# Rates of Imine Formation from Acetone and Some N,N-Dimethyl Vicinal Diamines[1]

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Received August 18, 1980

The $pK_a$ values of several derivatives of N,N-dimethylethylenediamine having methyl groups on carbons 1 and 2 suggest that gem dimethylation gives diamines in which a major fraction of the monoprotonated form exists as a cyclic internally hydrogen-bonded species. The kinetics of formation of imines of acetone by these diamines was studied by using hydroxylamine to capture the imines. The monoprotonated forms of most of the diamines gave imines faster than the unprotonated forms did. Their reactions involve rate-controlling internal acid-catalyzed dehydration of intermediate carbinolamines. The effect of structure on the rate of this process is discussed.

A number of monoprotonated primary-tertiary diamines have been found to react with acetone,[2-4] isobutyraldehyde,[5] cyclopentanone,[4,6] and 3-pentanone[6] to give imines much more rapidly than sterically similar primary amines without acidic substituents. The high rate of reaction is believed to be due to internal acid catalysis of the dehydration of the intermediate carbinolamine, as shown in Scheme I for tertiary-protonated N,N-dimethylethylenediamine. Among amines of the type $Me_2N-(CH_2)_nNH_2$, with n being 2-5 for the studies of acetone and isobutyraldehyde and 2 and 3 in the other cases, the greatest reactivity was found when n was 2, i.e., with monoprotonated N,N-dimethylethylenediamine (1). We

$$H_2NCH_2CH_2NMe_2$$
**1**
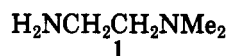
wondered whether methylation of the carbon atoms between the amino groups might stabilize the cyclic transition states relative to the reactants and thus give more reactive species.

## Results

**Synthesis of Diamines.** Commercial samples of $N^1,N^1$-dimethyl-1,2-propanediamine (2) and $N^2,N^2$-di-

methyl-1,2-propanediamine (3) were purified before use.

CH₃CHCH₂NMe₂ (with NH₂)  CH₃CHCH₂NH₂ (with NMe₂)

**2**          **3**
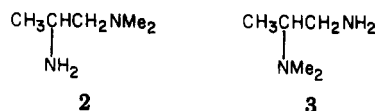
Minor modifications of literature procedures were used for the synthesis of $N^1,N^1,2$-trimethyl-1,2-propanediamine[7] (4), $N^2,N^2,2$-trimethyl-1,2-propanediamine[8a] (5), and $N^2,N^2,2$-trimethyl-2,3-butanediamine[8b] (6).

**4** CH₃C(CH₃)(NH₂)CH₂NMe₂

**5** CH₃C(CH₂NH₂)(NMe₂)CH₃

**6** CH₃C(CHNH₂CH₃)(NMe₂)CH₃
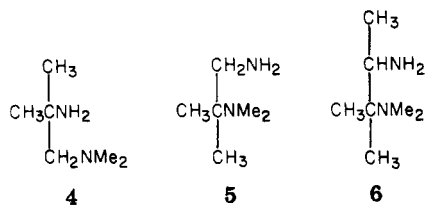
The product we obtained by treating erythro-3-(dimethylamino)-2-butanol with chlorosulfonic acid and then with ammonium hydroxide was assumed to be erythro-N,N-dimethyl-2,3-butanediamine (7). Neighboring-group

**7** erythro-CH₃CH(NH₂)CH(NMe₂)CH₃
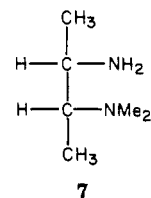
(1) Research supported in part by Grant GM 18593 from the National Institute of General Medical Sciences. Abstracted in part from the Ph.D. Dissertation of Yueting Chou, The Ohio State University, 1980.
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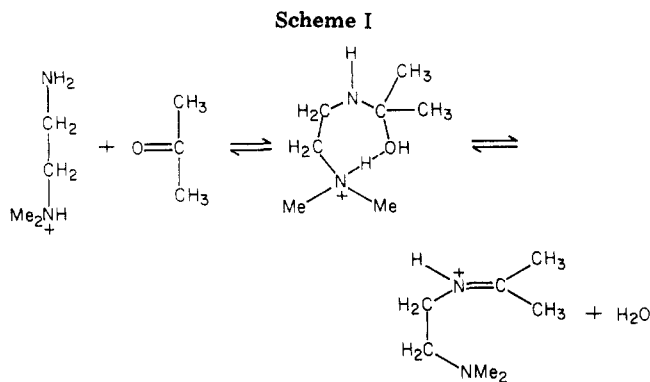(4) Hine, J.; Li, W.-S.; Zeigler, J. P. J. Am. Chem. Soc. 1980, 102, 4403-9.
(5) Hine, J.; Via, F. A. J. Org. Chem. 1977, 42, 1972-8.
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**Scheme I**



**Table I. Diamine $pK_a$ Values in Water at 35 °C**

| dia-mine | obsd $pK_1$ $(\sigma)^a$ | calcd[b] $pK_1$ | $\Delta^c$ | obsd $pK_2$ $(\sigma)^a$ |
|---|---|---|---|---|
| 1 | 9.30 (0.03) |  |  | 5.98 (0.01) |
| 3 | 9.52 (0.05) | 9.39 | 0.13 | 5.93 (0.02) |
| 5 | 9.97 (0.03) | 9.47 | 0.50 | 5.59 (0.02) |
| 2 | 9.33 (0.04) | 9.28 | 0.05 | 5.66 (0.01) |
| 4 | 9.41 (0.12) | 9.23 | 0.18 | 5.21 (0.05) |
| 7 | 9.36 (0.01) | 9.36 | 0.00 | 5.70 (0.00) |
| 6 | 9.94 (0.02) | 9.41 | 0.53 | 4.91 (0.02) |

[a] Estimated standard deviation.   [b] Calculated as described in the text.   [c] Observed − calculated.

participation to give the *N,N*-dimethyl iminium ion would involve one inversion of configuration and nucleophilic attack by ammonia would involve a second.
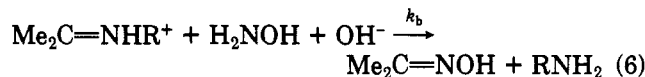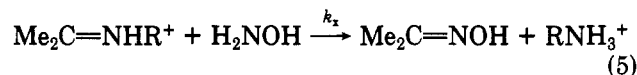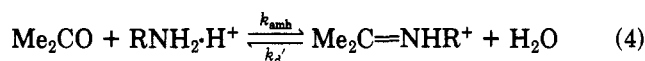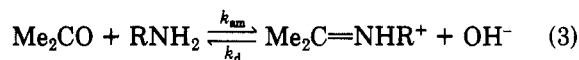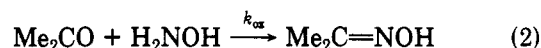
**pK Values.** Table I lists the $pK_a$ values for the conjugate acids of the diamines we studied and for the parent compound, which was studied previously.[2] There is evidence in the case of 1,3-propanediamine derivatives that methylation, especially gem dimethylation, of carbon-2 substantially increases the fraction of monoprotonated diamine that exists as a cyclic internally hydrogen-bonded species.[9]   The strongest evidence is that the gem dimethylated amines are considerably more basic than would otherwise be expected. In order to estimate how basic our vicinal diamines would be in the absence of internal hydrogen bonding by the monoprotonated species, we have examined the effect of $\alpha$ and $\beta$ methylation on the $pK_a$ values of simple primary amines and their *N,N*-dimethyl derivatives (Table II). We then assumed that the methyl substituent effects would be the same for our diamines. The effects on $K_1$ must be treated in terms of $K_{HTP}$, the acidity constant for tertiary-protonated diamine, and $K_{TPH}$, the acidity constant for primary-protonated diamine. The fraction of monoprotonated diamine that is internally hydrogen bonded is taken to be negligible in the case of the reference compound *N,N*-dimethylethylenediamine. In such a case eq 1 holds, and $pK_{HTP}$ and $pK_{TPH}$ values

$$pK_1 = \log\left(10^{pK_{HTP}} + 10^{pK_{TPH}}\right) \quad (1)$$

of 8.88 and 9.09, respectively, have been determined.[12] The $\alpha$- and $\beta$-methyl substituent effects are assumed to change these $pK_{HTP}$ and $pK_{TPH}$ values and from the changed values eq 1 was used to obtain a $pK_1$ value. For example, 6 was assumed to have its $pK_{HTP}$ increased by 0.50 by an $\alpha$-dimethyl effect and decreased by 0.08 by a

$\beta$-methyl effect. The calculated $K_a$ values are seen in Table I to be at least as large as the observed values. The largest deviations are for the three diamines containing *gem*-dimethyl substituents, especially the two for which the gem dimethylated carbon is adjacent to gem dimethylated nitrogen. It is suggested that the monoprotonated forms of these diamines exist to a major extent as internally hydrogen-bonded species.

**Rates of Imine Formation.** The equilibrium constants for formation of imines in aqueous solution are ordinarily too small to permit imine formation to be followed directly. Instead the reaction was followed, as it has been in previous cases,[2-6,13,14] by using hydroxylamine to capture the imine as it is formed, acetoxime formation being essentially irreversible in the presence of a slight excess of hydroxylamine. The reaction mechanism, shown in eq 2-6, is written in terms of iminium ions since these are the species formed in the rate-controlling step.   Inasmuch as the

$$Me_2CO + H_2NOH \xrightarrow{k_{ox}} Me_2C{=}NOH \quad (2)$$

$$Me_2CO + RNH_2 \underset{k_d}{\overset{k_{am}}{\rightleftharpoons}} Me_2C{=}NHR^+ + OH^- \quad (3)$$

$$Me_2CO + RNH_2{\cdot}H^+ \underset{k_{d'}}{\overset{k_{amh}}{\rightleftharpoons}} Me_2C{=}NHR^+ + H_2O \quad (4)$$

$$Me_2C{=}NHR^+ + H_2NOH \xrightarrow{k_x} Me_2C{=}NOH + RNH_3^+ \quad (5)$$

$$Me_2C{=}NHR^+ + H_2NOH + OH^- \xrightarrow{k_b} $$
$$Me_2C{=}NOH + RNH_2 \quad (6)$$

amine is not used up, capture of the iminium ion by hydroxylamine amounts to amine catalysis of the oximation of acetone. If such capture is much faster than hydrolysis of the iminium ion back to acetone, the reaction rate may be expressed as shown in eq 7, where $[Am]_T$ is the total

$$v = (k_{ox}[H_2NOH] + k_2[Am]_T)[Me_2CO] \quad (7)$$

concentration of amine in all states of protonation and $k_2$ is defined by eq 8, where $f_0$ is the fraction of amine that

$$k_2 = k_{am}f_0 + k_{amh}f_1 \quad (8)$$

is unprotonated and $f_1$ is the fraction that is monoprotonated. The values of $k_{ox}$ in water at 35 °C have been determined over the pH range 3–12.[15] A value for $k_{obsd}$, defined in eq 9, was calculated for each kinetic run.

$$k_{obsd} = k_{ox}[H_2NOH]_0 + k_2[Am]_T \quad (9)$$

For each of the diamines studied a plot of $k_{obsd}$ vs. the initial concentration of hydroxylamine at constant pH and constant total diamine concentration approximates a straight line of slope $k_{ox}$ above hydroxylamine concentrations of 0.05 M. This is illustrated in Figure 1 by the solid circles for 0.10 M 2 at pH 9.56 ± 0.03 and by the open circles for 0.10 M 5 at pH 10.29 ± 0.05. The lines were drawn with slopes equal to $k_{ox}$ at the respective pHs. Their intercepts are values of $k_2[Am]_T$ under the given conditions. For 0.10 M 4 at pH 9.50 the intercept was within the experimental uncertainty of zero. We conclude that 4 probably was forming iminium ions only very slowly or, less plausibly, that it gave iminium ions for which $k_x$ is,

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**Table II. Effects of $\alpha$- and $\beta$-Methyl Substituents on Amine Basicities[a]**

| R | $pK_a$ $RNH_3^+$ | $\alpha$ effect | $pK_a$ $RNHMe_2^+$ | $\alpha$ effect | $pK_a$ $RCH_2NH_3^+$ | $\beta$ effect | $pK_a$ $RCH_2NHMe_2^+$ | $\beta$ effect |
|---|---|---|---|---|---|---|---|---|
| $MeCH_2$ | $10.32^b$ | | $9.79^c$ | | $10.24^b$ | | $9.79^c$ | |
| $Me_2CH$ | $10.34^d$ | 0.02 | $10.08^c$ | 0.29 | $10.15^d$ | $-0.09$ | $9.71^c$ | $-0.08$ |
| $Me_3C$ | $10.34^d$ | 0.02 | $10.29^c$ | 0.50 | $9.91^e$ | $-0.33$ | $9.52^f$ | $-0.27$ |

[a] Thermodynamic values in water at 35 °C. [b] Interpolated between $pK_a$'s (ref 10) at 20 and 40 °C. [c] Calculated from $pK_a$ (ref 10a) at 20 °C and an assumed $\Delta S°$ of $-11.7$ eu (an average value for simple tertiary amines). [d] Calculated from $pK_a$ at 25 °C and experimentally determined $\Delta H°$ and $\Delta S°$ values (ref 11). [e] Calculated from $pK_a$'s at 16 and 25 °C (ref 10a) and an assumed $\Delta S$ of $-0.8$ eu (average value for simple primary amines). [f] Calculated from $pK_a$ (ref 10b) at 25 °C and an assumed $\Delta S°$ of $-11.7$ eu.
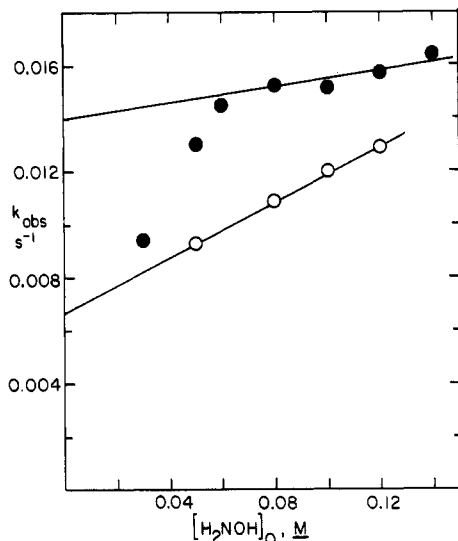


**Figure 1.** Plot of $k_{obsd}$ vs. the initial hydroxylamine concentration ($\bullet$) for 0.1 M total 2 at pH 9.56 and (O) for 0.1 M total 5 at pH 10.29.

for some reason, particularly small relative to $k_d$ and $k'_d$, so that capture of the iminium ions is particularly inefficient.

For each of the diamines 2, 3, 5, 6, 7, and ethylenediamine the capture of intermediate iminium ions by 0.10 M hydroxylamine was shown to be efficient at one pH high in the range to be covered and one pH low in that range. Then values of $k_2[AM]_T$ were determined, using 0.10 M hydroxylamine and 0.10 M total diamine over a pH range in which the fractions of diamine present in the unprotonated and in the monoprotonated form varied substantially. A plot of log $k_2$ vs. pH for 2 is shown in Figure 2. The line is based on values of $k_{am}$ and $k_{amh}$ obtained from a least-squares treatment of all the points using eq 8. The level segment of line around pH 8 refers to a range where almost all the diamine is monoprotonated and almost all the reaction comes from the $k_{amh}$ term. Although most of the diamine is unprotonated above pH 10, $k_{amh}$ is so much larger than $k_{am}$ that the $k_{am}$ term never became dominant. For this kind of reason, the $k_{am}$ values we obtained tend to be relatively unreliable when they are much smaller than the corresponding $k_{amh}$ values (which were the data of principle interest). The rate data obtained are listed in Table III.

## Discussion

Although the values of $k_{am}$ obtained are not very reliable, the only case in which $k_{am}$ is larger than $k_{amh}$ is that of 6 and even in this case the difference is smaller than the experimental uncertainty. For primary amines of the type $XCH_2CH_2NH_2$ in which internal acid catalysis of dehydration of the intermediate carbinolamine is impossible, a plot of log $k_{am}$ vs. $pK_a$ has a slope of 0.59.[2] That is, the rate decreases markedly with decreasing basicity of the
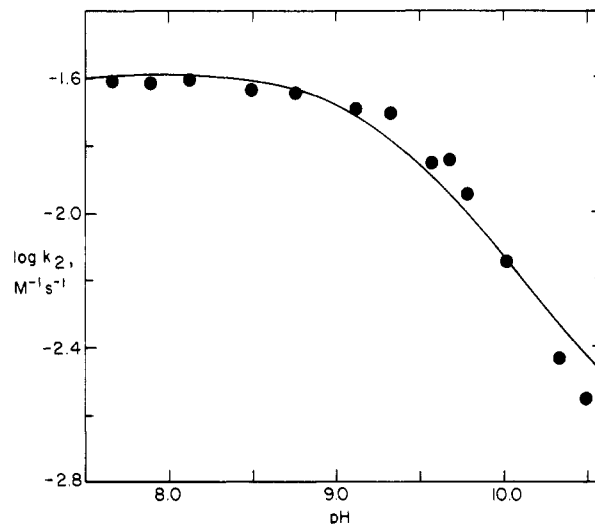


**Figure 2.** Plot of log $k_2$ vs. pH for 2.

**Table III. Rate Constants for Imine Formation from Acetone and Diamines[a]**

| diamine | $10^3 k_{am}$ $(\sigma),^b$ $M^{-1} s^{-1}$ | $10^3 k_{amh}$ $(\sigma),^b$ $M^{-1} s^{-1}$ |
|---|---|---|
| $Me_2NCH_2CH_2NH_2$ (1) | $\sim 21^c$ | $303^c$ |
| $Me_2NCHMeCH_2NH_2$ (3) | 44 (16) | 412 (16) |
| $Me_2NCMe_2CH_2NH_2$ (5) | <30 | 166 (15) |
| $Me_2NCH_2CHMeNH_2$ (2) | 15 (23) | 271 (31) |
| $Me_2NCH_2CMe_2NH_2$ (4) | <5 | <5 |
| $Me_2NCHMeCHMeNH_2$ (7) | 21 (8) | 111 (7) |
| $Me_2NCMe_2CHMeNH_2$ (6) | 69 (22) | 60 (5) |
| $H_2NCH_2CH_2NH_2$ | 76 (25) | 138 (12) |

[a] In water at 35 °C. [b] Estimated standard deviation. [c] Data from ref 2.

amines. Thus, in the absence of such internal acid catalysis the $k_{amh}$ values would all be much smaller than the corresponding $k_{am}$ values. Hence, the $k_{amh}$ term arises very largely from rate-controlling internal acid catalysis of dehydration of the intermediate carbinolamine. The reactant in this step is an internally hydrogen-bonded carbinolamine. This species contains a seven-atom ring including a hydrogen bond. Because of the tendency of hydrogen bonds to be linear and of bonds to hydrogen to be relatively short, we shall regard this ring as six sided. Since every apical atom is approximately $sp^3$ hybridized, the ring will be represented as having a chair structure, with one side considerably longer than the others (8).

The transition state will differ from 8 in having the C–O bond partly broken, the C–N double bond partly formed, and $C_1$, NH, and the three carbon atoms from acetone more nearly coplanar. However, we shall assume that 8 is a close enough approximation to the transition state that steric substituent effects on reactivity may be discussed in terms of their effect on the stability of 8. The major effects of structure on the magnitude of $k_{amh}$ shown in
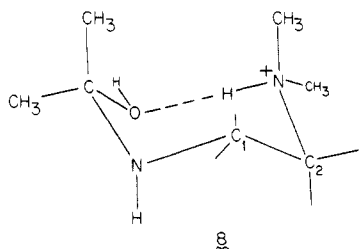
**8**

Table III may be so explained. The introduction of one methyl group on either $C_1$ or $C_2$ (to give 2 or 3) changes $k_{amh}$ by less than 40%; the first methyl group may occupy an equatorial position, where steric hindrance is not much different in 8 from what it was in the reactant. Introduction of a second methyl group on $C_2$ (going from 3 to 5) decreases the reactivity by a factor of 2.5; the second methyl group must be axial and hence somewhat more hindered. Introduction of a second methyl group on $C_1$ (going from 2 to 4) decreases $k_{amh}$ by more than 50-fold; not only must this methyl group be axial but it also must be involved in axial–axial interactions with two other methyl groups. Putting one methyl group each on $C_1$ and $C_2$ as in 7 decreases the reactivity by about threefold. Since 7 is erythro one of the methyl groups must be axial (presumably the one on $C_2$).

The smaller changes in reactivity accompanying the monomethylation of carbon-1 or -2 may arise more from changes in the stabilities of the various conformers of the reactant than from changes in transition-state hindrance.

It may be surprising that ethylenediamine has a $k_{amh}$ value less than half that for its N,N-dimethyl derivative when it is realized that the methyl–methyl diaxial interaction in 8 would be absent in the carbinolamine derived from ethylenediamine. However, the two axial methyl groups in 8 are kept much further apart than two ordinary axial groups by the long N–H—O bond between them. Unless the distance between axial methyl groups in 8 is such that van der Waals interactions are in the stabilizing range, the increased distances between these groups merely explains why $k_{amh}$ for ethylenediamine is not larger than that for 1. It does not explain why it is smaller. It may be that gem dimethylation of the nitrogen atom is stabilizing the transition state, because it is cyclic, relative to the reactant. It is also possible that this is another case where a dimethylamino group donates a proton faster than the corresponding primary amino group does. Primary amines have been found to remove protons from isobutyraldehyde,[16] acetone,[17] and nitroethane,[18] and to

catalyze the decomposition of nitramide[19] more slowly than tertiary amines (especially the N,N-dimethyl derivatives of the primary amines) of about the same basicity. It follows that in the reverse reactions tertiary ammonium ions are faster than primary ammonium ions.

## Experimental Section

**Reagents.** Recrystallization, usually from methanol–ethanol, was used to purify the dihydrochlorides of 5 [mp 250–254 °C (lit.[8a] mp 254–256 °C)], 6 [mp 252 °C (lit.[8b] mp 252–254 °C)], 2 [mp 168–169 °C. Anal. Calcd for $C_5H_{16}N_2Cl_2$: C, 34.29; H, 9.21. Found: C, 33.92; H, 9.31], 3 [mp 199–201 °C. Anal. Calcd for $C_5H_{16}N_2Cl_2$: C, 34.29; H, 9.21. Found: C, 34.28; H, 9.01], and 4 [mp 239–241 °C dec. Anal. Calcd for $C_6H_{18}N_2Cl_2$: C, 38.10; H, 9.51. Found: C, 38.29; H, 9.37].

*erythro*-N,N-Dimethyl-2,3-butanediamine.[20] To a solution of 5.0 g of *erythro*-3-(dimethylamino)-2-butanol[22] in 80 mL of ether at 0 °C was added 6.4 g of chlorosulfonic acid. The mixture was stirred for 1 h, the solvent removed, and the sticky residue dried for 5 h under vacuum. Next it was dissolved in 35 mL of concentrated ammonium hydroxide, saturated with ammonia at 0 °C, and heated to 105 °C in a sealed tube for 3 h. The combined organic layer and ether extracts were dried over potassium hydroxide and distilled to give a mixture of 55% product and 45% starting alcohol, bp 50–60 (18 mm). Heating 1 g of this mixture with potassium followed by vacuum distillation gave a small amount of diamine, which was transformed to its dihydrochloride: mp 182–184 °C; ^{1}H NMR (CDCl$_3$) δ 2.8–3.25 (m, 1, CHNH$_2$), 2.2 (s, 6, NCH$_3$), 2.8–2.2 (m, 1, CHNMe$_2$), 1.4 (br s, 2, NH$_2$), 1.0 (apparent t from overlapping d, 6, $J = J' = 6$ Hz, CH$_3$CCCH$_3$). Anal. Calcd for $C_6H_{18}N_2Cl_2$: C, 38.10; H, 9.59. Found: C, 38.42; H, 9.88.

**Acidity Constants.** Potentiometric titrations of 0.05 M amine dihydrochloride solutions (0.1 M in the case of 3) that were also 0.15 M in sodium chloride (0.3 M in the case of 3) with 0.2 M standard sodium hydroxide solutions were carried out at 35 °C. Apparatus and calculations (using the Davies equation[23] to calculate activity coefficients and thus estimate thermodynamic acidity constants) were as described previously.[6]

**Kinetic Measurements.** The reaction was followed by spectral measurements at 275 nm, near the absorption maximum for acetone as described previously.[2,3,15] Rate constants were calculated as described earlier for the cases of cyclopentanone and 3-pentanone.[6]

**Registry No.** 1, 108-00-9; 2 dihydrochloride, 75975-34-7; 3 dihydrochloride, 75975-35-8; 4 dihydrochloride, 75975-36-9; 5 dihydrochloride, 41805-72-5; 6 dihydrochloride, 41805-75-8; 7 dihydrochloride, 76023-55-7; H$_2$NCH$_2$CH$_2$NH$_2$, 107-15-3; acetone, 67-64-1; *erythro*-3-(dimethylamino)-2-butanol, 55261-16-0.

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(20) Although one of the enantiomers of this compound is known,[21] the racemic material does not appear to have been reported.

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