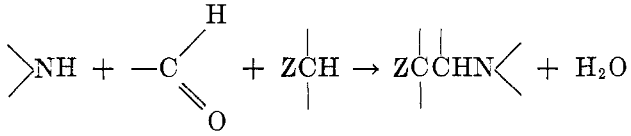
[Contribution from the Department of Chemistry and Chemical Engineering of the University of Pennsylvania]

THE COURSE OF THE MANNICH REACTION[1]

S. V. LIEBERMAN[2] and E. C. WAGNER

Received February 14, 1949

The Mannich reaction (1) may be represented in generalized form:



$$\rangle NH + -\overset{H}{\underset{\| O}{C}} + Z\overset{|}{\underset{|}{C}}H \rightarrow Z\overset{|}{\underset{|}{C}}\overset{|}{C}HN\langle + H_2O$$

I II III XI

in which I is a primary or secondary amine or ammonia, II is usually formaldehyde, though other aldehydes have been used (2), and III is a compound containing activated hydrogen on carbon (1, 3, 4, 5); similar condensations may occur when activated hydrogen is on nitrogen (6). The course of the reaction has proved elusive. Bodendorf and Koralewski (7) tested experimentally the hypothesis that the initial step is the condensation of formaldehyde (II) with either I or III to yield $Z\overset{|}{\underset{|}{C}}CH_2OH$ (V) or $-\overset{|}{N}CH_2OH$ (VI), but concluded that neither hydroxymethyl compound satisfies fully the requirements of an intermediate. The suggestion of Cromwell (8) that in alcohol solution the intermediate may be the ether of VI, and the discussion of the manner of interaction of nitroparaffins, formaldehyde, and amines, by Johnson (2d), led to no tested conclusion of sufficient scope to account for the Mannich reaction.

The view that methylene-*bis*-amine (VII) may serve as intermediate has not been suggested hitherto but is entirely plausible. Feldman and Wagner (6) obtained Mannich bases by interaction of phenols with methylene-*bis*-amines, as well as with amines and formaldehyde. Methylene-*bis*-amines can form under the usual conditions of the Mannich reaction. An accumulation of evidence showing that in presence of acid methylene-*bis*-amines (VII) participate in reactions involving the grouping $R\overset{|}{N}CH_2-$ led to the conclusion (9) that in acid-induced reactions an alkylidene-*bis*-amine may accept a proton to form a salt (such salts are known) which by loss of amine leaves a carbenium ion $R\overset{|}{N}CH_2^+$. The same ion is obtainable from VI in analogous manner (with elimination of water), and also from a Schiff base by addition of proton (9). These preliminary operations are shown in Figure 1. The assumption that these condensation products may yield a common ion is consistent with the observation that all three

---

[1] Constructed from the Ph.D. dissertation of S. V. Lieberman, University of Pennsylvania, 1948. Presented in brief before the Philadelphia miniature meeting of the American Chemical Society, January 20, 1949.

[2] Present address: Wyeth Institute of Applied Biochemistry, 900 North Broad Street, Philadelphia.

can be used interchangeably in certain reactions which involve the grouping $\mathrm{R}\overset{|}{\mathrm{N}}\mathrm{CH_2}$—. In view of the fact that this grouping is formed during the Mannich reaction, it seemed desirable to test experimentally the hypothesis that the methylene-*bis*-amine is eligible to function as intermediate. Its eligibility was established by successful use of methylene-*bis*-amines in abbreviated Mannich reactions. There were used in this way the methylene-*bis*-amines of piperidine, morpholine, and dibenzylamine. As reactant III there were used acetophenone, antipyrine, β-naphthol, dibenzoylmethane, and dimethyldihydroresorcinol (methone). For comparison, ordinary Mannich reactions were run with formaldehyde, amine, and the same compound of type III. In all cases the two procedures yielded the same products and, for similarly favorable conditions, in approximately the same amounts (Tables I and II). The reactions thus realized with VII and III, and with I, II, and III, yielded the following normal Mannich products: β-piperidinopropiophenone, 4-piperidinomethylantipyrine, 4-dibenzylaminomethylantipyrine, 4-morpholinomethylantipyrine, 1-dibenzylaminomethylnaphthol-2, and 1-morpholinomethylnaphthol-2; Feldman and Wagner (6) obtained analogous Mannich bases from naphthol-1 and naphthol-2 and carvacrol, using the methylene-*bis*-amines from piperidine, *p*-toluidine, and *p*-chloroaniline. When III was dibenzoylmethane or methone both dibenzylamine or morpholine with formaldehyde and their methylene-*bis*-amines yielded not the Mannich bases but secondary compounds of familiar types, *viz.*, 1,1,3,3-tetrabenzoylpropane and methylene-*bis*-methone. It is interesting to note that 1,1,3,3-tetrabenzoylpropane was obtained by Wesenberg (11) from dibenzoylmethane and formaldehyde, but only in the presence of piperidine or dimethylamine as "catalyst", and that Desai (12) found piperidine to catalyze condensations of aldehydes with methone. These are presumed to be Mannich reactions each followed by elimination of amine in a further condensation to yield a bimolecular methylene compound; although proof of an intermediate Mannich base is lacking, these reactions respond to alkaline and acidic catalysis in much the same manner as other Mannich reactions. The Knoevenagel reaction, when catalyzed by primary or secondary amines, may follow a similar course. Several of the reactions of methylene-*bis*-amines were realized under rigorously anhydrous conditions, and were therefore not due to formaldehyde produced hydrolytically from VII by small amounts of water operating cyclically. The hydroxymethyl amine (VI), probably the primary product of condensation of amine and aldehyde, was shown by Bodendorf and Koralewski (7) to give subnormal yields of Mannich products. It is easily converted to methylene-*bis*-amine except in presence of excess of aldehyde (10). Since, as shown later, excess of aldehyde does not promote the Mannich reaction (when conditions otherwise are favorable), a preference for VII as the active intermediate is justified, though because of a result discussed later VI cannot be entirely excluded.

That these reactions of methylene-*bis*-amines or hydroxymethyl amines are induced by proton attack and may involve ion X is inferable from the fact that under mild conditions they occur only in presence of some acidic compound,[3] which may be hydrochloric acid, or III, or even ammonium chloride.[4] The existence of ion X cannot be demonstrated experimentally, but assumption of such an intermediate has permitted rationalization of a number of superficially diverse acid-induced reactions of aldehydes with primary or secondary amines, or of corresponding methylene-*bis*-amines or Schiff bases previously studied in this laboratory (6, 13, 14, 15).

Compound III is in some degree acidic and is the source of ion IV which finally unites with ion X to form the Mannich base. If III is frankly acidic (*e.g.*, a phenol) it can participate in Mannich reactions under mild conditions and in absence of added acid (6) or even in presence of alkali in small amount (4).

The simultaneous formation of cation X and of anion IV requires, or may be subject to, a dual catalysis in an amphoteric system. This is possible during a Mannich reaction, for one reactant is a base and one is in some degree an acid, and added acid (if not more than equivalent to the amine) is not free, but throughout the reaction is combined more or less completely with amine I, with any basic intermediates, and with the Mannich base. Compound III, when sufficiently acidic, may induce reaction in absence of added acid, and conversely the basic components of the mixture may promote formation of ion IV. The acid-base relationships suitable for individual Mannich reactions can be associated qualitatively with differences in the acid characters of compounds of type III and in the basic characters of the amines used. Optimum initial acid-base relationships thus established semi-empirically may not persist throughout the reaction but may change progressively as I and III are consumed in formation of the Mannich base. Experimental results support this view, for with favorable acid-base relationships Mannich reactions gave good yields in relatively short periods, but when conditions were initially less favorable, or became so, reactions were slow and yields low in the same periods of time, though improved if reaction periods were considerably extended. This effect of time is consistent with the reaction course suggested, for in it the Mannich base is represented as a terminal compound. The view that decrease in reaction rate is due to depletion of the mixture with respect to a primary reactant is represented by the common practice of

---

[3] Reaction of methylene-*bis*-amine can be forced in absence of acid by operation at higher temperature; antipyrine and methylene-*bis*-dibenzylamine at 150–160° and in absence of added acid formed 4-(dibenzylaminomethyl)antipyrine in high yield (Table II). The thermally induced reaction may involve either the radical R_2NCH_2— or thermal dissociation of antipyrine as an acid. Methylene-*bis*-amines of the type $ArNHCH_2NHAr$ are thermally cleaved in part during distillation (17), forming some amine and Schiff base which appears as trimer. Compounds of the type $R_2NCH_2NR_2$ cannot undergo similar cleavage into isolable products, but in presence of compounds with reactive hydrogen, and capable of involvement with the cleavage fragments R_2N and CH_2NR_2, thermally induced reactions may yield the same products as do acid-induced reactions (9).

[4] The effectiveness of ammonium chloride at room temperature is slight, but at somewhat elevated temperatures its influence may be marked (Table I). A slow evolution of ammonia from the predominantly basic reaction mixture suggests that the action of ammonium chloride is not specific but is due to hydrogen chloride.

introducing additional formaldehyde during the reaction period. Since under favorable conditions the best yields were obtained when reactants were taken in equivalent quantities, it seems that decrease in reaction rate is not a merely statistical effect but is a result of deteriorating acid-base relationships, which interfere by obstructing the condensation of amine and aldehyde.

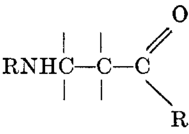
The acid-base relationships in the Mannich reaction, hitherto neglected, seem to be essential to an understanding of the process. They constitute in each case a controllable variable which affects the rapidity and degree of completeness of the reaction, and this view is capable of experimental testing. Reactions leading to ion X require presence of acid in at least catalytic amount, but amine-aldehyde condensations are impeded by excess acid,[5] which will operate also to depress formation of ion IV. It follows that for each set of reactants there should be some optimum concentration of acid and also some concentration above which the formation of Mannich base will be impeded or checked. This was verified experimentally for the reactions of antipyrine, naphthol-2, and dibenzoylmethane with formaldehyde and the amines morpholine and dibenzylamine (Table I), which were progressively slowed and in most cases finally inhibited by increasing amounts of acid. The effect of added alkali upon condensation of amine and aldehyde is not obstructive (17), but alkali sufficient to depolarize most of the protons present will check formation of ion X and prevent the Mannich reaction, even though formation of IV is favored. This also was verified experimentally for the reactants named (Table I). It is believed that these experimental results afford significant support for the proposed reaction course which made them predictable.

Retention of the hydroxymethyl amine (VI) as a possible intermediate seems advisable because in absence of added acid addition of formaldehyde to a mixture of antipyrine and dibenzylamine led to formation of methylene-*bis*-dibenzylamine and a small amount of the Mannich base, though methylene-*bis*-dibenzylamine and antipyrine failed to react, and no reaction occurred when antipyrine was added to a mixture of dibenzylamine and formaldehyde. In the first case a little Mannich base was obtained by a path other than *via* the methylene-*bis*-amine (here inoperative in absence of acid stronger than antipyrine), and this may involve compound VI, though hydroxymethyldibenzylamine is a compound thus far not reported [*cf.*(10)].

The final step in the reaction (union of polar fragments IV and X) is probably substantially irreversible, but this cannot be asserted dogmatically in view of the reversibility of certain carbon-carbon condensations such as those leading to diacetone alcohol,[6] aldols, etc. The carbon-carbon bonds established in the

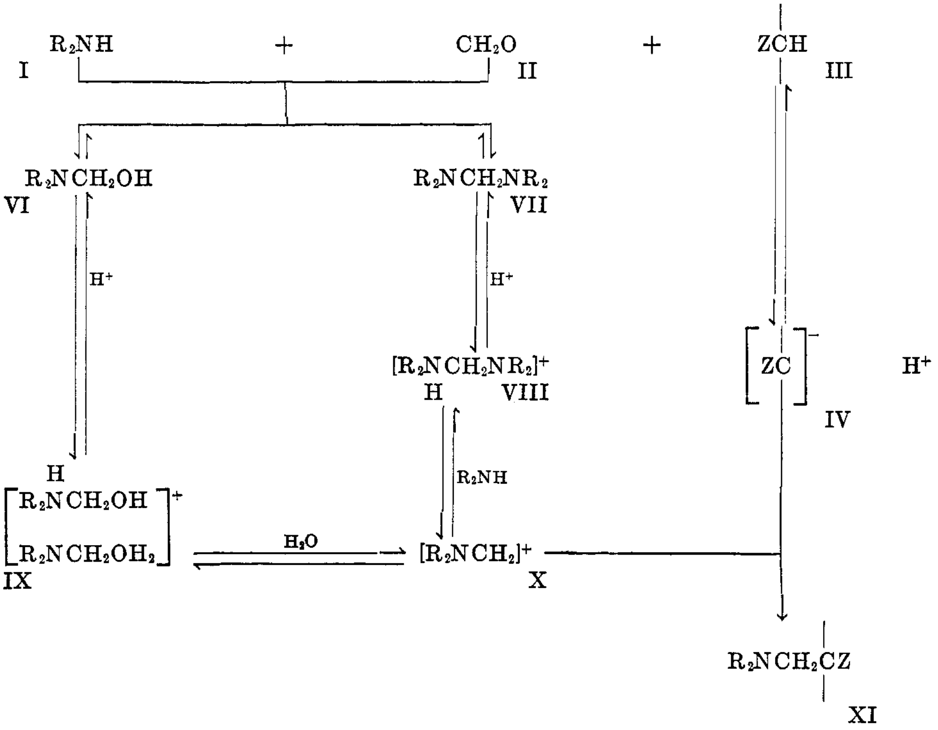
---

[5] Methylene-*bis*-arylamines, and also Schiff bases derived from arylamines, may not persist owing to secondary reactions.

[6] Mannich bases of the type  $\mathrm{RNH}\overset{|}{\underset{|}{\mathrm{C}}}{-}\overset{|}{\underset{|}{\mathrm{C}}}{-}\mathrm{C}(=\mathrm{O})\mathrm{R}$, retaining a reactive hydrogen, are nitrogen system analogs of diacetone alcohol and may form reversibly.

Mannich reactions studied appear to be resistant to cleavage, but the carbon-nitrogen bonds could be cleaved. When 1-(dibenzylaminomethyl)naphthol-2 was heated with morpholine the product was 1-(morpholinomethyl)naphthol-2; when the latter was heated with dibenzoylmethane the morpholine unit was displaced, yielding 1-(2,2-dibenzoylethyl)naphthol-2. The use of Mannich bases for alkylations involves similar exchanges, which may be attributed to carbenium ions (X) or to a direct replacement mechanism, the latter suggested by Snyder and Eliel (16). The course of the Mannich reaction, derived as explained above, is shown in Figure 1.

FIGURE 1. THE COURSE OF THE MANNICH REACTION[a]



[a] Representation of I as a secondary amine and II as formaldehyde are restrictions imposed for simplicity. If I is a primary amine, the initial condensation product may be the Schiff base $RN{=}CH_2$, which by addition of H^+ may yield X (9).

Experiments to test the rate of interaction of antipyrine, morpholine, and formaldehyde under uniform conditions led to yields determined with insufficient accuracy to permit estimation of rate or the order of the reaction, but it is clear that with reactants in equivalent amounts the rate is initially high and decreases rapidly, though reaction may continue during a considerable further period. The optimum acid-base relationships in any case, and the advisability or admissibility of adding acid or alkali, depend upon the basic character of I and the acidic character of III. The results reported point to the conclusions (a) that with increasing basicity of I the favorable influence of acid, and the amount that may be added profitably, decreases and that of alkali increases, (b) that with increasing acidity of III the favorable influence of acid decreases and that of alkali increases, and (c) that Mannich reactions which require considerable initial acidity may give maximum yields in reasonable periods only if a compensatory increase in the amount of an initial reactant is made during or at the outset of the reaction, or if the concentration of acid is progressively decreased by neutralization as reaction proceeds.

EXPERIMENTAL

Melting points reported are corrected values. Elementary analyses were performed by Sarah M. Woods. New compounds are designated by asterisk*. Constants for chemicals used, and references for their preparations, are as follows: Morpholine and piperidine, fractions of b.p. 127–128° and 105–105.5°, respectively; dibenzoylmethane (18), m.p. 77–78°; methylene-*bis*-piperidine (6) and methylene-*bis*-morpholine (9), b.p. 78–79° (1 mm.) and 136° (20 mm.), respectively; methylene-*bis*-dibenzylamine (19) after crystallization melted at 97–98°, a value slightly low, so identity was confirmed by analysis: Calc'd: C, 85.8; H, 7.38; Found: C, 85.8; H, 7.32.

MANNICH REACTIONS. GENERAL PROCEDURES AND EXPERIMENTAL TRIALS

Preparations of piperidinopropiophenone (20) and 4-(piperidinomethyl)antipyrine (21) under usual conditions gave yields of 86% and 66%, but the nature of the isolations did not qualify these reactions for the semiquantitative experiments planned. The examples studied are outlined below. In experiments designed to test the catalytic effects of added acid or alkali the conditions selected for the comparison experiments were such as to give relatively low yields in reactions without added catalyst.

******1-(Dibenzylaminomethyl)naphthol*-2. A solution of 7.2 g. of naphthol-2, 9.85 g. of dibenzylamine in 75 ml. ethanol, and 4.0 ml. of 35% formalin (added last; all reactants 0.05 mole) was heated under reflux for an hour, then chilled; yield 15.8 g. (90%), m.p. 117–117.5° (cryst. from ethanol).

Anal. Calc'd for $C_{25}H_{23}NO$: C, 85.0; H, 6.51; N, 3.97.
Found: C, 85.0; H, 6.40; N, 3.77.

The same compound was obtained from naphthol-2 (1.44 g.; 0.01 mole) and methylene-*bis*-dibenzylamine (4.06 g.; 0.01 mole) by similar treatment; yield 3.0 g. (86%), m.p. 116.5–117°.

**1-(Morpholinomethyl)naphthol*-2. Solutions of 1.44 g. of naphthol-2, 0.9 ml. of morpholine, and 0.8 ml. of formalin (added last; all reactants 0.01 mole) in 25 ml. of 95% ethanol were allowed to stand at room temperature; upon chilling the solution the product crystallized. Reaction periods and yields: 30 min., 49%; 60 min., 74%; 180 min., 82%. After crystallization from ethanol the compound melted at 114.5–115°.

Anal. Calc'd for $C_{15}H_{17}NO_2$: C, 74.1; H, 7.05.
Found: C, 74.0; H, 7.20.

Experiments in the presence of added hydrochloric acid or sodium hydroxide yielded the results included in Table I; these products all melted in the range 113.5–114.5°. The same compound was obtained from naphthol-2 (1.44 g.; 0.01 mole) and methylene-*bis*-morpholine (1.9 g.; 0.1 mole) by similar treatment; yield 1.0 g. (41%), m.p. 112.5–114°. An experiment under anhydrous conditions gave a yield of 39%. The effects of added hydrochloric acid or sodium hydroxide are shown in Table II.

**4-(Dibenzylaminomethyl)antipyrine*. A solution of 1.97 g. of dibenzylamine, 1.88 g. of antipyrine, and 0.8 ml. of formalin (added last; all reactants 0.01 mole) in 20 ml. of ethanol

TABLE I

INFLUENCE OF ACID, BASE, TIME, TEMPERATURE ON YIELDS BY MANNICH REACTION

REACTANTS, SOLVENTS	CATALYST (EQUIV.)			TIME, HRS	TEMP.	YIELD, %
	HCl[a]	NH₄Cl	NaOH[b]			
Naphthol-2, dibenzylamine, HCHO[c] (1:1:1) in 95% ethanol	0	0	0	1	reflux	90[d]
Naphthol-2, morpholine, HCHO (1:1:1) in 95% ethanol	2.0			3	room	0
	1.0			3	"	50[e]
	0.1			3	"	74
	.05			1	"	72
	.01			0.5	"	49
	0	0	0	.5	"	49
	0	0	0	1.0	"	74
	0	0	0	3.0	"	82
			0.01	0.5	"	57
			.05	1	"	71
			.1	3	"	70
			1.0	3	"	30
			2.0	3	"	0
Antipyrine, dibenzylamine, HCHO (1:1:1) in 95% ethanol	1			2	reflux	0
		0.01		2	"	89[f]
	0	0	0	2	"	12
			0.1	2	"	0
			1.0	2	"	0
Antipyrine, morpholine, HCHO (1:1:1) in water	5			24	room	4[g, h]
	3			24	"	17
	2			24	"	42
	1			24	"	72
	0.1			24	"	76
	.01			24	"	48
	0	0	0	24	"	41
			.01	24	"	43
			.1	24	"	44
			1	24	"	36
			5	24	"	11[h]
Dibenzoylmethane, dibenzylamine, HCHO (1:1:1) in ethanol	2			2	reflux	0
	1			2	"	100[i, j]
		0.4		2	room	50
		.2		2	"	45
		.1		2	"	40
		.1		2	reflux	81
		.05		2	room	29, 37
	0	0	0	2	"	37
	0	0	0	18	"	78
	0	0	0	2	reflux	86
			0.05	2	room	81
			.05	18	"	77
			1.4	18	"	0

TABLE I—*Concluded*

REACTANTS, SOLVENTS	CATALYST (EQUIV.)			TIME, HRS.	TEMP.	YIELD, %
	HCl[a]	NH_4Cl	NaOH[b]			
Dibenzoylmethane, morpholine, HCHO (1:1:1) in 95% ethanol	1[k]			2	room	0
	0.1			2	"	28[i]
	.05			2	"	31
	0	0	0	2	"	30
			0.1	2	"	76
			1.0	2	"	0

[a] HCl taken as 0.447 *N* or conc'd HCl. [b] NaOH taken as 4% aqueous sol. [c] Formaldehyde taken as 35% formalin in all experiments. [d] Product is 1-(dibenzylaminomethyl) naphthol-2. [e] Product is 1-(morpholinomethyl)naphthol-2. [f] Product is 4-(dibenzylaminomethyl) antipyrine. [g] Product is 4-(morpholinomethyl)antipyrine. [h] This small yield probably due to reaction during isolation procedure following neutralization. [i] Crude product. [j] Product is 1,1,3,3-tetrabenzoylpropane. [k] Morpholine used as hydrochloride.

was heated under reflux for 2 hours. Hot water was added to incipient turbidity and the mixture was chilled, causing separation of some methylene-*bis*-dibenzylamine. The filtrate was concentrated to about 10 ml., hot water was added to faint turbidity, and the mixture was chilled overnight, yielding 0.5 g. (12%) of dibenzylaminomethylantipyrine, m.p. 122–125°. In the presence of 0.1 equiv. of ammonium chloride the same reactants yielded 3.53 g. (89%) of product, m.p. 126.5–128.5°. During the heating, ammonia was detected in the vapors. Recrystallization from ethanol yielded pure 4-(dibenzylaminomethyl)antipyrine, m.p. 131–132°.

Anal. Calc'd for $C_{26}H_{27}N_3O$: C, 78.6; H, 6.80; N, 10.6.
Found: C, 78.5; H, 6.82; N, 10.5.

By use of dibenzylamine hydrochloride (1 equiv. of acid) with antipyrine and formalin no Mannich base was obtained; the isolated materials were 64% of dibenzylamine hydrochloride and a 74% yield of methylene-*bis*-antipyrine of m.p. 153–154° (22). Antipyrine, dibenzylamine, and formalin in presence of 0.1 equiv. of sodium hydroxide yielded no Mannich base but 80% of methylene-*bis*-dibenzylamine. In presence of 1 equiv. of sodium hydroxide the mixture yielded no solid product. The sensitivity of this reaction to added acid or base is noteworthy; a good yield is obtained only in presence of a small amount of acid (Table I).

4-(Dibenzylaminomethyl)antipyrine was obtained similarly from methylene-*bis*-dibenzylamine (4.06 g., 0.01 mole), antipyrine (1.88 g., 0.01 mole), and ammonium chloride (0.05 g., 0.001 mole) in 20 ml. of ethanol. After heating the mixture for two hours, addition of hot water to turbidity, and chilling, there separated 3.35 g. (84%) of product, m.p. 124–127°. A reaction attempted in absence of ammonium chloride produced no Mannich base, and 96% of the methylene-*bis*-dibenzylamine was recovered.

Reaction under anhydrous conditions. Into a dried flask provided with a reflux condenser and calcium chloride tube, and containing 1.88 g. (0.01 mole) of antipyrine, 4.06 g. (0.01 mole) of methylene-*bis*-dibenzylamine, and 0.3 g. (0.001 mole) of dibenzylamine hydrochloride, there was distilled about 25 ml. of anhydrous ethanol directly from a mixture with sodium ethoxide and diethyl phthalate. After heating under reflux for two hours the mixture was cooled, seeded, and kept overnight in a refrigerator. The product (2.8 g., 70%) melted at 124–128°, and after recrystallization from ethanol, at 131–132°.

A reaction without added catalyst was thermally forced by heating in a sealed tube at 150–160° for 3 hours a mixture of 0.005 mole each of methylene-*bis*-dibenzylamine (2.0 g.)

and antipyrine (0.94 g.). The chilled liquid yielded 1.05 g. (53%) of Mannich base (m.p. 128–130°), and a second crop of 0.68 g. (34%, m.p. 118–124°) was obtained from the filtrate.

4-(Morpholinomethyl)antipyrine. A solution of 1.88 g. of antipyrine and 0.87 g. of morpholine in 20 ml. of water, and with or without added acid or alkali as indicated in Table I, was treated with 0.8 ml. of formalin (all reactants 0.01 mole). After 24 hours at room temperature the mixture was treated with 2 ml. of conc'd hydrochloric acid and any surviving antipyrine was removed by three 10-ml. extractions with chloroform. The aqueous liquid was made alkaline (40% aqueous sodium hydroxide) and 4-(morpholinomethyl)antipyrine was extracted in three 10-ml. portions of chloroform. The combined extracts were dried over potassium carbonate, the solvent was removed under reduced pressure, and the residue was crystallized from 15–20 ml. of ethyl acetate. The products obtained in eleven experiments (Table I) under varied conditions all melted between 128.5° and 130.5°; the m.p. reported for 4-(morpholinomethyl)antipyrine is 131° (23). The fact that a large excess of either acid

TABLE II

MANNICH REACTIONS WITH METHYLENE-*bis*-AMINES

REACTANTS, SOLVENTS	CATALYST (EQUIV.)			TIME, HRS.	TEMP.	YIELD, %
	HCl	NH_4Cl	NaOH			
Napthol-2, methylene-*bis*-dibenzylamine, (1:1) in 95% ethanol	0	0	0	1	reflux	86[a]
Naphthol-2, methylene-*bis*-morpholine (1:1) in 95% ethanol	0.05			1	room	58[b]
	0	0	0	1	"	41
			0.05	1	"	29
Antipyrine, methylene-*bis*-dibenzylamine (1:1) in 95% ethanol		0.1		2	reflux	84[c]
	0	0	0	2	"	0
	0	0	0	3	150–160°	87[d]
Antipyrine, methylene-*bis*-morpholine (1:1) in water	0.1			24	room	22[e]
	.01			24	"	52
	0	0	0	24	"	48
			0.1	24	"	5, 14[f]
			5	24	"	23[f]
Dibenzoylmethane, methylene-*bis*-dibenzylamine (1:1) in ethanol	0	0	0	2	room	28[g]
	0	0	0	2	reflux	88
		0.1		2	room	27
		.1		2	reflux	93
Dibenzoylmethane, methylene-*bis*-morpholine (1:1) in ethanol	0	0	0	2	room	28[g]
	0.1			2	"	32
			0.1	2	"	65

[a] Product identified as 1-(dibenzylaminomethyl)naphthol-2. [b] Product identified as 1-(morpholinomethyl) naphthol-2. [c] Product identified as 4-(dibenzylaminomethyl)antipyrine. [d] Thermally induced reaction. [e] Product identified as 4-(morpholinomethyl) antipyrine. [f] This small yield probably due to reaction during isolation procedure following neutralization. [g] Product identified as 1,1,3,3-tetrabenzoylpropane.

or alkali failed to prevent formation of Mannich base, and also the relatively low sensitivity to changes in acid or alkali, may be attributed to incidental reaction during the isolation procedure when, owing to necessary neutralizations, conditions more favorable than those set for the reaction were temporarily operative.

4-(Morpholinomethyl)antipyrine was obtained also from methylene-*bis*-morpholine and antipyrine as recorded in Table II.

Time-yield experiments. A solution of 18.8 g. (0.1 mole) of antipyrine, 8.7 g. (0.1 mole) of morpholine, and 22 ml. of 0.447 *N* hydrochloric acid (0.01 mole, the optimum amount; see Table I) in 200 ml. of water in a 250-ml. volumetric flask was cooled in an ice-bath, and 8.0 ml. of 35% formalin (0.1 mole of formaldehyde) was added rapidly. The volume was made up to 250 ml. and the flask was placed in a constant temperature bath at 25 ± 0.1°. At intervals 25-ml. aliquots were removed and Mannich base was isolated as outlined above. A uniform procedure was used for these operations and for crystallization from 20 ml. of ethyl acetate. The results of two such experiments are as follows:

Time, min.	20	30	40	60	80	120	160	180	320	360	24 hr.
Exp. 1 Yield, %	—	29	—	31	—	37	—	43	—	59	70
Exp. 2 " "	26	—	32	—	41	—	44	—	54	—	—

1,1,3,3-Tetrabenzoylpropane was obtained as the sole product when dibenzoylmethane was used as compound III with formaldehyde and either dibenzylamine or morpholine. In experiments with dibenzylamine, reactions at room temperature were incomplete in 2 hours, and in 18 hours approached the maximum, which was reached in 2 hours when the mixture was heated under reflux. The product separated when the mixture was chilled. When reactions were incomplete more or less methylene-*bis*-dibenzylamine was present. This was removed by warming the mixture for several minutes with ethanol containing hydrochloric acid (1 conc'd HCl: 40 EtOH). Upon chilling the solution the nearly pure product (m.p. 171–175°) separated. After crystallization from ethanol it was pure, m.p. 175.5–176°. Since this was not the expected product its identity as tetrabenzoylpropane (11) was corroborated by analysis.

Anal. Calc'd for $C_{31}H_{24}O_4$: C, 80.8; H, 5.25;
Found: C, 80.8; H, 5.15.

Results obtained without catalyst and in the presence of varying amounts of acid, ammonium chloride or alkali appear in Table I. This reaction was inhibited by excess of acid or alkali, but otherwise was more affected by temperature than by identity or amount of catalyst, suggesting that tetrabenzoylpropane may not be formed *via* the Mannich base, though the persistence of methylene-*bis*-dibenzylamine in incomplete reactions suggests the reverse. In similar experiments with morpholine (Table I) reaction at room temperature was promoted by 0.1 equiv. of alkali, and was inhibited by excess of either acid or alkali, the effects of catalysts resembling those in the Mannich reactions studied, suggesting a course *via* the Mannich base. Tetrabenzoylpropane was obtained also by interaction of methylene-*bis*-dibenzylamine or methylene-*bis*-morpholine with dibenzoylmethane in equivalent amounts (Table II).

Methylene-bis-methone. Methone (0.7 g., 0.005 mole) and 0.0025 mole of methylene-*bis*-amine (0.45 g. of methylene-*bis*-piperidine, 1.01 g. of methylene-*bis*-dibenzylamine, or 0.47 g. of methylene-*bis*-morpholine) in 10 ml. of 50% ethanol reacted at 100° to yield in 5 minutes 0.5–0.6 g. of methylene-*bis*-methone, which separated upon chilling the solution; m.p. 191–191.5° (12b).

Transposition reactions. 1. Conversion of 1-(dibenzylaminomethyl)naphthol-2 (3.53 g., 0.01 mole) to 1-(morpholinomethyl)naphthol-2 was effected by heating the former with 0.9 ml. (0.01 mole) of morpholine in 20 ml. of 95% ethanol for seven hours under reflux; the product (1.8 g., 77%) separated upon chilling the mixture. The m.p. 105–109° was raised to 113.5–114° by two recrystallizations from ethanol. A mixture with an authentic specimen of

1-(morpholinomethyl)naphthol-2 had the same m.p. 2. Conversion of 1-(morpholinomethyl)naphthol-2 (1.21 g., 0.005 mole) to *1-(2,2-dibenzoylethyl)naphthol-2 was effected by heating the former with dibenzoylmethane (1.12 g., 0.005 mole) in 25 ml. of 95% ethanol in the presence of 0.6 ml. of 0.45 *N* hydrochloric acid for two hours under reflux. On chilling the mixture the crude product (1.0 g., 53%; m.p. 103–109°) separated slowly. Recrystallization from ethanol yielded the pure compound, m.p. 121–121.5°.

Anal. Calc'd for $C_{26}H_{20}O_3$: C, 81.8; H, 5.30.
Found: C, 81.9; H, 5.27.

SUMMARY

The Mannich reaction is believed to involve a dual catalysis in an amphoteric system in which the cation $R_2N\overset{|}{\underset{|}{C}}{}^+$ is formed from the condensation product(s) of amine and carbonyl compound, and combines finally with the anion of the reactive-hydrogen compound. Formation of the cation is induced by added acid or by the acidity of the reactive-hydrogen compound or both. Formation of the anion is promoted by the bases present or by added alkali or both. The inferences that excessive acid would interfere with the primary condensation of amine and carbonyl compound and would depress the ionization tendency of the reactive-hydrogen compound, and that excessive alkali would decrease or prevent formation of the cation $R_2N\overset{|}{\underset{|}{C}}{}^+$, and therefore would obstruct or stop the reaction, were supported experimentally. The probability that the cation originates in the alkylidene-*bis*-amine formed from aldehyde and amine was strengthened by demonstration that methylene-*bis*-amines, used instead of aldehydes and amines, produced normal yields. A suggested reaction scheme which incorporates these views appears to be consistent with available evidence.

PHILADELPHIA 4, PENNA.

REFERENCES

(1) BLICKE, *Org. Reactions*, **1**, 303 (1942).
(2) PECKELHOFF, Dissertation, Stuttgart, 1933; Ger. Patent 510,184; HIERONIMUS, Dissertation, Berlin, 1938; MANNICH AND MOHS, *Ber.*, **39**, 608 (1930); PETRENKO-KRITSCHENKO AND ZONEFF, *Ber.*, **39**, 1358 (1906); *Ber.*, **42**, 3683 (1909).
(3) BLOMQUIST AND SHELLEY, *J. Am. Chem. Soc.*, **70**, 147 (1948); CERF, *Bull. soc. chim.*, (5), **4**, 1451, 1460 (1937); SENKUS, *J. Am. Chem. Soc.*, **68**, 10 (1946); JOHNSON, *J. Am. Chem. Soc.*, **68**, 12, 14 (1946).
(4) BRUSON AND BUTLER, *J. Am. Chem. Soc.*, **68**, 2348 (1946).
(5) HARTOUGH AND MEISEL, *J. Am. Chem. Soc.*, **70**, 4018 (1948).
(6) FELDMAN AND WAGNER, *J. Org. Chem.*, **7**, 31 (1942).
(7) BODENDORF AND KORALEWSKI, *Arch. Pharm.*, **271**, 101 (1933).
(8) CROMWELL, *J. Am. Chem. Soc.*, **68**, 2634 (1946).
(9) MCLAUGHLIN AND WAGNER, *J. Am. Chem. Soc.*, **66**, 251 (1944).
(10) HENRY, *Bull. acad. roy. Belg.*, (3), **28**, 366 (1895).
(11) WESENBERG, Dissertation, Leipzig, 1898, p. 31.
(12)(a) DESAI, *J. Indian Chem. Soc.*, **10**, 663 (1938); (b) HORNING AND HORNING, *J. Org. Chem.*, **11**, 95 (1946).

(13) von Braun, *Ber.*, **41,** 2145 (1908); Wagner, *J. Am. Chem. Soc.*, **56,** 1944 (1934).
(14) Miller and Wagner, *J. Am. Chem. Soc.*, **63,** 832 (1941).
(15) Young and Wagner, *J. Am. Chem. Soc.*, **59,** 854 (1937).
(16) Snyder and Eliel, *J. Am. Chem. Soc.*, **70,** 1703 (1948).
(17) Bischoff and Reinfeld, *Ber.*, **36,** 41 (1903).
(18) *Org. Syntheses*, Coll. Vol. I, 2nd Ed., 199 (1941); *Org. Syntheses*, **20,** 32 (1940).
(19) von Braun and Röver, *Ber.*, **36,** 1196 (1903).
(20) Mannich and Lammering, *Ber.*, **55,** 3510 (1922).
(21) Mannich and Kather, *Arch. Pharm.*, **257,** 18 (1919).
(22) Marcourt, *Bull. soc. chim.*, (3), **15,** 520 (1899).
(23) Harradence and Lions, *J. Proc. Roy. Soc. N.S. Wales*, **72,** 233 (1938).