[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

# Effect of Structure on Reactivity. V. The Amine Catalyzed Dealdolization of Diacetone Alcohol[1]

BY ROBERT P. KOOB,[2] JOHN G. MILLER AND ALLAN R. DAY

The catalytic effect of a series of amines on the dealdolization of diacetone alcohol has been studied dilatometrically at 25°. Anhydrous ethylene glycol was used as solvent to avoid hydroxyl-ion catalysis. The amines showed the following relative order of activity: methyl- > *n*-butyl- > ethyl- > *n*-propyl- > *n*-amyl- > isopropyl- > *s*-butyl- > dimethyl- > di-*n*-propyl-, diethyl- and morpholine > di-*n*-butyl. Additional measurements were made in water and in mixed solvents. These and the data of other workers show that the relative order of catalytic activity is the same for the molecular amines in water and that ethylene glycol promotes this catalysis greatly.

Previous investigations have shown that the dealdolization of diacetone alcohol is a base-catalzyed reaction which follows a first-order course in aqueous as well as in some non-aqueous media.[3] Among the bases used in these earlier studies have been amines of various types.[3a,b,e,h] Westheimer and Cohen[3h] have shown that tertiary amines have negligible molecular catalytic effect in aqueous medium and pointed out that apparently the amine must have hydrogen attached to the nitrogen atom to act as a catalyst. In the present work it was decided to study the effects of amines on the dealdolization of diacetone alcohol in anhydrous media. The results show the effects of the number and kind of the groups attached to the amine nitrogen atom and are used to help clarify the picture of the mechanism of the reaction.

## Experimental

The dilatometric method was used to follow the rate of the reaction. The dilatometers were similar to those used by Akerlof[3b] except that they were constructed of Pyrex glass and had a small bulb above the stopcock so that mercury could be introduced between the stopcock and the reaction mixture to prevent leakage through the stopcock. The method of Guggenheim[4] was followed in spacing the observations and calculating the rate values. The true rather than the 0.434*k* values were calculated.

The amines, with the exception of methylamine, were commercial products. They were dried over potassium hydroxide pellets and distilled through an all-glass system. Methylamine was generated by dropping water onto an intimate mixture of methylammonium chloride and sodium hydroxide pellets. The gas was dried by passage over potassium hydroxide pellets and liquefied by passage into a trap immersed in a mixture of Cellosolve and Dry Ice: methylamine, b.p. 6.7° at 758 mm., ethylamine, 16.6° at 760 mm.; *n*-propylamine, 49–50° at 760 mm., $n_D$ 1.3901 at 16.6°; isopropylamine, 31.7° at 760 mm., 1.3742 at 20°; *n*-butylamine, 77.8° at 760 mm., 1.4008 at 20°; *s*-butylamine, 66° at 772 mm., 1.3950 at 16.7°; *n*-amylamine, 103° at 760 mm., 1.4118 at 20°; dimethylamine, 7.4° at 760 mm.; diethylamine, 55.5° at 759 mm., 1.3873 at 17.6°; di-*n*-propylamine, 110.7° at 760 mm., 1.4046 at 19.5°; di-*n*-butylamine, 159° at 761 mm., 1.4175 at 20°; morpholine, 126° at 760 mm., 1.4523 at 25°.

Ethylene glycol was dried over anhydrous potassium carbonate and distilled under reduced pressure, b.p. 72° at 1 mm., $n_D$ 1.4319 at 20°. 1,4-Dioxane was purified by prolonged refluxing over sodium followed by distillation, b.p. 101.5° at 760 mm., $n_D$ 1.4224 at 20°. Diacetone alcohol was purified by distillation under vacuum through a packed column until the distillate was colorless and had a refractive index of 1.4237 at 20° (b.p. 30° at 1 mm.).

Preliminary work showed that when dioxane was used as the solvent no apparent reaction occurred in the presence of amines. This parallels the earlier observation[5] that reaction takes place very slowly when dioxane is used as the solvent for the ammonolysis of esters. This parallelism of solvent effect led to a trial of ethylene glycol and excellent results were obtained. Consequently, anhydrous ethylene glycol was used as the solvent for this investigation. The reaction was studied at 25 ± 0.01°. The temperature fluctuations during any one determination did not amount to more than 0.003°.

## Results and Discussion

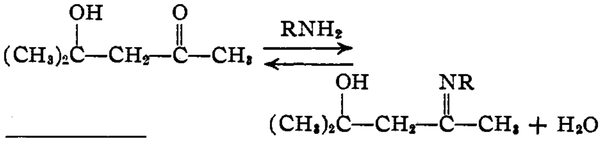
**Primary Amines.**—Table I lists the velocity constants and relative rates for the dealdolization of diacetone alcohol catalyzed by a number of primary amines. The $pK_a$ values of the amines in water solution at the same temperature are listed. The concentration of diacetone alcohol and amine is 0.1 molar each in all cases. No significant change in rate constant was obtained at constant amine concentration when the diacetone alcohol concentration was reduced to one-half this value.

TABLE I

THE RATES OF DEALDOLIZATION OF DIACETONE ALCOHOL CATALYZED BY PRIMARY AMINES IN ANHYDROUS ETHYLENE GLYCOL AT 25°

| Amine | Velocity constant (min.$^{-1}$) | Relative rate | $pK_a$ |
|---|---|---|---|
| Methyl | 0.0352 | 100 | 10.64 |
| *n*-Butyl | .0173 | 49.2 | 10.61 |
| Ethyl | .0170 | 48.4 | 10.67 |
| *n*-Propyl | .0161 | 45.8 | 10.58 |
| *n*-Amyl | .0158 | 45.0 | 10.70 |
| Isopropyl | .00385 | 10.9 | 10.63 |
| *s*-Butyl | .00374 | 10.6 | 10.56 |

Westheimer and Cohen[3h] concluded that an intermediate in the dealdolization reaction must be a compound formed from the diacetone alcohol and the amine. This conclusion is in agreement with the data obtained from the present study and the following course is written for the reaction.



$$(CH_3)_2\overset{OH}{\overset{|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-CH_3 \underset{}{\overset{RNH_2}{\rightleftarrows}} (CH_3)_2\overset{OH}{\overset{|}{C}}-CH_2-\overset{NR}{\overset{\|}{C}}-CH_3 + H_2O$$

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[1] From a thesis submitted by Robert P. Koob in partial fulfillment of the requirements for the degree of Doctor of Philosophy, University of Pennsylvania, June, 1949.

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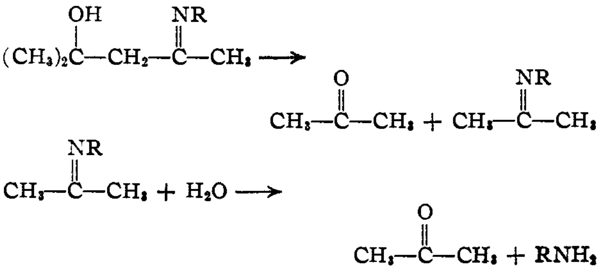
[3] (a) K. Koelichen, *Z. physik. Chem.*, **33**, 129 (1900); (b) G. Akerlof, THIS JOURNAL, **48**, 3046 (1926); *ibid.*, **49**, 2955 (1927); *ibid.*, **50**, 733 (1928); *ibid*, **50**, 1272 (1928); *ibid.*, **51**, 984 (1929); (c) C. C. French, *ibid.*, **51**, 3215 (1929); (d) G. M. Murphy, *ibid.*, **53**, 977 (1931); (e) J. G. Miller and M. Kilpatrick, Jr., *ibid.*, **53**, 3217 (1931); (f) V. K. La Mer and M. L. Miller, *ibid.*, **57**, 2674 (1935); (g) J. M. Sturtevant, *ibid.*, **59**, 1528 (1937); (h) F. H. Westheimer and H. Cohen, *ibid.*, **60**, 90 (1938); F. H. Westheimer, *Ann. N. Y. Acad. Sci.*, **XXIX**, 401 (1940); F. H. Westheimer and W. A. Jones, THIS JOURNAL, **63**, 3283 (1941).

[4] E. A. Guggenheim, *Phil. Mag.*, [7] **2**, 538 (1926).

[5] M. Gordon, J. G. Miller and A. R. Day, THIS JOURNAL, **70**, 1946 (1948); *ibid.*, **71**, 1245 (1949).



$$(CH_3)_2\overset{OH}{\overset{|}{C}}-CH_2-\overset{NR}{\overset{\|}{C}}-CH_3 \longrightarrow CH_3-\overset{O}{\overset{\|}{C}}-CH_3 + CH_3-\overset{NR}{\overset{\|}{C}}-CH_3$$

$$CH_3-\overset{NR}{\overset{\|}{C}}-CH_3 + H_2O \longrightarrow CH_3-\overset{O}{\overset{\|}{C}}-CH_3 + RNH_2$$

Westheimer and Jones[3b] ruled out the possibility that the rate determining step is the decomposition of a dipolar-ion form of the Schiff base formed in the first step because the methylamine catalyzed process showed no dependence on dielectric constant in water, water–ethanol and water–methanol solutions, being constant for different ratios of water to alcohol. This was confirmed by some preliminary measurements made in the present study. Using *n*-butylamine at 0.1 molar concentration, the rate in a solution composed of equal volumes of water and dioxane was nearly the same as in pure water, the velocity constants being 0.0060 and 0.0061 min.$^{-1}$, respectively, for the two reactions at 25°.

The results with mixed solvents may also be taken as evidence that the first step, the reaction of amine with diacetone alcohol, is rate determining. If this were a rapid reaction opposed by an equally rapid reverse process, the amount of water present should have a noticeable effect.

The catalytic effects are compared at equal concentrations for the amines in Table I. The small size of methylamine is the predominant factor in placing it well to the front of the list of these primary amines in catalyzing this reaction. Although *n*-butylamine might be expected to be more sterically hindered than ethylamine, its catalytic effect is nearly the same as that of ethylamine and it is more effective than *n*-propylamine. This inversion of order has been noted before for other aminolytic reactions.[6] Isopropylamine and secondary butylamine occupy expected positions in the series because of marked increases in steric hindrance.[7]

The results show clearly the superiority of ethylene glycol over water in aiding the action of the amines, similar to the relative effects of these solvents in ammonolysis[5] and also in primary aminolysis[6] of esters. Table II compares the effects of ethylene glycol and water in the primary-amine catalysis by listing the molar rate constants, $k_{\text{RNH}_2}$, at 25° for those amines for which data have been obtained in both solvents. Where the data for water were obtained from unbuffered solutions, the amine constant was computed by writing

$$k_{\text{obsd}} = k_{\text{OH}^-}C_{\text{OH}^-} + k_{\text{RNH}_2}C_{\text{RNH}_2}$$

taking $k_{\text{OH}^-}$ as 0.488 min.$^{-1}$ mole$^{-1}$ liter[3g] and estimating $C_{\text{OH}^-}$ from the $pK_a$ value listed in Table I.

The amines fall in the same order in both solvents although the water values are decidedly lower. That a complex between amine and glycol is responsible for these differences is probable. From a study of the ammonolysis of esters,[5] it was postulated that the ammonia molecule was activated through hydrogen bonding with ethylene glycol. Primary amines would form a similar complex.

TABLE II

THE MOLAR SPECIFIC RATE CONSTANTS AT 25° FOR SOME PRIMARY AMINES IN ETHYLENE GLYCOL AND WATER

| Amine | Ethylene glycol | Water |
|---|---|---|
| Methyl | 0.352 | 0.0454[a] |
| *n*-Butyl | .173 | .0302[b] |
| Ethyl | .170 | .0117[a] |
| *s*-Butyl | .0374 | .0068[b] |

[a] Obtained from the data of Miller and Kilpatrick.[3e] [b] Data from present study using unbuffered 0.1 molar amine.

**Secondary Amines.**—While measurements with primary amines showed that the reactions were strictly first order over a considerable range of amine and diacetone alcohol concentrations, this was not true in all cases with secondary amines. In some cases when the secondary amine concentration was equal to or twice that of the diacetone alcohol, the Guggenheim plots were curved, the negative slope of log $\Delta V$ against time diminishing as the reaction progressed. Increase of the amine concentration to ten times that of the alcohol in these cases produced good first-order plots. In Table III are shown the results for the reaction using the secondary amines. The diacetone alcohol concentration was 0.1 molar throughout and for the cases in which curved plots were obtained the velocity constant is listed as "not determinable." The $pK_a$ values in aqueous solution are given for the amines.

TABLE III

THE VELOCITY OF THE REACTION IN THE PRESENCE OF SECONDARY AMINES IN ETHYLENE GLYCOL AT 25°

| Amine | Molarity of amine | Velocity constant (min.$^{-1}$) | $pK_a$ |
|---|---|---|---|
| Dimethyl | 1.0 | 0.00610 | 10.71 |
| | 0.2 | Not determinable | |
| Di-*n*-propyl | 1.0 | 0.000743 | 10.91 |
| | 0.2 | Not determinable | |
| Diethyl | 1.0 | 0.000734 | 10.98 |
| | 0.2 | .000211 | |
| Morpholine | 1.0 | .000728 | 8.74 |
| | 0.2 | Not determinable | |
| Di-*n*-butyl | 1.0 | 0.000551 | 11.34 |

The catalysis by secondary amines in all probability involves intermediates corresponding to those noted for the reaction with primary amines.

Good straight lines were also obtained in the Guggenheim plots by the addition of water to the reaction system. This was realized in two experiments with di-*n*-butylamine in which water was added to the extent of 300 ml. per liter of reaction system where the amine concentration was 0.1 molar in one case, and 6 ml. per liter where the amine was 0.2 molar in the second case. The velocity constants were 0.000707 and 0.000343 min.$^{-1}$, respectively, at 25°.[8]

The results in Table III show that the catalytic effect of the secondary amines is much smaller

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[6] E. McC. Arnett, J. G. Miller and A. R. Day, THIS JOURNAL, **72**, 5635 (1950).

[7] B. V. Thosar, *J. Chem. Phys.*, **6**, 654 (1938); G. Vavon and L. Bourgeois, *Compt. rend.*, **202**, 1446 (1936).

[8] Discussion of the reaction mechanisms involved will be found in the original Thesis.

than that of the corresponding primary amines despite the greater basicity of the secondary amines. Steric factors would be expected to have a great effect and this is revealed by comparison of the dimethylamine value with that of the other amines of this class. The catalytic effects of diethylamine, di-*n*-propylamine and morpholine are almost the same. Even though morpholine is a weaker base than the other two, it is almost as active because of reduced steric hindrance around its nitrogen atom. Di-*n*-butylamine is the poorest catalyst of the amines studied.

Again the action of ethylene glycol in promoting the catalysis was observed. The molar value, 0.0305, for the rate constant of dimethylamine in ethylene glycol is far greater than the value, 0.00468, obtained by Miller and Kilpatrick[3e] for that amine in pure water at the same temperature, and Akerlof's results[3b] indicate that diethylamine shows practically no molecular catalysis in pure water.

Westheimer and Cohen[3h] were the first to show conclusively that the tertiary amines, trimethyl- and triethylamine, exhibit little or no molecular catalysis in the dealdolization of diacetone alcohol in water solution, although Koelichen[3a] and Akerlof[3b] had previously obtained data which showed the same lack of catalysis by those amines. The steric hindrance caused by the two methyl groups and the methylene group surrounding the hydroxyl group of diacetone alcohol should render most bases ineffective in the process by which hydroxyl ion catalyzes the breakdown.[3h] Nevertheless, there is no reason to suppose that other bases will not catalyze the reaction by the mechanism exhibited by the hydroxyl ion. Search for such catalysis should be made in non-aqueous media to avoid the domination by hydroxyl ion. With this and the promoting effect of ethylene glycol in mind, triethylamine was tried and definite evidence was found for catalysis by this base in anhydrous ethylene glycol. However, the rate of the reaction was too low to measure. This adds to the evidence that the catalysis by the other amines studied in this solvent is safely taken to be of the same type as found for these amines in water solution.

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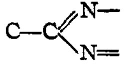
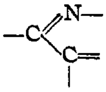
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE]

# Quinazolines. XII. Mannich Reactions of 4-Methyl Substituted Quinazolines[1]

BY JOHN SIEGLE AND BERT E. CHRISTENSEN

This work was undertaken to determine the structures of the Mannich products prepared from certain acetyl-2,4-dimethylquinazolines. Although this question has still not been settled further information pertaining to the reactivity of methyl substituents in the 2- and 4-positions have been obtained. The methylenic character of the 4-methyl substituent in 4-methyl and 2,4-dimethylquinazoline has been demonstrated by condensation reactions. The 4-methyl substituent acts as a methyl ketone in the presence of alkaline sodium hypobromite; the intermediate product 4-tribromomethylquinazoline has been isolated and identified. A new and improved procedure for the preparation of 4-methylquinazoline is described.

The structures of the amino alcohols prepared from the acetyl derivatives of 2,4-dimethylquinazoline *via* the Mannich reaction[2] have never been assigned due to the uncertainty as to which of the three methyl groups may have been involved in the condensation. This uncertainty stems from the unusually mild conditions necessary to obtain a Mannich product and the fact that Bogert and Nabenhauer had reported certain methyl substituents of methyl substituted quinazolines to be reactive.[3] Although the question of the structure of the Mannich products still has not been settled further information regarding the relative reactivity of methyl substituted quinazolines has been obtained.

The methyl substituents in 2-(and 4)-methylquinazolines are members of entirely different structural units. The 2-methyl substituent is part of an amidine structure  $\mathrm{C{-}C}\substack{\diagup \mathrm{N}{-} \\ \diagdown \mathrm{N}{=}}$ while the 4-methyl substituent is a typical ketimine  $-\mathrm{C}\substack{\diagup \mathrm{N}{-} \\ \diagdown \mathrm{C}{=} \\ \mid}$ which may well impart methylenic character to the 4-methyl substituent. The 4-position in the quinazoline compounds has been found by Tomisek and Christensen[4] to be extremely reactive. Furthermore, similar structural units occurring in $\alpha$-picoline,[5] 2-methylquinoline[5] and 1-(and 3)-methylisoquinoline[6] have been reported as having methyl substituents sufficiently active to undergo condensation reactions. In view of these considerations the decision was made to investigate the 2- and 4-methyl substituted quinazolines for methylenic activity.

2-Methylquinazoline[3] and 2,4-dimethylquinazoline[7] were prepared for these studies by well known procedures. 4-Methylquinazoline has been prepared by Bogert by the hydrolysis and decarboxylation of 4-methylquinazoline-2-carbonamide.[3] In this Laboratory a new and improved procedure for the preparation of this intermediate was perfected. 4-Methylquinazoline was obtained through the formylation of *o*-aminoacetophenone which in turn was cyclized to 4-methylquinazoline. As had been surmised, the methyl substituent in 2-methylquinazoline was sufficiently unreactive that it did not form condensation products with dimethyl-

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[1] The work described in this paper was made possible by a grant from the Shell Fellowship Committee. Published with the approval of the Monograph Publications Committee, Oregon State College, as Research Paper No. 185, School of Science, Department of Chemistry.

[2] Isensee and Christensen, THIS JOURNAL, **70**, 4061 (1948).

[3] Bogert and Nabenhauer, *ibid.*, **46**, 1932 (1924).

[4] Tomisek and Christensen, *ibid.*, **67**, 2112 (1945).

[5] Tseou, *Compt. rend.*, **192**, 1242 (1931).

[6] Mills and Smith, *J. Chem. Soc.*, **121**, 2724 (1922).

[7] Bischler and Burkart, *Ber.*, **46**, 1349 (1893).