thienylacetic acid and phenyl-2-thienylglycolic acid were prepared and characterized. From the results of some preliminary antispasmodic screening, brief conclusions are drawn on the relationship between structure and activity.

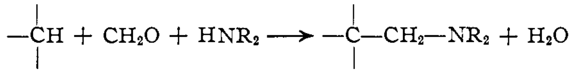
DETROIT, MICH. RECEIVED JUNE 22, 1949

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Studies on the Mechanism of the Mannich Reaction. I. Ethylmalonic Acid, A Methynyl Compound

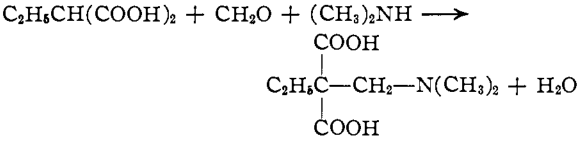
BY ELLIOT R. ALEXANDER AND ELIZABETH J. UNDERHILL

When a compound containing an active hydrogen atom is treated with formaldehyde and ammonia or a primary or secondary amine, the active hydrogen atom is replaced by an aminomethyl group.



$$-\overset{|}{\underset{|}{C}}H + CH_2O + HNR_2 \longrightarrow -\overset{|}{\underset{|}{C}}-CH_2-NR_2 + H_2O$$

This reaction is commonly called the Mannich reaction,[1] and it has been used widely in synthesis. Its mechanism, however, has not been elucidated. Many types of active methylene and methynyl compounds undergo the reaction and it has been run in both acidic and basic media. The purpose of this investigation was to study the kinetics of the reaction of ethylmalonic acid with formaldehyde and dimethylamine.



$$C_2H_5CH(COOH)_2 + CH_2O + (CH_3)_2NH \longrightarrow C_2H_5\overset{\overset{\displaystyle COOH}{|}}{\underset{\underset{\displaystyle COOH}{|}}{C}}-CH_2-N(CH_3)_2 + H_2O$$

Ethylmalonic acid, it will be observed, is a compound with only one replaceable hydrogen atom.

Experimental

Materials

Ethylmalonic Acid.—The ethylmalonic acid (m. p. 110–110.5°) used in this investigation was prepared by the saponification of commercial ethyl ethylmalonate.[2] Before commencing the preparation, however, the ester was shaken with half its volume of 25% aqueous potassium hydroxide for one half hour in order to remove any ethyl malonate which might have been present.

Formaldehyde.—In order to depolymerize any polyoxymethylenes present,[3a] commercial 37% formalin was diluted twenty-fold to give a solution approximately 2% in formaldehyde, which was allowed to stand for at least two days. The solution was standardized by the method outlined below.

Dimethylamine.—A solution, 2.616 *N* in dimethylamine, was made up by diluting commercial 25% aqueous dimethylamine. It was standardized with normal hydrochloric acid, using methyl orange as an indicator.

Nessler reagent (K_2HgI_4) was prepared according to the procedure given in the "Handbook of Chemistry and Physics."[4] It was found convenient to prepare it in quantities of 16 liters.

Dimethylaminomethylethylmalonic Acid.—The method used for the preparation of this acid was essentially that of Mannich and Ganz.[5] From 6.6 g. (0.05 mole) of ethylmalonic acid, 10 ml. (0.05 mole) of 22.5% dimethylamine solution, and 4.1 ml. (0.05 mole) of 37% formalin, was obtained 7.3 g. (77%) of the amino-acid, m. p. 100.5–101° (dec.).

Dimethylaminomethanol.—For the preparation of dimethylaminomethanol the procedure of Henry[6] was modified as follows. To 114 ml. (1.5 moles) of 37% formalin cooled in an ice-salt-bath, 270 ml. (1.5 moles) of 25% dimethylamine solution was added dropwise with stirring. The stirring was continued for two and one-half hours after addition was complete. Anhydrous potassium carbonate was then added in small portions until an oily layer formed. This was separated and dried over anhydrous potassium carbonate. During the entire preparation the temperature was kept below 5°, and the product was kept in a refrigerator. The yield of crude, undistilled material was 79 g. (70%), n^{20}_D 1.4060 (The refractive index changed to 1.4050 over a period of twenty four hours and then remained constant.). This substance was dissolved in water and analyzed as described for formaldehyde and dimethylamine.

Anal. Calcd. for C_3H_9NO: CH_2O, 40.0; $(CH_3)_2NH$, 60.0. Found: CH_2O, 36.8; $(CH_3)_2NH$, 61.2.

The infrared absorption spectrum of the substance showed only a very weak absorption band in the region characteristic of the OH group.

Procedures

Determination of Formaldehyde.—The determination of formaldehyde was carried out by a modification of the mercurimetric method of Bougault and Gros.[7] To 50 ml. of Nessler reagent was added a sample containing 0.0002 to 0.0006 equivalent of formaldehyde. A precipitate formed at once, the resulting mixture was shaken for five minutes, and it was then acidified by the addition of 30–40 ml. of 2 *N* acetic acid. Twenty-five ml. of 0.1 *N* iodine solution was added immediately and the precipitate was dissolved by agitation. The excess iodine was titrated with 0.1 *N* sodium thiosulfate solution. Care was taken to keep the mixture alkaline until the addition of the acetic acid by adding to the Nessler reagent 2–6 ml. of 10% sodium hydroxide solution in cases where the formaldehyde sample was strongly acidic. Blanks were run and corrections made for the effects of Nessler reagent, buffer, amine, ethylmalonic acid and dimethylaminomethylethylmalonic acid, on the thiosulfate titer. The corrections were not more than a few tenths of a ml. and were in such directions that they tended to cancel each other.

Determination of the Order of Reaction.—To study the kinetics of the formation of dimethylaminomethylethyl-

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[1] Blicke in Adams, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 303.

[2] Gattermann, "Laboratory Methods of Organic Chemistry," The Macmillan Co., New York, N. Y., 1937, p. 255.

[3] (a) Walker, "Formaldehyde," Reinhold Publishing Corp., New York, N. Y., 1944, p. 31; (b) p. 263.

[4] "Handbook of Chemistry and Physics," 27th ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1943, p. 1277.

[5] Mannich and Ganz, *Ber.*, **55**, 3486 (1922).

[6] Henry, *Bull. Acad. roy. belg.*, [3] **28**, 355 (1894).

[7] Bougault and Gros, *J. pharm. Chim.*, **26**, 5 (1922) [*C. A.*, **16**, 3281 (1922)].

malonic acid from ethylmalonic acid, dimethylamine, and formaldehyde, the reaction was run in a solution kept at *p*H 4.20 ± 0.08 by the use of a buffer consisting of 4.102 g. of sodium acetate and 8–11 ml. of 12.56 *N* acetic acid, depending on the relative concentrations of amine and ethylmalonic acid.[8] The buffer, formaldehyde and amine were mixed in a 50-ml. volumetric flask, diluted to about 40 ml., and allowed to stand at room temperature for at least twelve hours. The solution was then cooled to 0°, ethylmalonic acid was added, the solution was made up to the mark, and the flask was immersed in a bath maintained at 0.09 ± 0.27°. Aliquots containing 0.0002 to 0.0006 equivalent of formaldehyde were withdrawn from time to time and analyzed immediately for formaldehyde in order to determine the extent of reaction. In each run the reaction was allowed to proceed to 52–80% of completion. The results are summarized in Table I and a typical reaction curve is shown in Fig. 1. Included in Table I is one run (54) in which the ionic strength was approximately doubled by adding 5.0 g. of potassium chloride.[9] When the reaction was run without allowing the amine and formaldehyde to stand at room temperature, complex curves (Fig. 1) were obtained.

TABLE I

DETERMINATION OF THE ORDER OF THE REACTION AT 0.09 ± 0.27°

Run	*p*H	*M* CH_2O	*M* $(CH_3)_2NH$	*M* $C_2H_5CH(COOH)_2$	*k*, (liter²/mole² hr.)
27	4.26	0.2056	0.2616	0.1971	0.434
30	4.23	.2056	.2616	.3942	.353
31	4.14	.2056	.1308	.3942	.300
32	4.12	.3541	.2616	.3942	.364
33	4.15	.1028	.2616	.3946	.330
35	4.26	.2056	.5232	.3940	.295
36	4.28	.2056	.2616	.1062	.455
44[a]	4.22	.2090[b]	.2324[b]	.3942	.431
49[a]	4.15	.2210	.1831	.3942	.410
51	4.18	.2238	.2616	.3942	.370
53	4.18	.1119	.2616	.3942	.337
54[c]	4.16	.2210	.2616	.3942	.360
				Average[d]	.360 ± 0.033

[a] Temperature is 0.48 ± 0.17°. [b] Formaldehyde and dimethylamine in the form of dimethylaminomethanol. [c] Ionic strength doubled by the addition of 5.0 g. of potassium chloride. [d] Excluding runs 44 and 49.

To investigate the reversibility of the reaction, a solution made up of the buffer and 3.78 g. (0.02 mole) of dimethylaminomethylethylmalonic acid was diluted to 50 ml. After maintaining this solution at 0° for one week, no precipitate characteristic of formaldehyde was formed upon analysis of an aliquot. Control runs were also made to discover whether there was an independent reaction between formaldehyde and either dimethylamine or ethylmalonic acid. A 50-ml. solution containing 0.02 mole of ethylmalonic acid, 0.01 mole of formaldehyde and the buffer was left at 0° for three days, and the loss in formaldehyde content was found to be 3%. In another run the acid was replaced by 0.013 mole of dimethylamine, and the formaldehyde content decreased by only 1.5% in three days.

In order to ascertain that ethylmalonic acid did not react with formaldehyde to form a compound which was decomposed under the basic conditions of the formaldehyde analysis, hydroxymethylethylmalonic ester was prepared[10] and tested for formaldehyde with Nessler reagent and also with methone.[3b] In the former case it gave formaldehyde quantitatively, but in the latter case, under acidic conditions, only a negligibly small trace of formaldehyde was detected. The control with ethylmalonic acid and formaldehyde was repeated at 0–5°, and when followed by the methone analysis it was found that 5% reaction occurred in three days.

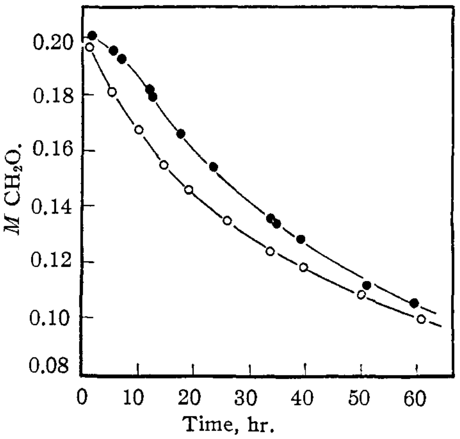

Fig. 1.—Course of the Mannich reaction at 0.16 ± 0.10° using solutions 0.2056 *M* in formaldehyde, 0.2616 *M* in dimethylamine and 0.1971 *M* in ethylmalonic acid: ⊙, Run 27, in which the formaldehyde and amine were mixed twelve hours before the addition of the ethylmalonic acid; ●, all the reagents mixed at once.

Dependence of the Specific Rate Constant, *k*, on *p*H.—By following the procedure outlined above, the dependence of the specific rate constant on *p*H was determined. In all cases the quantities of reagents used were: 2.6011 g. (0.01971 mole) of ethylmalonic acid, 5.00 ml. (0.01308 mole) of 2.616 *N* dimethylamine solution, 16.25 ml. 0.01028 mole) of 0.6324 *M* formaldehyde solution. The *p*H was varied by changing the composition of the buffer, and the temperature was held at 0.48 ± 0.04°. The buffers used and the rate constants calculated are summarized in Table II and Fig. 3. Control runs were made to determine the extent of the independent reactions of formaldehyde with dimethylamine and with ethylmalonic

TABLE II

DEPENDENCE OF REACTION RATE ON *p*H

Run	*p*H	Buffer	*k*, (liter²/mole² hr.)
39	2.90	3.728 g. KCl	0.342
40	3.95	4.102 g. NaOAc + 16.1 ml. 12.56 *N* HOAc	.455
41	4.60	4.102 g. NaOAc + 2.5 ml. 12.56 *N* HOAc	.306
42	5.03	4.102 g. NaOAc	.222
46	5.50	4.102 g. NaOAc + 4 ml. 10% NaOH	.121
47	1.00	4.102 g. NaOAc +16 ml. 5 *N* HCl	No reaction
59	11.57	20 ml. 10% NaOH	No reaction[a]
62	8.37	10 ml. 10% NaOH	0.007[b]

[a] No reaction in excess of the reaction between formaldehyde and dimethylamine. [b] Calculated roughly from the extent of reaction after three days.

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[8] The volumes of acetic acid necessary to attain a *p*H of 4.2 were determined by previous experiments.

[9] The ionic strength was calculated by assuming that the sodium acetate and potassium chloride were completely dissociated, and that the dissociation constants of ethylmalonic acid and dimethylamine are 1.09 × 10^{-4} and 5.2 × 10^{-4}, respectively. The second dissociation constant of ethylmalonic acid was assumed to be negligible.

[10] Welch, *J. Chem. Soc.*, 257 (1930).

acid over the *p*H range investigated. In acid solutions these reactions were found to be negligible, but in strongly basic solutions there was a noticeable reaction between formaldehyde and the amine.

Reaction of Dimethylaminomethanol with Ethylmalonic Acid.—The buffer, 2.6011 g. (0.01971 mole) of ethylmalonic acid, and 1.0 ml. of dimethylaminomethanol (corresponding to 0.01045 mole of formaldehyde and 0.01162 mole of dimethylamine), were mixed and diluted to 50 ml. at 0°. The reaction was followed in the usual way, and the results are included in Table I. Identical results were obtained when an induction period of twelve hours was allowed before the addition of the ethylmalonic acid.

Results

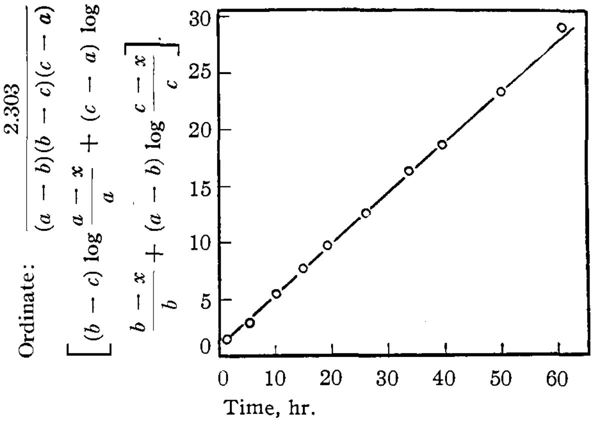


Fig. 2.—Plot for determining the order of the reaction, Run 27(see Fig. 1).

By plotting the function

$$\frac{2.303}{(a-b)(b-c)(c-a)}\left[(b-c)\log\frac{a-x}{a} + (c-a)\log\frac{b-x}{b} + (a-b)\log\frac{c-x}{c}\right]$$

against the time for the runs listed in Table I, straight lines were obtained. A typical line is shown in Fig. 2. In the above expression, a is the initial concentration of formaldehyde, b the initial concentration of dimethylamine, c the initial concentration of ethylmalonic acid, and x is the change in concentration of any of these components as calculated from the formaldehyde remaining in the solution. All concentrations are expressed in moles per liter. In no case was the scattering of points from the straight lines greater than experimental error, or was there a trend away from these lines as the reaction proceeded, even in the case where it was allowed to proceed to 80% of completion. This relationship indicates that at constant *p*H the reaction obeys the rate equation

$$dx/dt = k(a-x)(b-x)(c-x)$$

where t is the time in hours and k is the specific rate constant in liters^2/mole^2 hr. The kinetics of the reaction is, therefore, first order in each of the components and third order over-all. A value of 0.360 ± 0.033 was obtained for k at 0.09 ± 0.27°. Third order kinetics was followed only when the formaldehyde and amine were mixed and allowed to stand for twelve hours before the addition of the ethylmalonic acid. When all three components were mixed at once, complex reaction curves were obtained (Fig. 1). Although the ionic strength in these runs varied from 1.16 to 1.39, it can be seen that the rate constant is independent of ionic strength over this range, since an increase from 1.26 (runs 30 and 51) to 2.60 (run 54) in otherwise similar runs had no effect upon k. The ionic strength was not increased further because of the insolubility of potassium chloride, the neutral salt added. The reaction is non-reversible, and since no appreciable reaction was detected between formaldehyde and either dimethylamine or ethylmalonic acid in the *p*H range of 3 to 8, the disappearance of formaldehyde from the reaction solution was taken as a true measure of the extent of the Mannich reaction under these conditions.

In Table II are listed the third order rate constants calculated for runs at various *p*H values. It can be seen that the rate is critically dependent on *p*H, and passed through a maximum at about *p*H 3.8. In Fig. 3 the specific rate constant, k, is plotted against *p*H.

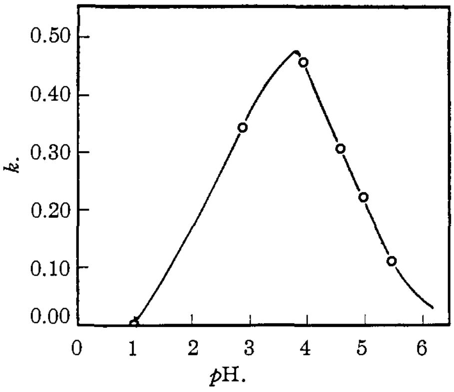


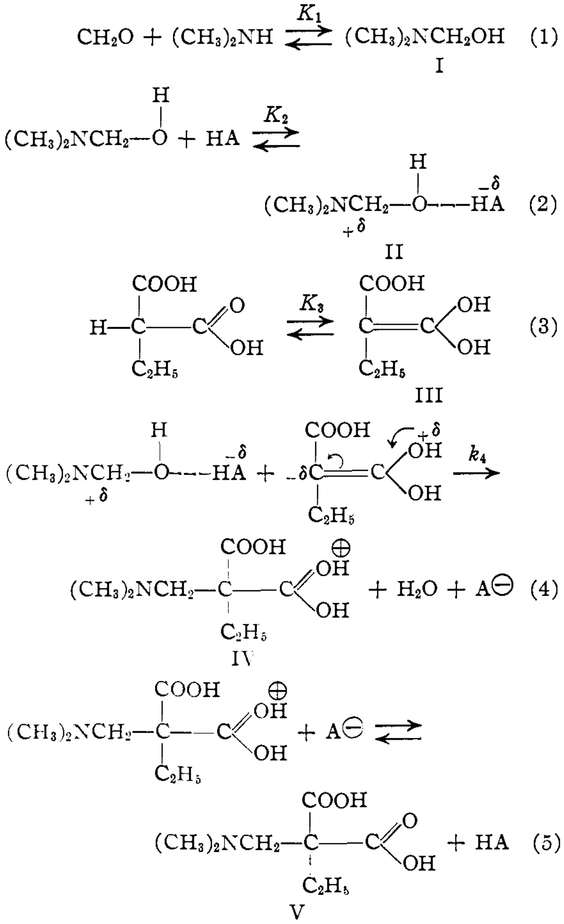
Fig. 3.

From runs 44 and 49 made at 0.48 ± 0.17°, it can be seen that the use of dimethylaminomethanol in place of formaldehyde and dimethylamine has no effect on the kinetics or on the rate constant of the reaction. The third order rate constants obtained were 0.431 (run 44) in which dimethylaminomethanol was used) and 0.410 (run 49 in which formaldehyde and dimethylamine were used), and these values are within the limits of experimental variation.

Discussion

Since it is quite possible that the Mannich reaction proceeds by different mechanisms depending on the number of replaceable hydrogen atoms and on the experimental conditions, this phase of our study was limited to an investigation of the behavior of a compound containing a methynyl group. Several compounds were tested in attempting to find one suitable for kinetic studies. In acid solution, antipyrine and indole condense with formaldehyde even in the absence of dimethylamine. Isobutyraldehyde interferes with the formaldehyde determination, and phenylacetylene reacts best in a non-aqueous, heterogeneous system. Ethylmalonic acid was used since it has none of these disadvantages, and it reacts in good yields under mild conditions. The temperature was kept at 0° to avoid decarboxylation of the dimethylaminomethylethylmalonic acid.

The most striking feature of the experimental data is that the Mannich reaction of ethylmalonic acid follows third order kinetics. Any mechanism must take this fact into consideration. While there are other reaction sequences which follow third order kinetics, two of which will be mentioned later, one mechanism consistent with our results is



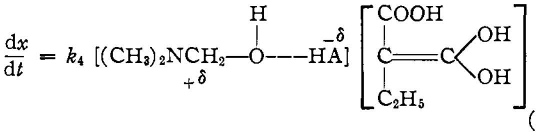
In these equations HA represents any acid present in the system.

Thus the reaction may be considered to be initiated by the reversible addition of dimethylamine and formaldehyde to give dimethylaminomethanol (I). In the presence of an acid HA, a reactive, hydrogen bonded addition complex (II) could be formed. A properly oriented collision of II with ethylmalonic acid, probably in the transitory enol form (III), would produce water, the conjugate base $A^{\ominus}$ and a protonated molecule of dimethylaminomethylethylmalonic acid (IV). Reaction of IV with the conjugate base $A^{\ominus}$ would give the free amino acid V.

The rate determining step of the over-all process is that represented by equation 4 since the rate is dependent upon the concentration of all three components and upon the concentration of acid present in the reaction mixture (Fig. 3).

Apparently, however, the rate of the establishment of the equilibrium of equation 1 is faster than but still in the same range as that of equation 4 since the initial over-all rate of the reaction was slower when all of the reagents were mixed at once than when the amine and formaldehyde were allowed to stand together for twelve hours before adding the ethylmalonic acid (Fig. 1). Presumably, in those reactions in which the amine and formaldehyde were not allowed to come to equilibrium, the initial concentration of complex II was small. Once equilibrium was established, however, it was not disturbed by the reaction of II with ethylmalonic acid. In order to obtain pure third order kinetics all of the equilibria must be established and maintained throughout the reaction.

From the above scheme it can be seen that


(6)

and, making the appropriate substitutions

$$dx/dt = K_1K_2K_3k_4[CH_2O][(CH_3)_2NH][C_2H_5CH(COOH)_2][HA] \quad (7)$$

At constant acid concentration this reduces to:

$$dx/dt = k[CH_2O][(CH_3)_2NH][C_2H_5CH(COOH)_2] \quad (8)$$

The complex variation of the rate of reaction upon *p*H indicates general acid catalysis.[11] Qualitatively, the reaction is acid catalyzed as shown by equation 7, but an increase in acid concentration decreases the concentration of the free amine and the free amine also enters into the reaction. It is presumably a superposition of these two effects which gives rise to the type of curve illustrated in Fig. 3). General acid catalysis explains the spread in rate constants at constant *p*H as the concentrations of ethylmalonic acid and dimethylamine are varied. To maintain a *p*H of 4.2 the amount of acetic acid in the buffer was varied, and thus the concentration of at least one of the acid catalysts was changed without being considered in the rate equation. It is therefore not surprising that there is a small spread in the rate constants (Table I).

While third order kinetics for the Mannich reaction merely supports the mechanism which was

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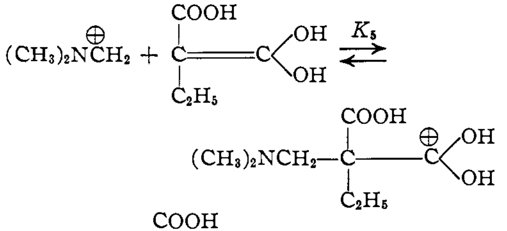
[11] Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, pp. 329-333.

proposed in equations 1–5, two facts strongly imply the formation of dimethylaminomethanol as an intermediate. First, under the experimental conditions employed, the reaction of formaldehyde with ethylmalonic acid was found to be negligible when followed by the methone method of analysis for formaldehyde. Since this method gave a negative test for formaldehyde in the presence of ethyl hydroxymethylethylmalonate, it is probable that any reaction between formaldehyde and ethylmalonic acid to form the corresponding hydroxymethyl acid would be detected by this method. Consequently, mechanisms based upon the preliminary condensation between these two components have been eliminated from consideration. Second, not only is the formation of some necessary intermediate between the amine and formaldehyde indicated (Fig. 1), but also it appears to be of the methylolamine type. It is particularly significant that smooth third order curves are obtained from formaldehyde, dimethylamine and ethylmalonic acid only after allowing the amine and formaldehyde to stand together for twelve hours. With dimethylaminomethanol, however, the preliminary equilibration may be omitted and the rate constant is identical with that obtained from dimethylamine, formaldehyde and ethylmalonic acid. It is clear, therefore, that dimethylaminomethanol does not react by a preliminary hydrolysis to dimethylamine and formaldehyde, and the identity of the rate constants suggests that dimethylaminomethanol is an actual intermediate in the process. Equations 2–5 illustrate the sequence which seems to be the most probable for the reaction of dimethylaminomethanol with ethylmalonic acid.

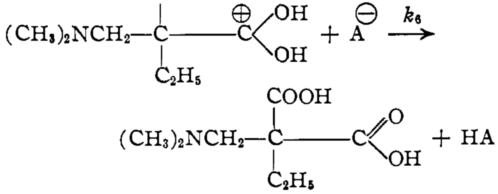
There are a number of other mechanisms which we have considered and rejected. The reaction may be assumed to proceed by the attack of a free carbonium ion upon the enol form of ethylmalonic acid

$$(CH_3)_2NH + CH_2O \overset{K_1}{\rightleftarrows} (CH_3)_2NCH_2OH \quad (9)$$

$$(CH_3)_2NCH_2OH + HA \overset{K_4}{\rightleftarrows} (CH_3)_2\overset{\oplus}{N}CH_2 + H_2O + \overset{\ominus}{A} \quad (10)$$

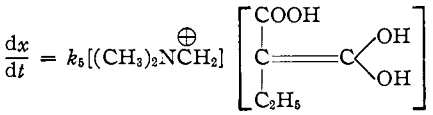


$$(CH_3)_2\overset{\oplus}{N}CH_2 + \underset{C_2H_5}{\overset{COOH}{C}}{=}C\begin{matrix}OH\\OH\end{matrix} \overset{K_5}{\rightleftarrows} (CH_3)_2NCH_2{-}\underset{C_2H_5}{\overset{COOH}{C}}{-}\overset{\oplus}{C}\begin{matrix}OH\\OH\end{matrix} \quad (11)$$



$$(CH_3)_2NCH_2{-}\underset{C_2H_5}{\overset{COOH}{C}}{-}\overset{\oplus}{C}\begin{matrix}OH\\OH\end{matrix} + \overset{\ominus}{A} \xrightarrow{k_6} (CH_3)_2NCH_2{-}\underset{C_2H_5}{\overset{COOH}{C}}{-}C\begin{matrix}{=}O\\OH\end{matrix} + HA \quad (12)$$

This series of equations, however, requires equation 12 to be the slowest step in the sequence for if equation 11 were non-reversible and rate determining the over-all rate equations would be



$$\frac{dx}{dt} = k_5[(CH_3)_2\overset{\oplus}{N}CH_2]\left[\underset{C_2H_5}{\overset{COOH}{C}}{=}C\begin{matrix}OH\\OH\end{matrix}\right]$$

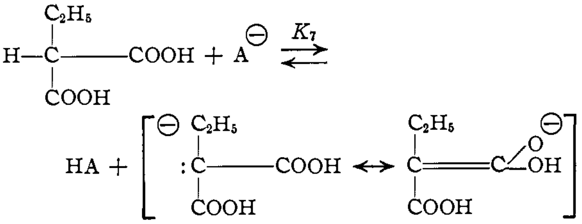
$$= k_5K_1K_3K_4[CH_2O][(CH_3)_2NH][C_2H_5CH(COOH)_2] \\ [HA]/[A^{\ominus}]$$

and since

$$[OH_3^{\oplus}][A^{\ominus}]/[HA] = Ka$$

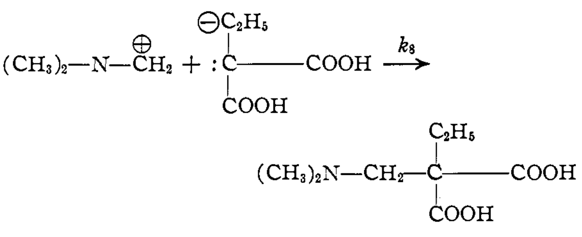
this reduces to specific oxonium ion catalysis which does not explain the complex variation of rate constant with *p*H which was found. It seems improbable that reaction 12 could be considered the rate determining step of the entire sequence since this involves a reaction between the conjugate acid of a carboxylic acid group (presumably a very strong acid) and a base such as acetate ion.

Another attractive mechanism[12] suggests that reaction occurs between a carbanion formed from ethylmalonic acid and the carbonium ion shown in equation 10. This hypothesis also has certain disadvantages. First, if the transition complex of the rate determining step involves the neutralization of unit charges, an increase in ionic strength should decrease strongly the rate of reaction.[13] This was not observed (run 54, Table I). Second, if carbanion formation exhibits general acid-base catalysis



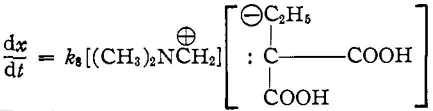
$$H{-}\underset{COOH}{\overset{C_2H_5}{C}}{-}COOH + \overset{\ominus}{A} \overset{K_7}{\rightleftarrows} HA + \left[\overset{\ominus}{:}\underset{COOH}{\overset{C_2H_5}{C}}{-}COOH \longleftrightarrow \underset{COOH}{\overset{C_2H_5}{C}}{=}C\begin{matrix}O^{\ominus}\\OH\end{matrix}\right]$$

and if the rate determining step is between a carbonium ion and a carbanion



$$(CH_3)_2{-}\overset{\oplus}{N}{-}CH_2 + :\underset{COOH}{\overset{\ominus C_2H_5}{C}}{-}COOH \xrightarrow{k_8} (CH_3)_2N{-}CH_2{-}\underset{COOH}{\overset{C_2H_5}{C}}{-}COOH$$

then the rate of reaction can be expressed by the equation



$$\frac{dx}{dt} = k_8[(CH_3)_2\overset{\oplus}{N}CH_2]\left[:\underset{COOH}{\overset{\ominus C_2H_5}{C}}{-}COOH\right]$$

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[12] Lieberman and Wagner, Abstracts of Papers, Third Meeting-in-Miniature of the American Chemical Society, Philadelphia, Pennsylvania, 1949, p. 49.

[13] Hughes, *Trans. Faraday Soc.*, **37**, 609 (1941).

Upon making the appropriate substitutions the expression becomes independent of the concentration of acid HA. This is also contrary to fact.

The mechanism outlined in equations 1–5 is interesting in view of the fact that in basic solution antipyrine has been reported to give a poorer yield of 4-dimethylaminomethylantipyrine with dimethylaminomethanol than with dimethylamine and formaldehyde under similar conditions.[14] This was interpreted to mean that the reaction did not proceed through the primary condensation of the amine with formaldehyde. We have repeated the experiments and have verified these results. While we do not, as yet, understand their significance to the base catalyzed transformation, it is clear that they have no bearing on our reaction carried out in acid solution. We have shown that the kinetics is unchanged when formaldehyde and dimethylamine are replaced by dimethylaminomethanol.

Summary

1. In acid solution the Mannich reaction of ethylmalonic acid, formaldehyde and dimethylamine, follows third order kinetics, first order in each of the three components.

2. The rate of reaction shows a critical dependence on *p*H. It passes through a maximum at about *p*H 3.8.

3. Under the conditions of our experiments, no reaction takes place between ethylmalonic acid and formaldehyde.

4. Smooth, third order curves are obtained for the reaction only if the amine and formaldehyde are mixed and allowed to stand for twelve hours before adding the ethylmalonic acid, but if the formaldehyde and dimethylamine are replaced by dimethylaminomethanol, the reagents may all be mixed at once.

These facts are in agreement with an ionic mechanism for the Mannich reaction of methynyl compounds, based upon a primary condensation of formaldehyde with the amine.

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[14] Bodendorf and Koralewski, *Arch. Pharm.*, **271**, 101 (1933).

[CONTRIBUTION FROM THE VENABLE CHEMICAL LABORATORY OF THE UNIVERSITY OF NORTH CAROLINA]

The Preparation of 5,5'- and 7,7'-Difluoroindigo

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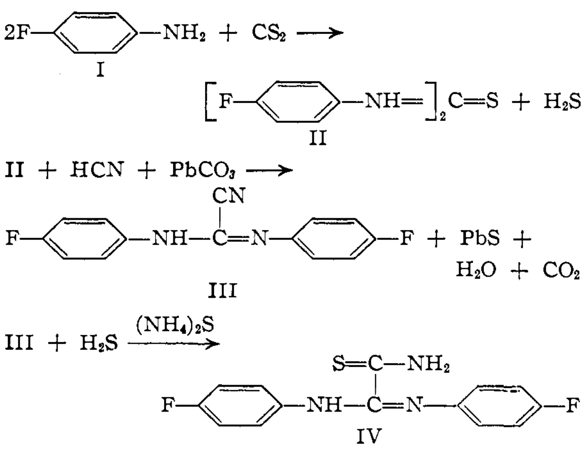
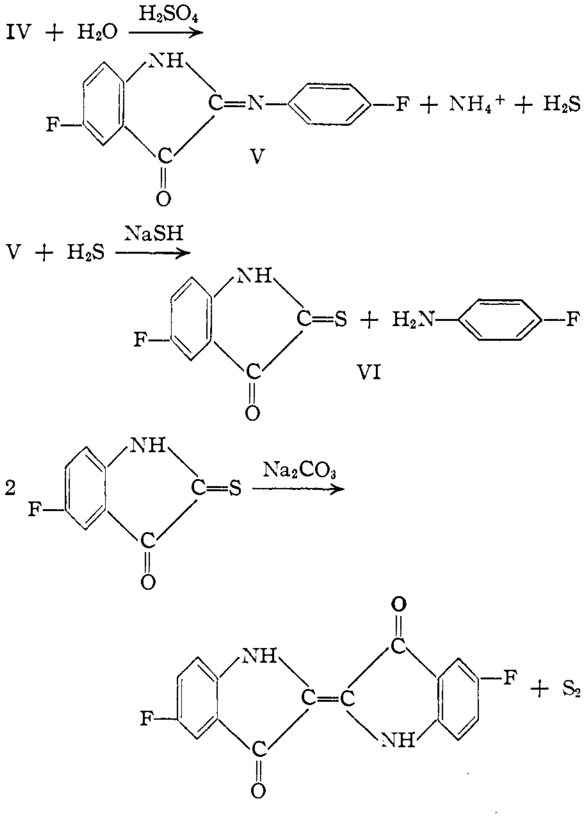
The preparation of several fluoroindigos was undertaken as part of a study of aromatic and heterocyclic fluorine compounds being carried out in this Laboratory. The method of Sandmeyer[1] was found to be the most satisfactory way to prepare these compounds; 5,5'- and 7,7'-difluoroindigo were prepared from *p*-fluoroaniline and *o*-fluoroaniline, respectively, by this method. The preparation of 5,5'-difluoroindigo is outlined in the accompanying equations.





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[1] (a) Sandmeyer, *Z. Farb. Text. Chem.*, **2**, 129 (1903); *J. Chem. Soc. Abst.*, **84**, I, 486 (1903); (b) Fierz-David, "Dye Chemistry," J. A. Churchill, London, 1921, p. 161–167.