

MECHANISM OF THE MANNICH REACTION
INVOLVING 2,4-DIMETHYLPHENOL AND MORPHOLINE

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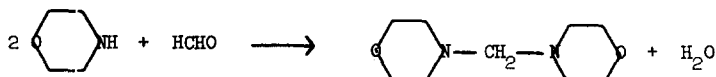
(Received 20 March 1964)

The Mannich reaction plays an essential role in the biosynthesis² and laboratory synthesis of important nitrogenous substances.³ In spite of the importance of the reaction, a satisfactory mechanism has not been elucidated. Several different mechanisms probably operate, depending upon pH and the nature of the active hydrogen reactant, A-H:

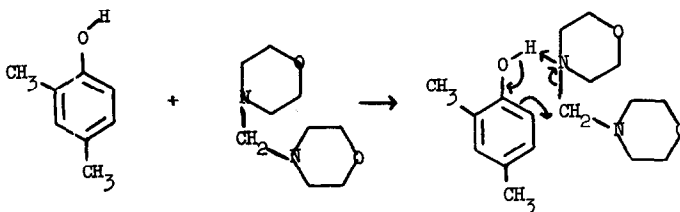


Kinetic studies involving methylmalonic acid as A-H were carried out by Alexander and Underhill,⁴ while Cummings and Shelton similarly studied cyclohexanone.⁵ The exact nature of rate determining reactants was not established in either case.

The present report describes a kinetic study of the Mannich reaction involving 2,4-dimethylphenol. Earlier, we postulated a quasi six-membered ring in explanation of preponderant ortho aminomethylation in phenols with the para and one ortho position open.^{6,7} The same type of postulated transition state (II) has been established by the present study as an essential step in the reaction between 2,4-dimethylphenol, formaldehyde and morpholine.

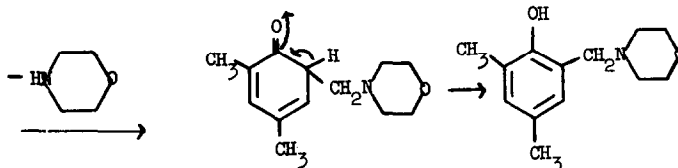


I



I

II



III

IV

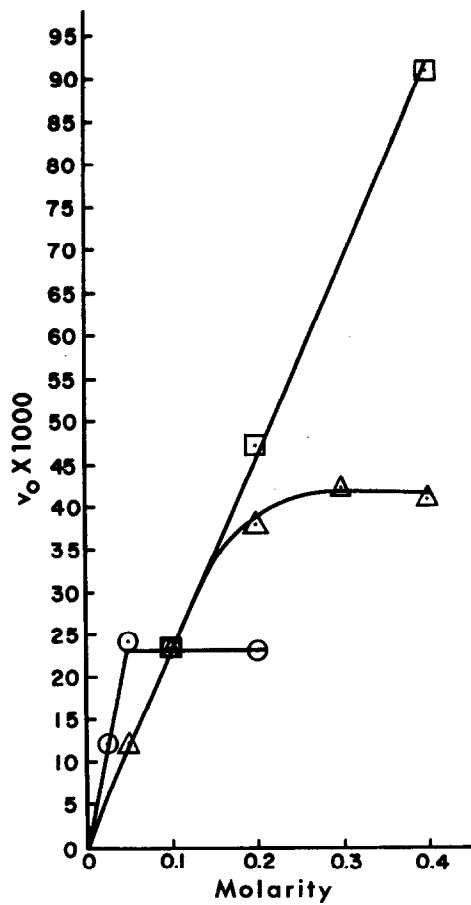
2,4-Dimethylphenol was chosen as the phenolic reactant because it offers only one reactive position and thus could yield only one product (IV). Failure of 2,4-dimethyl-6-hydroxymethylphenol to react with morpholine eliminated a possible reactive route.

Structure I represents one of three possible constituents of the Mannich reagent obtained by reaction between morpholine and formaldehyde in alcoholic solution. The other two are morpholinomethanol and morpholinomethyl ethyl ether. Each type of compound has been mentioned as an intermediate in the synthesis of phenolic Mannich bases,⁸ suggesting to us that one be selected for kinetic studies. Nevertheless, experiments employing buffered solutions of phenol, formaldehyde, morpholine and alcohol fortuitously pointed to the methylenebisamine (I) as a rate determining intermediate.¹

The mechanism was established by the following experimental considerations.

Reaction of 2,4-dimethylphenol, formaldehyde and morpholine was studied by varying the concentration of each reactant. In the rate equation $v = k[P]^X [M]^Y [F]^Z$, where P represents phenol, M morpholine and F formaldehyde, the effect of change in concentration of phenol may be determined by holding constant all variables, including temperature and pH, and evaluating v at different values of $[P]$. A plot of v against $[P]$ should give a line which shows that as the concentration is doubled v is also doubled if $X = 1$, and a line with no slope if $X = 0$. Any other values of X should give a curve. This method has shown that the reaction with respect to 2,4-dimethylphenol is first order, i.e. $X = 1$ at pH 10 (Fig. 1).⁹

Interesting results were obtained by varying the concentrations of formaldehyde and morpholine (Fig. 1). These studies indicate the involvement of an intermediate whose concentration is controlled by the concentration of either formaldehyde or morpholine. The concentration of the intermediate is controlled by formaldehyde if the concentration of formaldehyde is less than one half that of morpholine present and is controlled by morpholine if the concentration of morpholine is less than twice that of formaldehyde present. These results, as well as those conducted at pH 9 and 10.45, suggest a rate determining intermediate of the N,N'-methylenebismorpholine (I) type. Pure I, which can be distilled over alkali,¹⁰ gave the same kinetic results as a mixture of morpholine and formaldehyde (Fig. 1). Further support for the predominant or exclusive presence of methylenebisamine in the Mannich reagent was recently supplied by the calorimetric studies of Fernandez and Butler.¹¹

FIG. 1. Plot of v_0 vs. molarity. $T = 78 \pm 0.05^\circ$, $\text{pH} = 10.0$. \square = 2,4-Dimethylphenol (CH_2O and morpholine constant at 0.1 molar). \triangle = Morpholine (CH_2O and 2,4-dimethylphenol constant at 0.1 molar). \circ = CH_2O (Morpholine and 2,4-dimethylphenol constant at 0.1 molar).

Four different reactive combinations of 2,4-dimethylphenol and N,N'-methylenebismorpholine are possible: (A) free phenol reacting with amine; (B) free phenol reacting with singly protonated amine; (C) phenolate anion reacting with amine; and (D) phenolate anion reacting with singly protonated amine. Identity of the reactive species was revealed by conducting the reaction between 2,4-dimethylphenol and N,N'-methylenebismorpholine at various pH's above and below 10.49, the pKa of 2,4-dimethylphenol¹² (Fig. 2). For combination C to be valid, the rate of reaction should continue to increase with pH until the phenolate anion is maximally present and then remain constant, while increased acidity would be necessary for B to operate. Propositions A and D are kinetically indistinguishable. Their profiles are analogous, since the rate of reaction increases with pH until insufficient phenol (proposition A) or protonated amine (proposition D) is present and then it decreases.

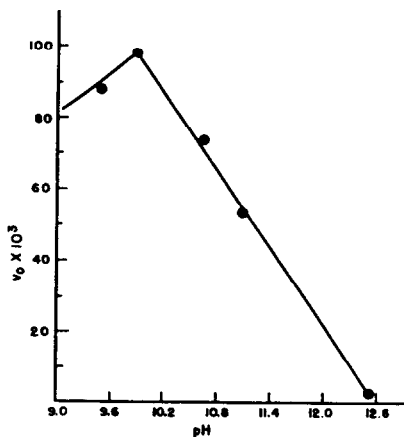


FIG. 2. Plot of v_0 vs. pH.

Profile of Reaction
between N,N'-Methylene-
bismorpholine and
2,4-Dimethylphenol.

The reaction profile, as shown in Figure 2, rules out postulates B and C. Even though methylenebisamines are highly unstable in acidic media,¹³ the protonated form may be capable of momentary existence, and so proposition D can not be completely ruled out. Only proposition A, involving the hydrogen bonded transition state II in a concerted mechanism, becomes acceptable in the light of earlier studies relating to the preponderant ortho-aminomethylation of phenols.⁶

Discovery of a gem diamine (I) as a rate determining intermediate may be of special interest in view of the fact that the related 5,10-methylenetetrahydrofolic acid is involved as an active methylene intermediate in the biosynthesis of thymidylate.¹⁴ In fact, our laboratory synthesis of 5-morpholinomethyluracil and hydrogenolysis of it to thymine constitutes a non-biological model¹⁵ lending support to the Friedkin postulate.¹⁴

Preliminary results suggest that a different mechanism operates in acidic media.¹

Acknowledgement: These studies were made possible through generous financial support from Monsanto Chemical Company, Eli Lilly and Company and the American Foundation for Pharmaceutical Education. Our thanks go especially to Dr. R. M. Stiles for helpful discussions.

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