When the hydrogenation product from the aged solution of 1-dimethylamino-4-pentyne was dry distilled, 1,2-dimethylpyrrolidine was obtained, and similarly N-methyl-2-pipecoline was formed from 1-dimethylamino-5-hexyne. These cyclic tertiary amines were identified by comparison with authentic samples.

Work on the synthesis and properties of acetylenic amines is being continued in these laboratories.



n = 0 or 1

## EXPERIMENTAL[3]

*1-Dimethylamino-2-heptyne.* Dimethylamine (45 g., 1 mole) was added during 15 minutes to a cold suspension of 30 g. of paraformaldehyde in 100 ml. of anhydrous dioxane. The clear solution was transferred to an autoclave, 82 g. (1 mole) of *n*-butylacetylene was added, and the mixture was heated at 100° for 12 hours (maximum pressure 35 p.s.i.). The solvent was removed at atmospheric pressure, and the residue was fractionated through a helix-packed column under reduced pressure. There was obtained 112 g. (81%) of 1-dimethylamino-2-heptyne, b.p. 110°/90 mm.

*1-Dimethylamino-3-octyne.* Sodium butylacetylide was prepared from 82 g. (1 mole) of butylacetylene and 1 mole of sodamide in 1.5 l. of liquid ammonia. N,N-Dimethyl-β-bromoethylamine hydrobromide (116 g., 0.5 mole) was added, with stirring, as rapidly as the frothing of the mixture permitted (about two hours). The reaction mixture was allowed to stand overnight, and then was hydrolyzed by the drop-wise addition of 200 ml. of ice-water. The organic layer was dried over magnesium sulfate and distilled under reduced pressure. There was obtained 17 g. (27%) of 1-dimethylamino-3-octyne as a colorless liquid, b.p. 131°/90 mm.

*1-Dimethylamino-4-nonyne.* Sodium butylacetylide was prepared from 41 g. (0.5 mole) of butylacetylene and an equivalent amount of sodamide in 500 ml. of liquid ammonia. Trimethylene chlorobromide (78 g., 0.5 mole) was added during the course of 20 minutes. The mixture was stirred for an additional two hours and allowed to stand overnight. It was then hydrolyzed with ice-water. Distillation of the dried organic layer gave 29 g. (35%) of 1-chloro-4-nonyne, b.p. 117°/40 mm.; $n_D^{20}$ 1.4590, $d_4^{20}$ 0.9167; $MR_d$ obs., 47.33; $MR_d$ calc'd, 47.01.

The halogen atom was replaced by a dimethylamino group as follows: A mixture of 18 g. (0.16 mole) of 1-chloro-4-nonyne, 20 ml. (0.45 mole) of anhydrous dimethylamine, and 10

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[3] The analyses reported here were carried out at the Microtech Laboratories, Skokie, Illinois.

ml. of toluene was heated in a steel bomb at 120° for eight hours. The cooled reaction mixture was acidified with 6 *N* hydrochloric acid and extracted with ether to remove unreacted halide. The acid solution was treated with 50% sodium hydroxide and again extracted with ether. Distillation of the dried extracts yielded 8 g. (50%) of 1-dimethylamino-4-nonyne, b.p. 117°/33 mm.

*1-Dimethylamino-2-propyne.* 1-Dimethylamino-2-bromo-2-propene was prepared by adding slowly with stirring, a solution of 100 g. (0.5 mole) of 1,2-dibromo-2-propene in 100 ml. of benzene to a cold solution (0°) of 48 g. (1.1 mole) of anhydrous dimethylamine in 200 ml. of benzene. The reaction mixture was allowed to stand overnight, and then was filtered from the precipitated dimethylamine hydrobromide. The filtrate was extracted with 150 ml. of 6 *N* hydrochloric acid, and the amine liberated from this solution by addition of 50% sodium hydroxide. There was obtained 66 g. (80%) of 1-dimethylamino-2-bromo-2-propene, b.p. 131°, $n_D^{20}$ 1.4701, $d_4^{20}$ 1.2600; MR$_D$ obs., 36.32; MR$_D$ calc'd, 36.69.

The general procedure of Lespieau and Bourguel (9) was used to remove hydrogen bromide. From 65 g. (0.4 mole) of 1-dimethylamino-2-bromo-2-propene and 1.5 moles of sodamide in 200 ml. of mineral oil (reaction temperature 165°) there was obtained 8 g. (25%) of 1-dimethylamine-2-propyne, b.p. 82°. This amine is very soluble in water, and large losses occurred in attempting to extract it from aqueous solution, even when a continuous extractor was used.

*1-Dimethylamino-3-butyne. (a). From β-ethynylethanol.* β-Ethynylethanol was prepared in 40% yield from sodium acetylide and ethylene oxide as described by Kreimer (10). It was obtained as a colorless, water-soluble liquid of b.p. 127–127.5°. It was converted to 1-bromo-3-butyne by treatment with phosphorus tribromide in pyridine at 0°, by the general procedure of Juvala (11). The bromobutyne was obtained in 35% yield as a colorless liquid, b.p. 112–114°, and was not characterized further. A mixture of 22 g. of this bromide and 26 g. of anhydrous dimethylamine in 100 ml. of benzene was heated in a steel bomb at 115° for 7 hours. There was obtained 9 g. (50%) of 1-dimethylamino-3-butyne, b.p. 105–108°. This formed a *hydrochloride*, m.p. 147–148°.

*(b). From N,N-dimethyl-β-bromoethylamine hydrobromide.* Sodium acetylide was prepared from 28 g. (1.2 moles) of sodium and excess acetylene in 500 ml. of liquid ammonia, and the solution was then treated with 116 g. (0.5 mole) of N,N-dimethyl-β-bromoethylamine hydrobromide. The addition required about two hours, and the mixture was stirred for two hours longer. It was hydrolyzed by the cautious addition of 150 ml. of ammonium hydroxide followed by 200 ml. of water. The solution was extracted with ether, and the dried extracts were distilled. There was obtained 16 g. (33%) of 1-dimethylamino-3-butyne b.p. 106°.

*1-Dimethylamino-4-pentyne and 1-dimethylamino-5-hexyne.* One mole (157 g.) of trimethylene chlorobromide was added over a period of 15 minutes to a solution of 1.2 moles of sodium acetylide in 1 l. of liquid ammonia. The mixture was stirred for two hours, and then hydrolyzed as described above. There was obtained 53 g. (52%) of 1-chloro-4-pentyne, b.p. 114°, $n_D^{20}$ 1.4440, $d_4^{20}$ 0.9695; MR$_D$ obs., 28.05; MR$_D$ calc'd, 28.03.

A mixture of 75 g. (0.75 mole) of 1-chloro-4-pentyne, 100 ml. of benzene, and 90 g. (2 moles) of anhydrous dimethylamine was heated in a glass bomb at 80° for 13 hours. The reaction mixture was worked up in the usual way, and there was obtained 33 g. (40%) of 1-dimethylamino-4-pentyne, b.p. 129°.

When sodium acetylide and tetramethylene chlorobromide (12) were reacted as described above, the yield of 1-chloro-5-hexyne was 65%. It has b.p. 140–144°, $n_D^{20}$ 1.4491 $d_4^{20}$ 0.9543; MR$_D$ obs., 32.77; MR$_D$ calc'd, 32.65. The halogen atom was replaced by the dimethylamino group as described for the lower homolog. The yield of 1-dimethylamino-5-hexyne of b.p. 91°/110 mm., was 60%.

*cis-1-Dimethylamino-2-heptene.* A solution of 0.1 mole of 1-dimethylamino-2-heptyne in 50 ml. of 95% ethanol was treated with 60 mg. of 5% palladium-on-calcium carbonate and shaken with hydrogen until 0.1 mole had been absorbed. The catalyst was removed, the alcohol distilled off, and the amine distilled under reduced pressure.

1-Dimethylamino-2-propyne was hydrogenated similarly, but the product has a lower index of refraction and lower density than the material from sodium-liquid ammonia reduction, and appeared to contain some of the saturated amine. In this case there was no sharp break in the hydrogenation curve at half reduction.

*trans-1-Dimethylamino-2-heptene.* 1-Dimethylamino-2-heptyne (0.5 mole) was added dropwise, below the surface of the liquid, to a solution of 34.5 g. (1.5 mole) of sodium in liquid ammonia. Addition required 40 minutes; the mixture was stirred for two hours longer and was then hydrolyzed with ammonium hydroxide. *trans*-1-Dimethylamino-2-heptene was obtained in 65% yield, b.p. 103°/90 mm.

This same method was used to reduce 1-dimethylamino-2-propyne to the olefin. The yield was only 15%, however, due to the difficulty of isolating the product from aqueous solution.

*Determination of base strengths.* An accurately weighed sample of the amine was dissolved in 50.0 ml. of carbon dioxide-free distilled water to make approximately a 0.1 *N* solution, and 10-ml. aliquots were titrated immediately with standardized 0.03 *N* hydrochloric acid. A Beckman glass electrode *p*H meter was used to measure the *p*H of the solution, and the $pK_H$ value was read from the titration curve. The concentrations of the base and its salt at the mid-point of the neutralization were about 0.02 *M*. In the case of the higher amines sufficient methanol was used to make a 30% methanol solution at the mid-point of the titration. The determinations were made in triplicate and agreed with each other within 0.05 $pK_H$ units.

The effect of time on the base strengths was determined by titrating aliquot portions of the stock solution immediately after preparation, and again after 20 minutes, 40 minutes, 60 minutes, and three days. In the cases of 1-dimethylamino-4-pentyne and 1-dimethylamino-5-hexyne the base strength increased, and the basicity of the amine (before titration) also increased. (Figure 1).

When aged solutions (3-days standing) of these amines were titrated with hydrochloric acid and the neutralized solutions were hydrogenated over palladium, only one molar equivalent of hydrogen was taken up in the case of the dimethylamino-pentyne and -hexyne, but the other amines absorbed two molar equivalents of hydrogen under the same conditions.

*N-Methyl-2-pipecoline from 1-dimethylamino-5-hexyne.* A solution of 2.516 g. (0.02 mole) of the acetylenic amine in 5 ml. of methanol and 10 ml. of water was allowed to stand for five days, and 2 *N* hydrochloric acid was added until the solution was slightly acidic. It was then shaken with hydrogen in the presence of 100 mg. of 10% palladium-charcoal; 0.02 mole of hydrogen was taken up in 20 minutes and absorption then ceased. The solution was evaporated to dryness and the white crystalline residue was dry-distilled. A basic oil was obtained from which several derivatives were prepared: *picrate*, m.p. 240–241°; *styphnate*, m.p. 218–219°; *methiodide*, m.p. 325°; *hydrochloride*, m.p. 255°.

An authentic sample of N-methyl-2-pipecoline was prepared by methylation of 2-pipecoline with formaldehyde-formic acid. The product boiled at 123–125°, and formed the following derivatives: *picrate*, m.p. 240–241°; *styphnate*, m.p. 219–220°; *methiodide*, m.p. 236°; *hydrochloride*, m.p. 258°. These derivatives did not depress the melting points of the corresponding derivatives described above.

*1,2-Dimethylpyrrolidine from 1-dimethylamino-4-pentyne.* The reaction was carried out as described above. The oil obtained from the dry distillation formed a *picrate*, m.p. 233°, which did not depress that of the *picrate* from known 1,2-dimethylpyrrolidine (m.p. 233–234°).

## SUMMARY

Several new acetylenic amines of the general formulae $RC{\equiv}C\text{-}(CH_2)_nN(CH_3)_2$ have been prepared ($R = H$ or $n\text{-}C_4H_9$, $n = 1, 2, 3, 4$).

The base strengths of these amines have been determined potentiometrically,

and it has been found that a triple bond near the amino group weakens the basicity; this effect disappears as the triple bond is moved farther from the amino group.

1-Dimethylamino-4-pentyne and 1-dimethylamino-5-hexyne have been shown to undergo reversible cyclization in aqueous solution to form a piperidinium or pyrrolidinium quaternary hydroxide.

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