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Review Article

The Mannich Reaction

Mechanistic and Technological Considerations

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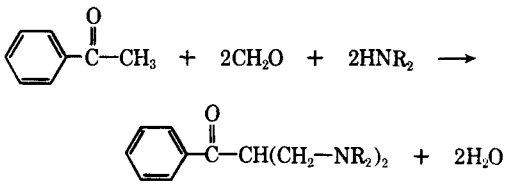
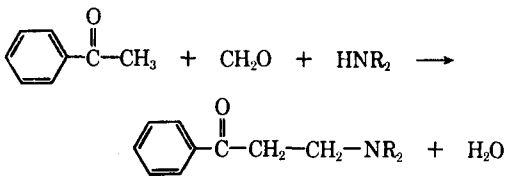
THE EARLIEST EXAMPLES of the Mannich reaction were published in succession by Tollens and co-workers (1, 2), Petrenko-Kritschenko and co-workers (3–6), and by Mannich and Krösche (7). Mannich was the first to recognize the reaction as a general one, and a detailed investigation was begun in 1917. The Mannich reaction was reviewed by Blicke (8), Karbe (9), Nobles (10, 11), Reichert (12), and others (13, 14) and it was the subject of recent books by Reichert (15) and by Hellmann and Optiz (16).

The Mannich reaction consists of the condensation of ammonia or a primary or secondary amine usually as the hydrochloride salt, an aldehyde, and a compound capable of supplying one or more active hydrogen atoms. As a result of the reaction an aminomethyl group generally replaces the active hydrogen atom. Products of the condensation are known as "Mannich bases." A typical condensation, with acetophenone as the active hydrogen compound, may be illustrated as in *Scheme I.*

As cited in the excellent review by Blicke (8), multiple product formation is possible. For example, multiple aminomethylations may occur at the α-position of compounds such as acetophenone of the previous example, *viz.*, *Scheme II.* Similarly, mono- and disubslituted products including position isomers, result from multiple aminomethylation of phenols.[1] In this case the replaceable hydrogens are not all equivalent as indicated in *Scheme III.* These examples illustrate the complications which may result from the presence of multiple replaceable hydrogen atoms in the molecule.



Scheme I



Scheme II

The amine used also promotes formation of mixed products. With secondary amines, only a single product is possible, however, with primary amines and ammonia, reacting ratios of active hydrogen compounds, formaldehyde, and amine may be 2:2:1 and 3:3:1, respectively. In the reaction of antipyrine salicylate, formalde-

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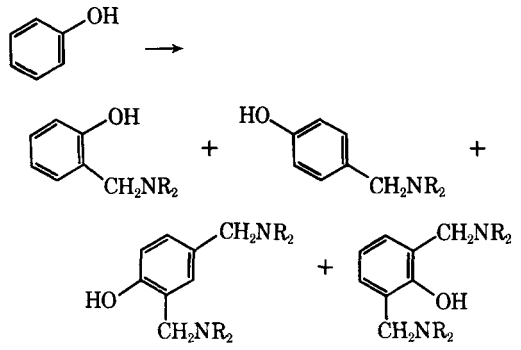
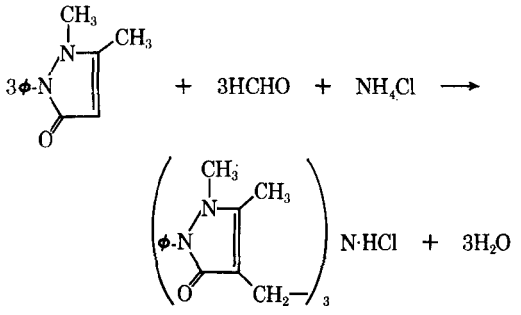
[1] The observation that *ortho*-mono-substitution predominates has been the subject of the mechanistic studies (17, 36).



Scheme III

hyde, and ammonium chloride (7), the reaction which reportedly stimulated Mannich's pioneering interest in the condensation which bears his name, the reaction ratio is 3:3:1, respectively, and may be illustrated as in Scheme IV.



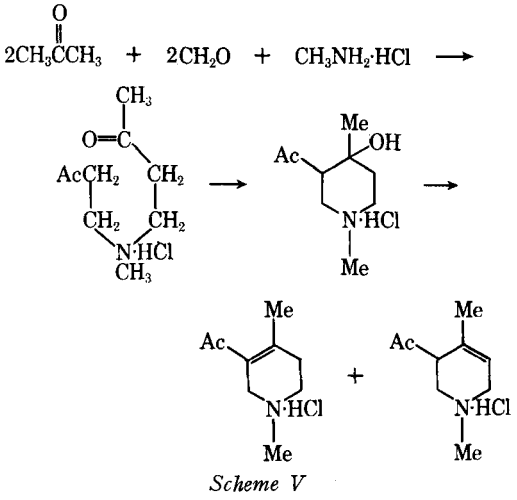
Scheme IV

Gautier *et al.* (18) have reported on the problem of isomer formation associated with utilization of compounds with mixed functionality such as ethynylalkyl aryl ketones as the active hydrogen compound. In this case both the hydrogen of the acetylenic substituent and the ketone's α-hydrogens are reactive under Mannich conditions.

A somewhat different isomer problem is presented in the case of methyl isopropyl ketone in which seemingly sound evidence for aminomethylation of the methyl group (19, 20) and of the isopropyl group (21) have been reported.

In many cases, by-products may be formed by side-reactions. In not a few cases, such processes may occur to the exclusion of normal Mannich reaction or, if sequential to the Mannich reaction, completely destroy the normal products. Such processes include (*a*) formation of α, β-unsaturated ketones (8, 22), a process which could result from deamination (elimination of amine) of the Mannich base, or alternatively, through hydroxymethylation followed by dehydration of the active hydrogen compound; (*b*) formation of methylene-bis derivatives of the active hydrogen compound; and (*c*) formation of methylene-bis-amines or similar compounds. These processes will be discussed within the framework of the Mannich reaction mechanism.

Mannich and Ball (23) and Mannich and Ritsert (24) reported formation of an unstable Mannich base derived from acetone, formaldehyde, and methylamine (2:2:1 reacting ratio). This Mannich base readily cyclizes as Scheme V shows:

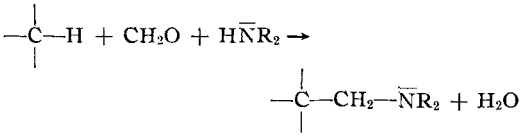


Scheme V

The stability of the products of the Mannich reaction will be covered more thoroughly in the succeeding sections.

MECHANISM OF THE CONDENSATION

The classical examples of the Mannich reaction involved reaction of an active hydrogen compound (reactive $\diagup$C—H $\diagdown$ linkage present) with formaldehyde and ammonia or a primary or secondary amine, *i.e.*, Scheme VI.



Scheme VI

The product, known as a "Mannich base," is an unsymmetrical derivative of methylene. Modern theoretical considerations permit inclusion of acidic $\diagup$NH, —OH, or —SH $\diagdown$ containing compounds as qualified "active hydrogen" compounds susceptible to the Mannich aminomethylation process.

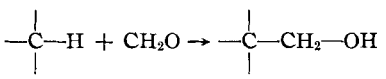
A great deal of work has been done relevant to the progress of the Mannich reaction (17–18, 22, 25–47), and several workers have proposed mechanisms (17, 22, 25, 34, 35, 40–47). A his-

torical development of the mechanism studies will be presented in the following paragraphs.

An evaluation of Scheme VI reveals that formaldehyde, an electrophilic agent, reacts with two nucleophilic components, the amine and a carbanic center derivable from the replaceable hydrogen compound. The product of the Mannich reaction is the result of an unsymmetrical condensation, and any satisfactory mechanism must take this factor into consideration.

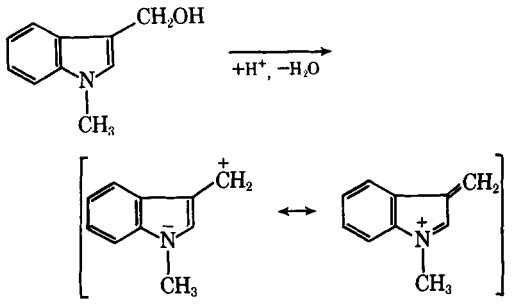
According to Hellmann and Opitz (25), the course of the condensation might be expected to follow one of the following sequences: (*a*) reaction of the labile hydrogen compound with formaldehyde to yield the hydroxymethyl derivative which then condenses with the amine to produce a Mannich base; or (*b*) addition of the amine to formaldehyde to form an *N*-hydroxymethyl or related derivative which then reacts with the labile hydrogen compound to produce a Mannich base.

In consideration of proposition *a*, if the nucleophilicity of the carbanion derived from the labile hydrogen compound be greater than that of the amine, formation of a hydroxymethyl derivative of the labile hydrogen compound would be favored (proposition *a*) over formation of an aminomethylol (proposition *b*). Thus the initial reaction, Scheme VII, would be expected to occur.



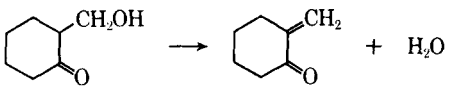
Scheme VII

This hydroxymethyl derivative will now react further if it can form either a resonance-stabilized carbonium ion, *e.g.*, Scheme VIII,



Scheme VIII

or if the loss of water can occur according to Scheme IX.



Scheme IX

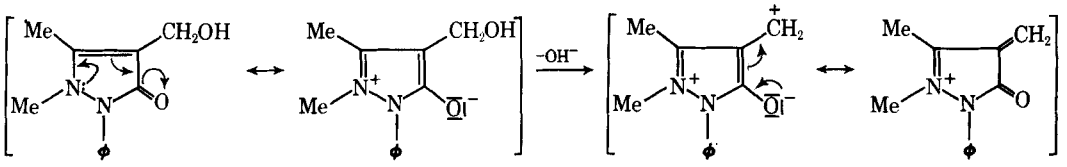
Either of these intermediates, *i.e.*, the resonance-stabilized carbonium ion in Scheme VIII or the unsaturated dehydration product shown in Scheme IX, would then be expected to condense with another molecule of the compound or ion with the highest nucleophilic potential, in this case, the carbanion derived from the labile hydrogen compound. Such a pathway could only lead to a symmetrical methylene derivative of the labile hydrogen compound and not to a Mannich base. If such reasoning is supported by experimental evidence, proposition *a* would seem untenable. Such evidence is available and will be presented below.

4-Hydroxymethylantipyrine, which forms a resonance-stabilized carbonium ion according to Scheme X, was studied by Bodendorf and Koralewski (31) as a possible intermediate in the Mannich reaction. 4-Hydroxymethylantipyrine, according to these workers, does not react with either free amine or with amine hydrochloride. Furthermore, free amine and variable amounts of acid likewise fail to yield the Mannich base of antipyrine. These observations were offered as proof against a hydroxymethyl derivative of the labile hydrogen compound as the intermediate in the Mannich reaction.

In their investigation of the Mannich reaction, Bodendorf and Koralewski (31) reported that the formation of methylene-bis(antipyrine) took place when 4-hydroxymethylantipyrine was warmed with dimethylamine hydrochloride but not with the free base. Hellmann and Opitz (25, 26) reinvestigated, based on the assumption that 4-hydroxymethylantipyrine is not the true intermediate in the Mannich, but that it is an intermediate in the synthesis of methylene-bis(antipyrine). If these be reasonable assumptions, then as the acidity of the media increases the yields of Mannich base and of methylene-bis(antipyrine) should not be coordinated closely. In fact, these workers (26) obtained 11.51% of Mannich base with piperidine, formaldehyde, and antipyrine with no methylene-bis(antipyrine), while piperidine hydrochloride under the same conditions gave 61.54% of Mannich base. When the quantity of acid present reached a 10% excess over the molar requirements, the yield of Mannich base fell to 16.8% and a yield of 9.7% of methylene-bis(antipyrine) also resulted.

While the above results disprove the participation of 4-hydroxymethylantipyrine as a resonance-stabilized derivative (formed *via* Scheme VIII) in the Mannich reaction is it equally unlikely that 2-methenylketones[2] (formed *via*

[2] These α-methenylketones may be viewed as vinylogs of formaldehyde. Free amines, but not their salts, will add to such compounds.



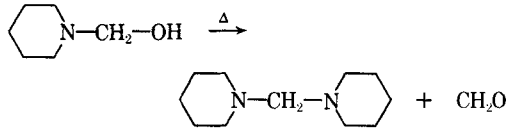
Scheme X

Scheme IX) could represent true intermediates? In answer to this question, such intermediates were discounted since dehydration of hydroxymethyl derivatives of the active hydrogen component often requires temperatures far in excess of those required by the Mannich reaction (25). Furthermore the observation that piperidine, formaldehyde, and cyclohexanone gave a 37% yield of Mannich base (31) while use of piperidine hydrochloride provided a 62% yield (48) appears to rule out addition to an α,β-unsaturated derivative as a possible course.

These data seem conclusive in proving that hydroxymethylation of the active hydrogen component does not represent a true course for the Mannich reaction. The conclusion that may, therefore, be drawn is that proposition *b* above probably is valid. This second postulate, that formaldehyde interacts with the amine as the initial step in the condensation, will now be discussed.

In order to present an effective discussion of the mechanistic aspects of *N*-hydroxymethylamine and related derivatives of aldehyde and amine, a brief discussion of the chemistry of these intermediates based on articles by Henry (49), Stewart and Bradley (50), Hellmann and Opitz (25–30), and by Wagner (51) will be covered below. For a more detailed discussion the reader should consult the original articles.

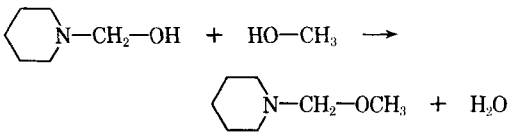
The *N*-hydroxymethylamines, as reported by Henry (49) in 1895, may be obtained from aqueous formaldehyde and the amine with cooling. These oily, nondistillable *N*-hydroxymethylamines are difficult to purify, and exist only in the cold. Warming causes decomposition to formaldehyde and free amine along with some recondensation to form methylenediamine, *e.g.*, Scheme XI.



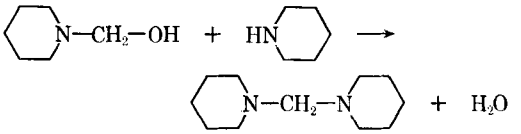
Scheme XI

Methylenediamines are formed exclusively when formaldehyde and amine are allowed to react without cooling.

In contrast to oxygen hemi-acetals, nitrogen hemi-acetals are converted to *O,N*-acetals with alcohols or to *N,N*-acetals (methylenediamine) with amines without added catalysts. For example, Schemes XII and XIII.



Scheme XII



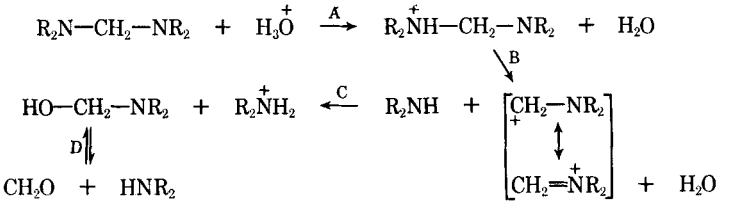
Scheme XIII

The members of both compound classes are very acid-sensitive and follow a well-defined reaction course in acid hydrolysis (50) from the symmetrical methylenediamine as illustrated in Scheme XIV.

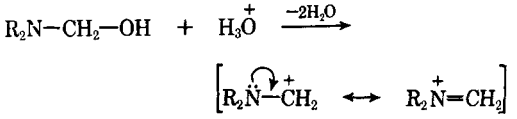
The ammonium salt of methylenediamine which formed in step A decomposes immediately in water to form an aminomethyl carbonium ion (reaction B). The acid in this system may react further to neutralize the free amine formed in equilibrium (D), or it may act directly on the intermediate, *N*-hydroxymethylamine. The latter action was discussed by Stewart and Bradley (50), who reported that addition of an *N*-hydroxymethylamine to a solution of aqueous acid followed the course illustrated in Scheme XV. The reverse order of mixing appeared to favor formation of the salt of the free amine.

The above cleavage at first glance appears to be unlikely since nitrogen, the most basic center of the molecule, ought to bind the proton. Experimentally, however, it has been demonstrated that the ammonium salt is unstable in aqueous solution and can be formed only under anhydrous conditions (31, 52).

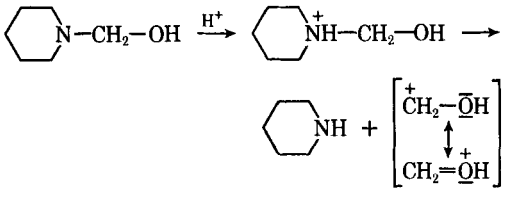
If the stability of the ionic species formed in the cleavage is considered, the formation of the aminomethyl carbonium ion according to Scheme XIV is understandable. The two possible courses for the cleavage are shown in Schemes XVI and XVII. The hydroxymethyl carbonium ion of Scheme XVI is considerably less stable than the aminomethyl carbonium ion of Scheme XVII, hence the greater resonance stabilization of the



Scheme XIV

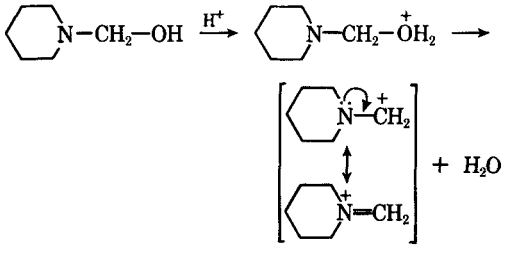


Scheme XV



Scheme XVI

or,



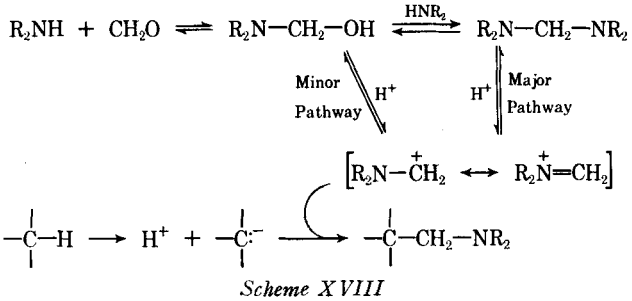
Scheme XVII

latter ion makes Scheme XVII the favored pathway.

In studying the possible role of *N*-hydroxymethylamines in the Mannich condensation, Bodendorf and Koralewski (31) condensed antipyrine with formaldehyde and piperidine hydrochloride to obtain the Mannich base, 4-piperidinomethylantipyrine, in 62% yield. With free piperidine and formaldehyde a 37% yield of the Mannich base was obtained. With preformed *N*-hydroxymethylpiperidine, the compound suggested by Mannich as the reaction intermediate, a yield of only 20% was obtained. These workers concluded that *N*-hydroxymethylamine is not the intermediate in the Mannich reaction.

Hellmann and Opitz later proved that the Mannich base in the latter two combinations is formed during the isolation procedure when acid conditions prevail (26). If the active aminomethylating agent is the electrophilic aminomethyl carbonium ion, which arises only under acidic conditions, then the conclusion of Bodendorf and Koralewski (31) against *N*-hydroxymethylamine as the intermediate was based on inaccurate information. Certainly knowledge of the formation of this ion, contributed by Stewart and Bradley (50), supports the work of Hellmann and Opitz (25–30).

The next significant studies of the mechanism of the Mannich reaction were published in 1949 by Liebermann and Wagner (32) and by Alexander and Underhill (33). Liebermann and Wagner concluded that each combination of reactants requires a different pH for the best results and that an initially high acidity is required. These workers concluded that the aminomethyl carbonium ion previously mentioned is the final electrophilic intermediate and that it reacts with a carbanion which arises from the acidic or labile hydrogen compound. According to the mechanism proposed by these authors, methylenediamine is the intermediate formed in the Mannich reaction prior to formation of the aminomethyl carbonium ion. However, the possibility that *N*-hydroxymethylamine might be required in a few reactions demands its retention in the overall



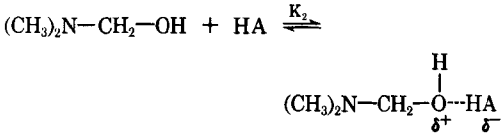
Scheme XVIII

mechanism. The complete sequence is shown in Scheme XVIII.

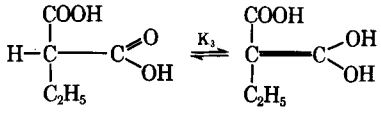
Alexander and Underhill (33) offered a mechanism which involved *N*-hydroxymethylamine as the intermediate and in which the acidic hydrogen compound was suggested to react in the enol form rather than to ionize as Liebermann and Wagner proposed. The reason for suggesting an enolic intermediate rather than an ionic intermediate was based on ionic strength effect experiments which failed to alter the rate of the reaction. Had an ionic intermediate been involved prior to the rate-controlling step, the reaction rate should have changed in proportion to the change in the ionic strength of the media. The reaction is observed to proceed immediately if preformed *N*-hydroxymethyl-*N*,*N*-dimethylamine is employed, but an induction period is required if formaldehyde and free amine are used instead. This observation indicates that a slow reaction between formaldehyde and dimethylamine is required before typical third-order kinetics are observed. It also indicates that the rate of this condensation between formaldehyde and dimethylamine, although faster than the rate-controlled step, is of the same general magnitude.

The mechanism proposed for the condensation of ethylmalonic acid with formaldehyde and dimethylamine shown in Schemes XIX–XXIII.

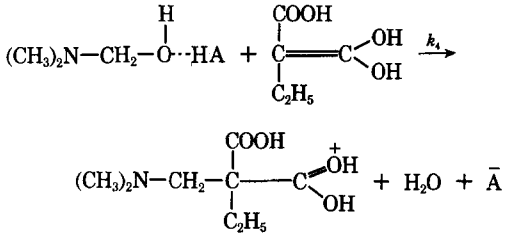
Scheme XIX



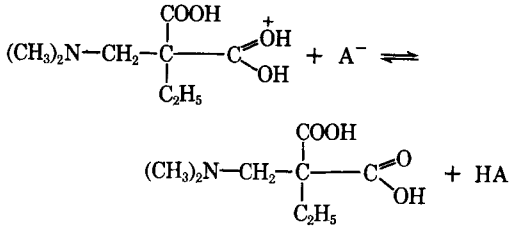
Scheme XX



Scheme XXI



Scheme XXII



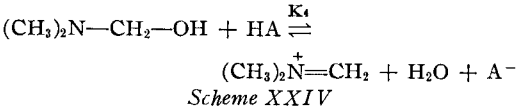
Scheme XXIII

This sequence calls for general acid catalysis by HA with Scheme XXII as the rate-controlling step. The rate expression reduces to:

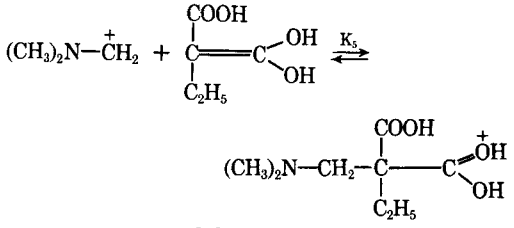
$$\frac{dx}{dt} = k[CH_2O][(CH_3)_2NH][C_2H_5 \cdot CH(COOH)_2]$$

where k includes the concentration of HA which remains constant.

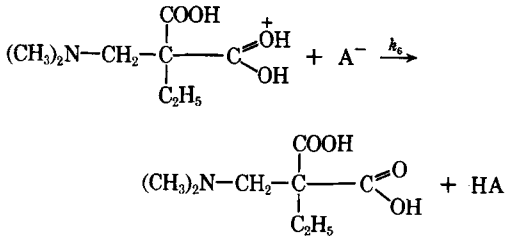
The possibility was considered that Schemes XX, XXII, and XXIII might be replaced by the sequence in Schemes XXIV–XXVII.



Scheme XXIV



Scheme XXV



Scheme XXVI

This was ruled out since Scheme XXVI is very unlikely to be the rate-determining step. Consideration of Scheme XXV as rate determining requires that the reaction velocity be dependent upon the oxonium ion concentration. Alexander and Underhill decided against this course because of the somewhat complex pH dependency of the reaction. As Hellmann and Opitz later indicated (25), the complicated nature of the pH dependency may be solved when one considers that acid retards formation of *N*-hydroxymethyldimethyl amine to such an extent that Scheme XIX, which

appears to be only slightly faster than the rate-controlling step, may finally become rate determining. Since dimethylaminomethyl carbonium ion is used up faster than it can be formed, the reaction may decrease with decreasing pH. This problem was also dismissed by Cummings and Shelton (34), who pointed out that the reaction in Scheme XXVII properly belongs in the kinetic

$$R_2\overset{+}{N}H_2 + \bar{A} \rightleftharpoons R_2NH + HA$$

Scheme XXVII

equation since, in acid solution, the amine exists largely in the salt form. This fact accounts for the conclusion (above) by Hellmann and Opitz (25) and simultaneously rids the kinetic expression of its "specific oxonium requirement." Therefore, Schemes XXIV, XXV, and XXVI cannot be eliminated as possibilities.

When, as in the example by Alexander and Underhill (33), an acid is employed as the active hydrogen compound and reacts in the acid form, a term to account for the acid to anion dissociation reaction must be included. It is probably in part for this reason that these workers observed the complex interaction between pH and the rate constant. Contrary to the opinion of Alexander and Underhill (33) that specific oxonium ion catalysis cannot explain this complex variation of rate constant with pH, it seems likely that the above-discussed factors could easily account for this complexity (34).

Hellmann and Opitz (25–30), in a series of comprehensive studies, proved that *N*-hydroxymethylamine, *N*-methoxymethylamine, and methylenediamine could all be formed in the course of the Mannich reaction, depending upon the conditions employed. Since highest yields were obtained when one of these materials was added to a mixture of excess aqueous acid and the acidic or labile hydrogen compound, a method which gives the highest concentration of the aminomethyl carbonium ion (50), it was concluded that this ion was the active aminoalkylating agent. The reverse order of addition, *i.e.*, adding acid to a mixture of the reactants, does not offer favorable pH conditions until the addition is essentially complete. It was also found that a pH as low as 1.0 is successful in some cases if the proper order of addition is used.

Based on the extensive experimentation carried out, Hellmann and Opitz (25) concluded that rather strong inductive effects must be operating in order to activate the labile hydrogen compound sufficiently to react as a carbanion, or there must be enol formation in the absence of strong inductive effects (28). The proposed mechanism offered is quite similar to the mechanism in acid media offered by Cummings and Shelton (34) and represents an S_E2 mechanism. The S_N2 mechanism under basic conditions was covered under the title of transmethylation owing to the opinion by Hellmann and Opitz that the Mannich reaction is that aminomethylation occurring under acidic conditions (25, 30).

Hellmann and Opitz (25, 26) reinvestigated the condensation between antipyrine, formaldehyde, and piperidine in the belief that the data of Bodendorf and Koralewski (31) simply did not seem to fit available postulates. Among other things they determined that the purification procedure of Bodendorf and Koralewski failed to remove methylene-bis(4-antipyrine), a major contaminant of the Mannich base. Following the published procedure (31), in which a 37% yield had been reported but purifying by *in vacuo* distillation, Hellmann and Opitz (26) were able to remove methylene-bis(4-antipyrine) (b.p. 238° at 760 mm.; 100° at 2 mm.) and thus effect an improved purification of the Mannich base. The yield of Mannich base amounted to only 11.51% (26). The use of *N*-hydroxymethylpiperidine and antipyrine gave 13.89% (26) instead of 20% as reported by Bodendorf and Koralewski (31). Using antipyrine, formaldehyde, piperidine, and an equimolar portion of hydrogen chloride provided 62% yields according to both groups (26, 31). These data point to an acid-catalyzed reaction for production of the Mannich base of antipyrine. Of itself, antipyrine is too weakly acidic to catalyze the reaction.

The negligible yields with basic conditions in the antipyrine example suggested that perhaps the Mannich reaction on antipyrine does not occur at all under these conditions. A careful study of the procedures of Bodendorf and Koralewski (31) led Hellmann and Opitz (26) to the conclusion that the small quantity of Mannich base formed in the procedure arises during product isolation, when acidic conditions prevail. By redesigning the workup procedure as little as 3–5% of product was obtained, an observation which certainly supports the "no-reaction" hypothesis.

According to Stewart and Bradley (50) the maximum concentration of the aminomethyl carbonium ion occurs on addition of *N*-hydroxymethylamine *N*-alkoxymethylamine or methylene-bis(amine) to aqueous acid. Reversing the order of addition leads to little or at best very slow production of the necessary ion. It may be inferred from these data that proper order of addi-

tion is important for the successful testing of these intermediates.

In order to evaluate the relative effectiveness of these intermediates, Hellmann and Opitz (25, 26) compared yields using the two different orders of addition with each of the three possible intermediates. *N*-Hydroxymethylpiperidine, when added to a solution of antipyrine and excess acid (10% excess, pH 2.5), gave a 71% yield of Mannich base, while the same ingredients gave only 56% of Mannich base along with some methylene-bis(4-antipyrine) when the acid was added to the antipyrine and *N*-hydroxymethylpiperidine mixture. Use of *N*-methoxymethylpiperidine gave, on addition to a mixture of antipyrine and excess acid (6% excess, pH 3.0), gave an 87% yield of Mannich base. When the acid was present to the extent of a 40% excess (pH 1.0), the reaction still gave a 77% yield of Mannich base. They found that with similar conditions but reversing the order of addition completely inhibited the Mannich reaction. Finally, Hellmann and Opitz report an 81% yield of Mannich base when methylene-bis(*N*-piperidine) is added to antipyrine and excess acid (12% excess, pH 2.0).

The above data certainly support the concept that *N*-hydroxmethylpiperidine, and methylene-bis(*N*-piperidine) can serve as a source of the aminomethyl carbonium ion. The apparent success of this procedure supports the contention that the Mannich reaction does require one of these substances as an intermediate. The possibility certainly exists that no one of these intermediates can serve for all examples of the Mannich reaction (17, 25–47). Additional results which should be cited for this study include the observation that addition of aldehyde decreases the pH of the solution (25), *i.e.*, Scheme XXVIII.

$$R_2\overset{+}{N}H_2 + \bar{A} + CH_2O \rightleftharpoons R_2N{-}CH_2{-}OH + HA$$

Scheme XXVIII

Hellmann and Opitz (25) also expressed doubt regarding the possible formation of methylene-bis(*N*-amines) under acidic conditions, particularly if water is present. These derivatives of formaldehyde and amine simply are not stable under these conditions (50).

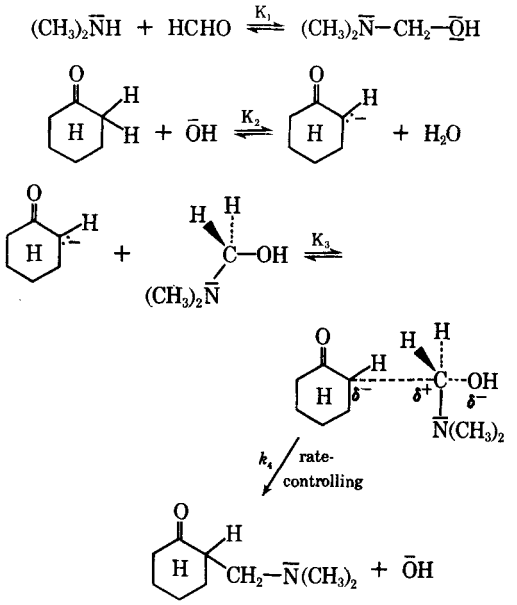
In the two major contributions to the mechanism of the Mannich reaction which had appeared in 1949, a divergence of views was obvious. Liebermann and Wagner (32) had proposed a process in which two ions, a carbanion derived from the active hydrogen compound and the aminomethyl carbonium ion, derived from an aminomethylol or a methylene-bis-amine, neutralized each other. Alexander and Underhill (33) found that no significant change in the rate occurred with changes in ionic strength of the media. If a carbanion-carbonium ion neutralization is present in the transition state of the rate-controlling process, a large change in rate with change in ionic strength ought to have been observed (53). Secondly, based on mechanistic pathways visualized by Alexander and Underhill, the outright liberation of a free aminomethyl carbonium ion for reaction with a carbanion would require kinetic independence of the reaction from pH influence. Alexander and Underhill had, however, observed a pH maxima at 3.8. They reasoned that below this pH, the rate began to be severely limited by extensive conversion of amine into its salt form.

Hellmann and Opitz (25–30) pointed out that the conversion of amine and formaldehyde into aminomethylol was reported by Alexander and Underhill to be only slightly faster than the rate-controlling step. They pointed out that the complex pH effects could be explained when one recalls that the effect of mounting acidity is to decrease the concentration of free amine. This deficiency of free amine can make the already slow conversion to aminomethylol finally become rate controlling. The mounting acidity, which does not favor carbanion formation, coupled with the absence of ionic strength effects, convinced Hellmann and Opitz that the reaction proceeded without involving the carbanion of the active hydrogen compound. The aminomethyl carbonium ion, derived from an *N*-hydroxymethylamine, was concluded to be the aminomethylating agent.

A recent kinetic study by Cummings and Shelton (34) reached conclusions quite similar to those of Hellmann and Opitz (25–30) concerning the mechanism of the Mannich reaction. The mechanisms proposed by these workers are given for basic media in Scheme XXIX and for acidic media in Scheme XXX. Several comments by Cummings and Shelton (34) were made relevant to the previous kinetic and qualitative studies. They pointed out, as did Hellmann and Opitz (25–30), that the amine is largely present as the salt under acidic conditions. Incorporating this factor into the reaction sequence they obtained a rate equation in which the rate was independent of the pH. At sufficiently low pH, this is precisely what was observed with cyclohexanone as the active hydrogen compound (34). The example chosen by Alexander and Underhill (33) involved an acid as the active hydrogen compound. If the reactive form is the acid, as shown in their mechanism, then another term to account for the acid form and ionic form equilibria should be present

in the equation. This would make the rate equation dependent upon the hydronium ion concentration.

It is of interest to note that the mechanistic pathway and rate equations of Cummings and Shelton (34) in acid media involve production of a dimethylaminomethyl carbonium ion from *N*-hydroxymethyldimethylamine and that this ion then reacts with an α-carbanic center developed



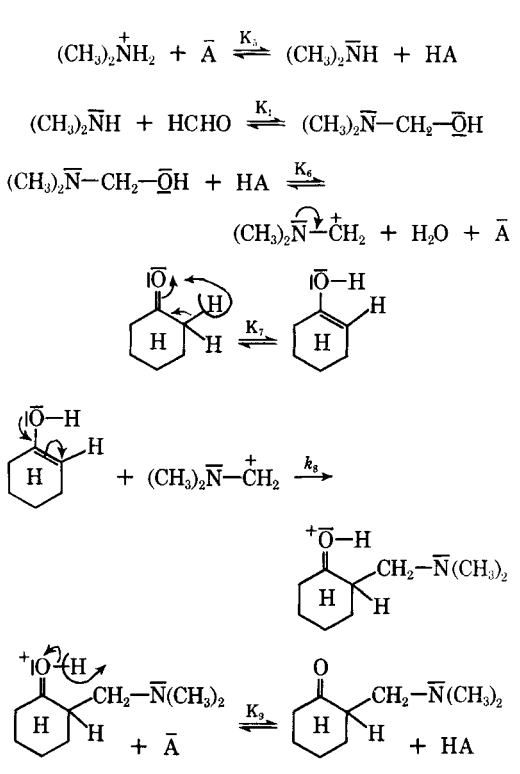
$$\frac{dx}{dt} = k[(CH_3)_2\bar{N}H]\cdot[CH_2O]\cdot[C_6H_{10}O]\cdot[\bar{O}H]$$

Scheme XXIX

on the enol form of cylcohexanone. The rate expression does not contain an HA or an H_3O^+ term. The view is, therefore, a composite of previous suggestions (33, 25–30).

The mechanism for basic media does not suggest formation of the dimethylaminomethyl carbonium ion, which indeed should only be present in acidic media. Instead dimethylaminomethanol is the intermediate on which an S_N2 displacement of OH^- by the cyclohexanone carbanion takes place. The appropriate carbanion presumably arises by base attack on the reactive α-protons of cyclohexanone.

The above-mentioned kinetic study does much to clarify the general views on the course of the Mannich reaction but have been unable to resolve problem of deciding among methylene-bis-amines, *N*-alkoxymethylamines, or *N*-hydroxymethylamines as the true intermediate in the Mannich reaction. Several recent kinetic studies provide further information on the mechanism and technology of the Mannich reaction (17, 35, 36, 43–47, 54–58).



$$\frac{dx}{dt} = k[(CH_3)_2\overset{+}{N}H_2]\cdot[CH_2O]\cdot[C_6H_{10}O]$$

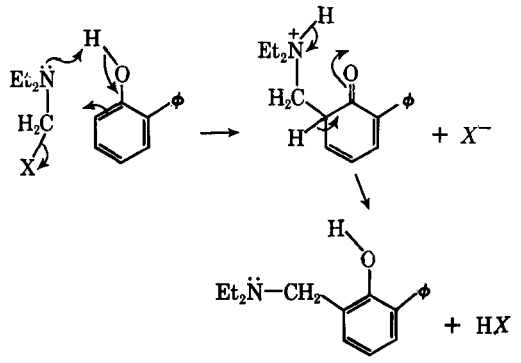
Scheme XXX

Burckhalter and co-workers (17, 36) have studied the mechanism of the Mannich reaction on phenols with emphasis on the observed preponderance of *ortho* substitution. For example, Burckhalter (59) obtained a preponderance of the *ortho*-substituted product (42%) of 2-phenylphenol and less than a third (13%) of the *para*-substituted isomer. Several additional references are cited by Burckhalter and Leib (36) in reviewing the subject.

In the mechanistic and kinetic studies carried out in basic media by Burckhalter and co-workers (17, 36), the rate of condensation of formaldehyde and morpholine with 2,4-dimethylphenol is controlled by formaldehyde if the concentration of formaldehyde is *less* than half the morpholine concentration. Conversely, morpholine concentration is critical if it is *less* than *twice* the formaldehyde concentration. These data suggest the participation of methylene-bis(*N*-morpholine) as an intermediate. A pure sample of this compound gave data kinetically indistinguishable from those of the formaldehyde and morpholine mixture. Calorimetric data by Fernandez and Butler (44) also supported a methylene-bis-(amine) intermediate.

Burckhalter and co-workers (17, 36) suggested that *ortho*-substitution predominates in amino-

methylation of phenols because of hydrogen bond participation. The process was visualized as in Scheme XXXI.



$X = -OH, -OR, -NR_2$.

Scheme XXXI

In view of preceding comments the most likely intermediate would be the methylene-bis(amine) ($X = -NR_2$). Since phenols are acidic and capable of existing as free phenol or phenolate ion and, since the reactive intermediate amine conceivably might react as a neutral molecule or as a positively charged molecule, a maximum rate ought to be observed at some definite pH if two neutral (phenol plus amine) or two charged ions (phenolate ion plus positively charged amine derivative[3]) interact. Conversely the reaction rate should increase with (*a*) decreasing pH if free phenol and protonated amine interact, and (*b*) with increasing pH if phenolate and free amine interact. The observed rate *versus* pH profile provided a maximum between pH 9.6 and 10.2 (maxima at approximately pH 10.0) indicating that the reaction occurs between either a pair of neutral reactants (phenol plus amine) or between a pair of ions (phenolate plus amine salt). Several factors weaken the case for the latter possibility. First, the pH at which the maximum occurs is basic. The methylenebis-(morpholine) salt should not be stable under strongly acidic conditions (25, 51) unless present in an anhydrous medium (52), and is not likely to form in the basic pH studied. Secondly, the preponderance of *ortho*-substitution isomers previously observed (36, 59) ought to involve a concerted mechanism (36) which is most favorably accommodated by a hydrogen bonded complex between the neutral phenolic molecule and the methylene-bis(amine) structure (Scheme XXXI).

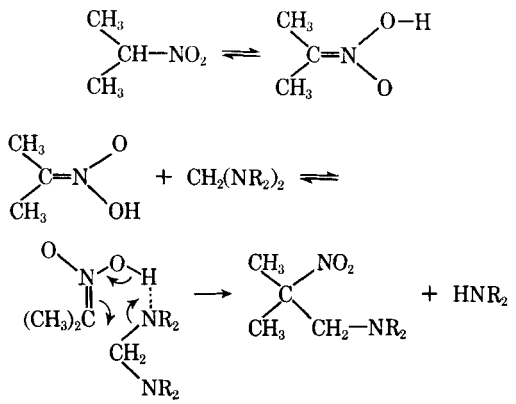
Fernandez and associates (44–47, 55–58) have contributed calorimetric, cryoscopic, and kinetic studies recently. Based on the colorimetric data obtained in the conversion of formaldehyde and amine to *N*-hydroxymethylamine and then, with a second mole of amine, to methylene-bis(amine), Fernandez and Butler (44) concluded that the reaction proceeds in most cases to methylene-bis-(amine). There seems to be little *N*-hydroxymethylamine at equilibria in most of the examples studied. This is not surprising in view of the technique used, *viz.*, amine (two parts), was treated slowly with aqueous formaldehyde (one part). It has been reported that the intermediate, *N*-hydroxymethylamine, is unstable in the presence of excess amine, reacting to yield the bis(amine) (49, 51). The previous study by Burckhalter *et al.* (17, 36) certainly supports the concept of a methylene bis(amine) as the most likely intermediate under basic conditions as did this calorimetric study (44).

Fernandez and Fowler (45) in 1964 reported the kinetics associated with the reaction of 2-nitropropane and methylene-bis(piperidine) or methylene-bis(morpholine). Choice of the methylene bis(amines) simplified the process and circumvented the necessity of speculation concerning identity of the intermediate form of the formaldehyde and amine. To further ensure the integrity of this intermediate, water was excluded by use of anhydrous solvents. The choice of methylene bis(piperidine) and methylene-bis(morpholine) provided widely different basicities (pKb 2.78 and 5.64 for the starting amines, respectively). Solvents included dioxane, DMF, nitrobenzene, and triethylamine.

Briefly, results of the experiments confirmed that the more basic methylene-bis(piperidine) exhibited much faster rates than did the morpholine derivative. Excessive basicity, as with excess methylene-bis(piperidine) or triethylamine as solvent, caused a slowing of the condensation. Fernandez and Fowler (45) reasoned that under these conditions the nitropropane reacts in the anionic form and produces an extremely reactive amide ion (R_2N^-) as the conjugate base. The latter is not a favored state and thus slows the overall rate. The rate also increased with an increase in dielectric constant. In media of low dielectric constant the mechanism is suggested to occur *via* a hydrogen-bonded complex of the *aci*-form of 2-nitropropane interacting with methylene-bis(amine). (See Scheme XXXII.)

At higher dielectric constant the activation parameters suggested to Fernandez and Fowler (45) that the mechanism changes to one involving a higher enthalpy of activation and lower entropy of activation. The mechanism visualized involves incorporation of a molecule of methylene-

[3] The charged amine was referred to as a protonated methylene-bis(amine) (17). The aminomethyl carbonium ion might also be a possibility.



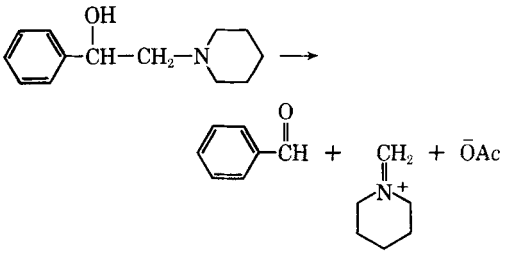
Scheme XXXII

bis(amine) into the solvent shell of 2-nitropropane. The transition state visualized thus involves coordination of the hydroxyl proton of *aci*-2-nitropropane with solvent, thus differing from the above cyclic or quasi-6-membered transition in which this hydroxyl proton is coordinated with the amino group which will be eliminated. The transition state for high dielectric media is, therefore, less rigid and restrained but yields the reactive amide ion, R_2N^-, on conversion to product. The value for ΔS^* is thus less and ΔE^* greater than for the low dielectric media transition state.

Methylene-bis(piperidine) gave accelerated rates when compared to the morpholine derivative. This was attributed to the enhancement of electron density at the α-methylene by the more basic piperidine moieties (45).

The mechanism studies on 2-nitropropane (45) were extended by Fernandez, Fowler, and Glaros (46) to nitromethane and nitroethane. Methylene-bis(piperidine) and methylene-bis(morpholine) again were used as the aminoalkylating agents. Previously all attempts to prepare mono-aminomethylated nitromethane resulted in multiple substitution (40, 60–63). In the study by Fernandez *et al.* (46) mono-substitution of nitromethane resulted when it was treated with methylene-bis(amines) under anhydrous conditions. When a small amount of water is present, or if *N*-ethoxymethylpiperidine is used, disubstitution results. These data suggest that the second alkylation step probably requires *N*-hydroxymethylamine or *N*-alkoxymethylamine in order to be successful. By inference, the initial aminoalkyl substitution probably may occur with any one of the three possible aminoalkylating agents. The evidence presented by Fernandez *et al.* (45, 46, 55) and by Burckhalter and coworkers (17, 36) certainly supports the hypothesis that basic conditions favor *formation* of methylene-bis(amines) (49, 51) and that these intermediates may function as aminoalkylating agents (25, 26). This does not lead to the conclusion that such an intermediate is necessarily the *best* agent for aminoalkylation based on rate or position of equilibria.

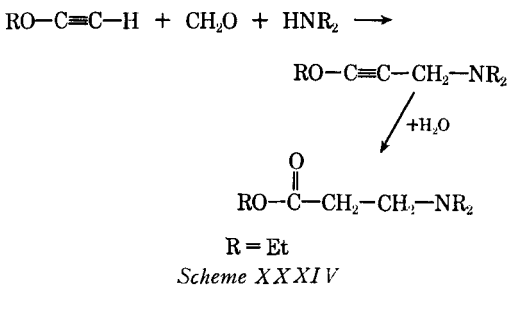
Roth, in 1961, suggested that the lead tetraacetate cleavage of 1, 2-amino-alcohols in which the amine is tertiary leads to formation of aminomethyl carbonium ions according to Scheme XXXIII (64).



Scheme XXXIII

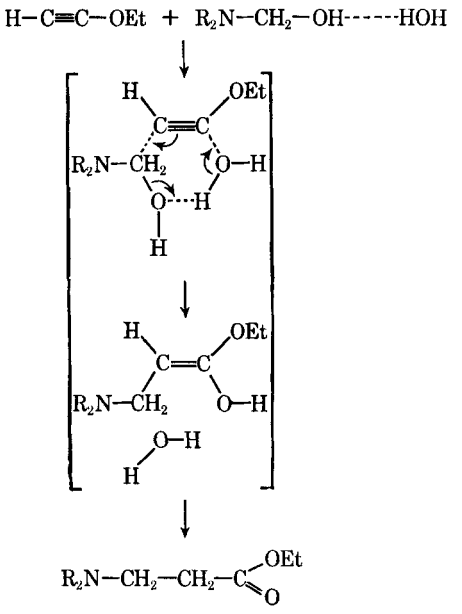
In a later study Roth was able to demonstrate that the aminomethyl carbonium intermediate did indeed occur in this cleavage (35). By adding typical Mannich reaction components (acidic C—H and N—H containing compounds) during the above type cleavage reaction, Roth was able to isolate the corresponding Mannich bases in high yields. Although this did not afford absolute proof that the aminomethyl carbonium ion is the true aminomethylating agent, it provided additional support for this hypothesis. In the absence of a suitable trapping agent, the aminomethyl carbonium ion formed in the study cited above (64) was hydrolyzed yielding formaldehyde and secondary amine hydrochloride or acetate. Among the compounds selected by Roth as suitable acidic hydrogen-containing compounds (either CH or NH) are phthalimide, theophylline, succinimide, carbazol, benzoxazolone, benzamide, isatin, saccharin, barbital, acetophenone, antipyrine, cyclohexanone, and indole (35).

Studies involving use of acetylenic compounds in the Mannich reaction have afforded successful condensations in the case of phenylacetylene and its substituted analogs (65). When ethoxyacetylene was employed in the Mannich reaction, Arens and co-workers (66) obtained what appeared to be the hydrolysis product of the corresponding Mannich base, *i.e.*, Scheme XXXIV. Under anhydrous conditions (dioxane as solvent) no trace of Mannich base was isolable. The mechanism proposed suggests that a hydrated *N*-hydroxymethylamine interacted as shown in Scheme XXXV. The alkoxy group in such acetylene derivatives tends to create electron-rich



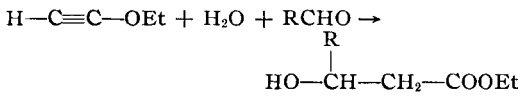
R = Et

Scheme XXXIV



Scheme XXXV

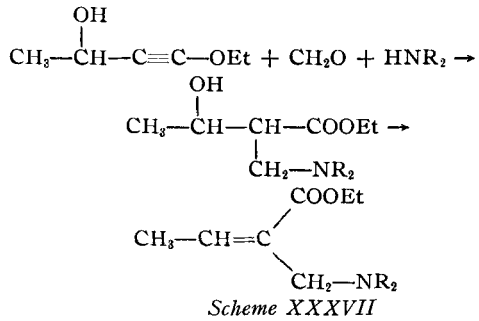
character about the carbon bearing the "replaceable" hydrogen. The above process obviously is not a Mannich reaction and the "replaceable" hydrogen never leaves the acetylenic group. Further proof was offered when, in 1957, Vieregge and Arens (67) demonstrated that ethoxyacetylene, water and aldehyde would react as in Scheme XXXVI.



Scheme XXXVI

The obviously similar product was formed in the absence of added amine. In the same paper, these workers cited experiments by van der Werf and Arens (unpublished data) in which the aminomethylation and hydrolysis had occurred in a molecule that did not contain a replaceable hydrogen (Scheme XXXVII).

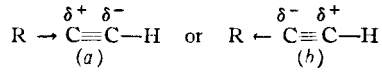
Fernandez *et al.* (55) reported that propargyl alcohol was aminomethylated at the hydroxyl group in preference to the acetylenic group in the absence of added catalyst. Salvador and Simon



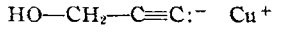
Scheme XXXVII

(43) undertook a more detailed study of the behavior of propargyl alcohol under Mannich reaction conditions. Under conditions chosen for the study, Salvador and Simon were not able to isolate the aminomethyl propargyl ethers said to be the preferred product under previously used conditions (55). Instead methylene-bis(amines) were the sole isolable products (43).

According to Salvador and Simon (43) the electronic nature of acetylenes can be represented as follows:



The presence of an α-hydroxyl group as in propargyl alcohol precludes formation of form *b* and, since this is thought to be the type of electron distribution required for a successful Mannich condensation with acetylenic substances, propargyl alcohol should not undergo the Mannich condensation. By conversion of propargyl alcohol to a copper salt,



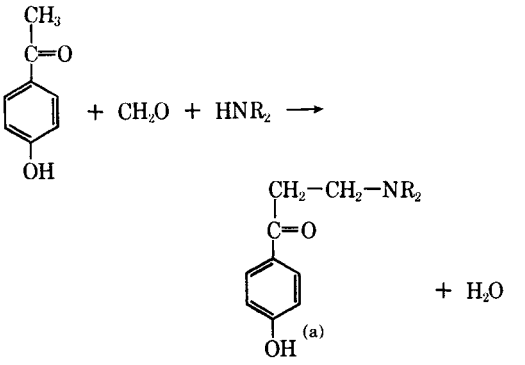
the problem of providing a suitable carbanic species for reaction with a suitable derivative of formaldehyde and amine was easily solved. In practice, the addition of a quantity of cupric sulfate to the buffered, aqueous solution was sufficient to catalyze the reaction (43).

Since the reaction was carried out in aqueous media, insoluble reaction products separated and were accessible for identification. During condensation of propargyl alcohol, piperidine, and formaldehyde, an oily layer separated (43). On distillation the oil produced a strong evolution of formaldehyde and gave methylene-bis(piperidine) as the distillate. Since formaldehyde and piperidine originally were introduced in 1:1 ratio infrared spectral data were obtained on the original oil prior to distillation. The original oil was thus identified as *N*-hydroxymethylpiperidine by comparison with an authentic sample (49). Salvador and Simon (43) then combined propargyl alcohol and *N*-hydroxymethylpiperidine in aqueous cupric sulfate and obtained poorer yields than was

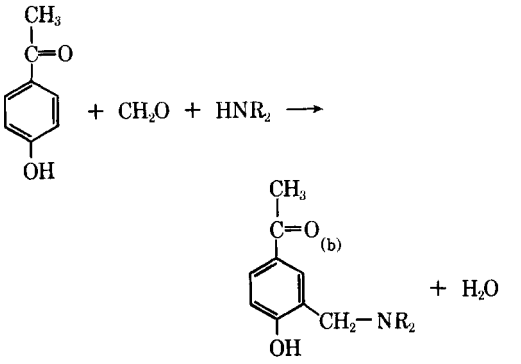
obtained with simple starting materials. Substitution of methylene-bis(piperidine) for the *N*-hydroxymethylpiperidine gave yields similar to those of the regular ingredients. These data indicate that methylene-bis(piperidine) is the true reaction intermediate. It should be recalled that the above-mentioned intermediates were isolated and identified from the reaction itself.

Based on isolation of *N*-hydroxymethylpiperidine from the reaction mixture, its ready conversion to methylene-bis(piperidine) on heating, and the significantly more favorable results on using the latter as a starting material, Salvador and Simon proposed the reaction pathway shown in Scheme XXXVIII. In this pathway the formation and existence of *N*-hydroxymethylpiperidine in mildly acidic conditions is not a very favorable pathway hence its further conversion to the aminomethyl carbonium ion is slow. This effect plus the decreasing availability of the acetylide ion in more acidic media results in slow condensation under mildly acidic conditions (about 80% yield in 5.5 hr. at pH 6.0) and no condensation below pH 3.0. In basic media the cupric acetylide formed more readily as did methylene-bis(piperidine). Thus an 80% yield was obtained in only 1.0 hr. at pH 8.4. The formation of a protonated methylene-bis(piperidine) in mildly basic media, and its subsequent decomposition to an aminomethyl carbonium ion is not very plausible. In this respect the proposed pathway of Salvador and Simon (43) probably is in error since much evidence to support methylene-bis(piperidine) *per se* as the intermediate under basic conditions has been presented (17, 36, 45, 46, 55).

Examples are available in which the Mannich reaction may occur at two different sites within a molecule, each of which represents a different class of active hydrogen. For example, with *p*-hydroxyacetophenone the following reaction courses are conceivable (68): Schemes XXXIX and XL.

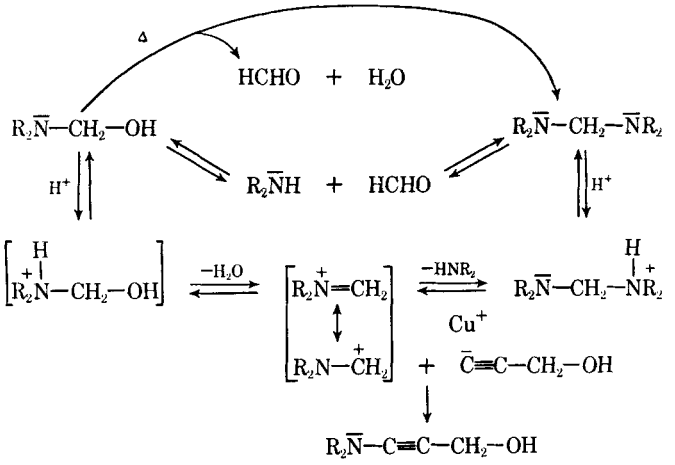


Scheme XXXIX



Scheme XL

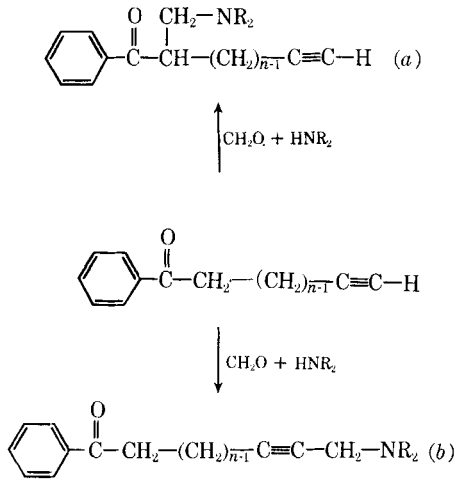
However, only examples of the first class of reaction were available (69–74) prior to 1964. Recently, the selective occurrence of reactions, illustrated as Scheme XL, has been recorded by Gautier *et al.* (68). Products were obtained in 50–60% yields. In general these workers found



Scheme XXXVIII

that acidic conditions favored condensation at the ketonic site, the suggested mechanism being similar to the Cummings and Shelton (34) proposal (Scheme XXX). Under basic conditions interaction with the neutral form of the aminomethylating agent [*N*-hydroxymethylamine or methylene-bis(amine)] occurs preferentially at the ring positions situated *ortho* to the phenolic group. Unfortunately, no examples were given for testing these "selective" conditions in which the phenolic group and ketonic carbonyl groups were not conjugated. This ought to affect the relative reactivities of the two sites to a noteworthy extent.

Gautier *et al.* (18) also have reported success in selective aminomethylation of ketonic and acetylenic moieties within the same molecule. The possible pathways, Scheme XLI, *a* and *b*, proved



Scheme XLI

to be accessible under acidic and basic conditions, respectively. Yields of type *a* compounds were in the 10–55% range while type *b* products were obtained in 48–63% yields. Gautier *et al.* (18) postulated an acetylide carbanion attack (SN2 mechanism) on *N*-hydroxymethylamine as the course of the reaction. In view of earlier discussions the methylene-bis(amine) is more likely to be present as the reactive intermediate. In acidic media, the reaction was considered to occur by means of an aminomethyl carbonium ion attack on the enol form of the ketone (18).

Faberov and Mironov (54) recently conducted a kinetic study of the Mannich reaction applied to ketones and aldehydes with subsequent amine elimination. Much of the data presented parallel data offered by Alexander and Underhill (33), Cummings and Shelton (34), and Fernandez *et al.* (45, 46). Both the product identity in one case (75) and the high yield reported (54) have been challenged (76). Such confusion concerning product identity in the case of unsymmetrical aliphatic ketones has been the subject of many publications (19–21, 75–82). Faberov and Mironov also calculated activation energies for some of the active hydrogen compounds used in the study.

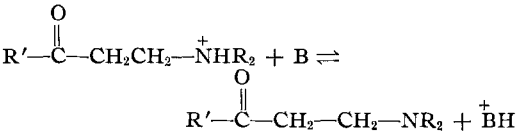
DECOMPOSITION REACTIONS OF MANNICH BASES

Mannich bases frequently are unstable. One type of instability, *i.e.*, propensity for amine elimination, has long been recognized (8, 11, 83–87). This type of decomposition can occur only if a proton is situated vicinal to the amine group and appears to be more prevalent when β-aminoketone salts or the free base form of β-aminocarboxylic acids are heated with water, *e.g.*, as in steam distillation. Faberov and Mironov (54) have reported obtainment of very high yields of α,β-unsaturated ketones and aldehydes by conducting the Mannich condensation in acidic solution and steam distilling without prior isolation of the intermediate Mannich base. Success of the method was reported to be dependent upon successful formation of Mannich base salts in high yields. These workers studied the relationship of pH to the rate of the Mannich reaction in order to assure rapid attainment of maximum yields (54).

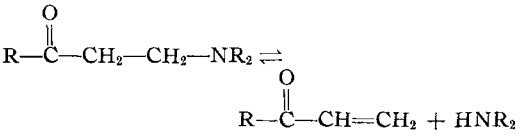
Angeloni and Tramontini (89) studied the rate of decomposition of β-aminoketone hydrochlorides in boiling water. They observed pseudo first-order kinetics for the decomposition. Their data are summarized as follows. The stronger the base (amine) present in the structure, the greater the stability of the Mannich base hydrochloride; addition of sulfuric acid slows the deamination reaction thus suggesting that the free Mannich base and not its salt is the reacting species. The unsaturated ketone product can add free amine but not amine salts. Because of this fact, elimination should be more complete with an equivalent of acid present even though the rate is greater in basic solution.

Horák and co-workers (88), using a polarographic method, were able to follow the deamination of 2-piperidinomethylcyclohexanone and of ω-piperidinopropiophenone and its methiodide. As they expected, different mechanisms for Mannich base salts and their quaternized derivatives were suggested by the data. As the pH increased, the value for the measured rate increased steadily for the methiodide but followed a typical "dissociation" curve in the case of the Mannich

bases. These data indicate that decomposition of the methiodide salt is a base-catalyzed reaction although other data suggest it to be more complex than an E2 mechanism. The data, including that relating occurrence of a dissociation reaction as given above, suggest that the Mannich base salts first undergo a dissociation followed by a unimolecular deamination of the free Mannich base. The process may be illustrated as given in Schemes XLII and XLIII.



Scheme XLII



Scheme XLIII

It is of interest to note that type and concentration of the buffer had no effect on the rate constant for the above process while the methiodide salt decomposition was very decidedly dependent upon these factors.

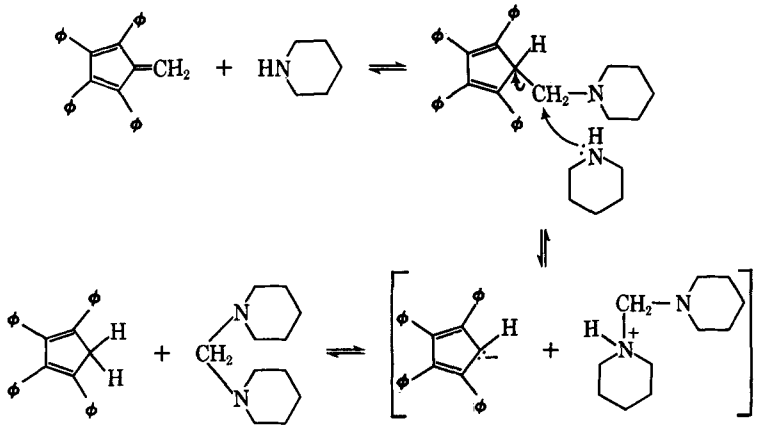
Rivière (22), in a study on the reversibility of the Mannich reaction, also discussed amine elimination to a limited extent. Principal among the stated conclusions is that elimination is especially important as a pathway if further, irreversible changes involving the unsaturated ketone can take place. Dimerization is a frequently seen irreversible process which forces the elimination reaction toward completion. Michael-type addition reactions also can force an elimination reaction toward completion (90–92). The presence of acid which can tie up the eliminated amine preventing reversal or the removal of the unsaturated ketone by steam distillation are adequate procedures.

Several studies on the application of the Mannich reaction to sulfones have been conducted (28, 92–98). With simple aryl alkyl sulfones the reaction failed (28, 92) but gave amine elimination products when arylsulfonylalkanoic acids and esters were used (92–98). Some Mannich base could be isolated in addition to the α,β-unsaturated sulfones when primary amines or ammonia were used along with aromatic aldehydes (92, 94–98). Either use of a secondary amine or of formaldehyde sufficed in order to result in complete elimination. The most likely mode of formation of the unsaturated sulfone is amine elimination (97, 98) rather than the concerted decarboxylation-amine elimination process previously suggested (93).

REVERSIBILITY OF THE MANNICH REACTION

Spoerri and co-workers (37, 38), in studying the addition of bases to 2,3,4,5-tetraphenylfulvene, obtained 1,2,3,4-tetraphenyl-1,3-cyclopentadiene when the starting material was heated with excess cold piperidine. They suggested that the phenomenon represents a reverse Mannich reaction and proposed the course shown in Scheme XLIV for the reaction. With brief contact time at 0° it was possible to isolate the intermediate Mannich base. Heating resulted in amine elimination while refluxing with excess piperidine yielded a reverse Mannich reaction. In literature references cited by Spoerri *et al.* (37) the most successful reversals took place in the presence of excess amine.

Larramona and Tchoubar (99) presented an informative review of the reversibility of the Mannich reaction. It is significant that they



Scheme XLIV

reported reversal with β-aminoalkyl aryl ketones but not with those Mannich bases containing only *alkyl* groups. Both water and amine were effective in catalyzing this reverse reaction.

Riviére (22) contributed much to an understanding of factors which can influence the reversibility of the Mannich reaction. His research further proves the reversibility of the Mannich condensation. In this report the reaction of free amines and amine hydrochlorides on β-aminoketones was studied and found to produce three competitive reactions: (*a*) desaminomethylation (reverse Mannich), (*b*) deamination (elimination), and (*c*) amine exchange between the β-aminoketone and reactant amine. The reversal of the Mannich reaction was found to be dependent on three factors. These are: (*a*) the carbon structure of the β-aminoketone must contain a C_6H_5—C=O— group although this, by itself, was not sufficient for desaminomethylation; (*b*) the presence of anilino as the amino group was unfavorable for reversal of the Mannich reaction; (*c*) aminoketones which were unable to undergo desaminomethylation could, after undergoing amine exchange with amines contained in the media, then undergo a reverse Mannich reaction.

Riviére concluded that the Mannich reaction is reversible in basic media and that its success therefore depends on the position of the equilibria. The position of the equilibria can be altered by irreversible side reactions or by amine exchange. The solvent also has a profound effect: in toluene the equilibria position could be approached from either side; in ethanol, the solvent seems to interfere with simple equilibria and provides different positions depending upon direction of approach.

FACTORS AFFECTING SELECTION OF CONDITIONS

Formaldehyde for use in the Mannich condensation may be provided by aqueous formalin, trioxymethylene (trioxane), or paraformaldehyde (100, 101). Unfortunately selection of one of these forms is not as simple as it may appear.

Aqueous *formalin* (37–40% usually) is a generally satisfactory source of formaldehyde for Mannich reactions which form stable products and have very favorable equilibria positions (8, 22). It must be remembered that the water present can both serve as a solvent and/or lead to reversal of the Mannich reaction in basic media (22). Aqueous formaldehyde may also be used for acidic media condensations, again providing some reversibility difficulties in certain cases.

Trioxymethylene (trioxane) is a cyclic trimer of formaldehyde (100, 101) and is prepared by allowing formaldehyde, obtained by distillation of 60% aqueous formaldehyde solution containing 2% of sulfuric acid, to polymerize and extracting the trioxane and linear polymer mixture with methylene dichloride. Trioxymethylene is a true acetal and can yield formaldehyde only in the presence of acid even in nonaqueous solvent systems. Studies have shown that trioxymethylene can provide formaldehyde in aqueous acid solution at a uniform rate (pseudo first order) (101). Unfortunately, the weakly acidic conditions of the Mannich reaction frequently result in such a slow depolymerization that trioxymethylene is impractical as a source of formaldehyde. A 75% depolymerization requires 2.3 hr. at 70° with 4 N H_2SO_4 and 2.3 days at 70° with 0.5 N H_2SO_4.

The third form of formaldehyde is a linear polymer called *paraformaldehyde* (100), more properly called polyoxymethylene, and may exist in three different forms. The first is *α-polyoxymethylene*, a linear polymer of moderate size (n of 30) and belonging to the "hemiacetal" class. The internal bonds are of the acetal type, hence depolymerization in base can occur, albeit from the terminal ends of the molecules. Cleavage may occur in aqueous or nonaqueous acid solutions all along the polymer chain and at both ends. The second type of polymer is *β-polyoxymethylene* which is similar chemically to the α form. The polymer size is significantly larger, hence this is a less soluble form. This β form of paraformaldehyde is formed by adding sulfuric acid during dehydration of formaldehyde. The third *polyoxymethylene* is the γ isomer which is formed from formaldehyde in methanol by sulfuric acid dehydration. This isomer is stable to bases since it is a true acetal formed from α- and β-polyoxymethylene and methanol. The rate of depolymerization probably is slow as it is with trioxymethylene.

Some chemical supply houses have persisted in using the name "trioxymethylene" as a substitute for "paraformaldehyde." This, of course, creates confusion regarding identity of the material. Furthermore, use of the name "polyoxymethylene" by other suppliers without specifying α-, β-, or γ-isomers may be an occasional source of difficulty.

In many cases it will be advantageous to use derivatives of the amine component and formaldehyde in order to overcome disadvantageous acidity, basicity, or stability of the acidic hydrogen compound or of the product (25).

In the acid-catalyzed Mannich reaction the aminomethylating agent seems to be an amino-

methyl carbonium ion (25, 34) which may be formed most easily and in highest yields by adding *N*-hydroxymethylamine, *N*-alkoxymethylamine, or methylene bis(amine) to a solution of the replaceable hydrogen compound in excess acid. The disadvantages of this procedure include the retarding influence of excess acid on formation of a carbanic center on the replaceable hydrogen compound. Addition of aliquot or aliquant quantities of the total acid followed by addition of a similar quantity of the aldehyde and amine derivative being used often overcomes this difficulty. The acid must always be in excess but, for most reactants, this excess should never be very great. Methylene-bis(amines) will require double the stoichiometric quantity of acid in order to neutralize the mole of amine given off. When amine hydrochloride and active hydrogen compound are dissolved in absolute ethanol and paraformaldehyde is added portionwise (8, 102), excellent results are likewise obtained. The addition of amine hydrochloride assures only moderate acidity and, as formaldehyde is gradually released and reacts with the amine salt, the observed release of free acid will likewise be gradual. The Mannich base, as it forms, will take up the acid and the acidity never builds up in this procedure. A similar procedure for free amine is used when the amine salt is not available (102).

In basic media the same three aminomethylating agents may be utilized with good results (25, 26, 45, 46). Although the actual aminomethylating agent under basic conditions probably is the methylene bis(amine) the experimental evidence offered by Fernandez presents a strong case for *N*-hydroxymethylamine as being a more forceful reagent (45, 46). In basic media in particular, methylene bis(amine) yields an equivalent of free amine which can, as previously shown, accelerate Mannich reaction reversal. Since the amine occurs as part of the equilibria, the position of equilibria will also be affected. When such unfavorable equilibrium positions occur with methylene bis(amine) the use of *N*-alkoxymethylamine or *N*-hydroxymethylamine will give differently constituted equilibria involving alcohols or water, respectively, and hence a totally different equilibrium constant. It is entirely possible that the new equilibria will now provide the desired product in high yield. It is sometimes possible to force the condensation if a solvent such as toluene is used in conjunction with a Dean-Stark trap to remove water from the equilibria. For small quantities of water a Soxhlet thimble containing a nonreacting drying agent is even more effective than the Dean-Stark trap.

With regard to the active hydrogen component of the condensation, two major methods of developing a carbanic center are applicable (25). These are ionization and electronic localization in enols and heterorings. For strongly acidic materials ionization may even take place in moderately acidic media, although it is rare that very low pH values will be conducive to formation of the necessary carbanion or to formation of the required aminomethyl carbonium ion if amine hydrochloride and formaldehyde are used *per se*. Excessive acidity also binds the free electron pairs in enols and heterocyclic systems sufficiently to prevent condensation with the aminomethyl carbonium ion.

The use of basic conditions with strongly acidic components often yields carbanions with greater nucleophilicity than that of the amine. Under such conditions a symmetrical methylene derivative of the active hydrogen compound results (25, 31, 32, 97, 98, 103–105). Basic conditions are favored over acidic conditions in the case of nitroalkanes, acetylenes, phenols, and related materials. The acetylenes in particular undergo the Mannich reaction more readily in the presence of cupric sulfate (43) or under more strongly basic conditions than most active hydrogen sources (18, 43, 68).

Choice of solvent frequently is of great importance (22). The common solvents for the Mannich reaction include water, acetic acid, ethanol, isoamyl alcohol, and toluene (8). The first four are possessed of varying degrees of polarity and thus foster the formation of ionic species to different degrees. Water, acetic acid, and isoamyl alcohol have more elevated boiling points than does ethanol, and their use can therefore speed up an otherwise slow approach to equilibria. The higher temperature also can hasten the elimination of amine from the Mannich base product (37, 38) and thus complicate the process. In base this elimination is reversible while in acid it is slower but tends to go to completion if heated long enough. Acetic acid as a medium can suppress ionization of the acidic compound and thus alter its reactivity. This phenomenon may sometimes be used to advantage. Toluene on the other hand tends to act uniformly to suppress all ion formation. For condensations which seem to involve nonionic reactants, *e.g.*, simple enols or heterosystems reacting with *N*-hydroxy- or *N*-alkoxymethylamines or methylene bis(amines), such media may afford excellent results.

The preceding comments have been quite general in order to afford a broad view of Mannich reaction technology. Other comments of value are to be found in Blicke's review (8) and in the discussions of Hellmann and Opitz (25), and others (11, 22, 99). When difficulties are encountered one must decide if these be in the nature of poor equilibrium position, formation of elimination products, incorrect solvent, or inappropriate conditions or ingredients for proper formation of the intermediates in the reaction. Often steps, such as those discussed above, may be taken which will circumvent these problems.

The value of varying the pH, changing solvents, and, in general, attempting to ascertain why difficulties seem to be occurring in an attempted Mannich condensation cannot be valued too highly. Such knowledge may lead to easily successful variations in the procedure. The observed simplicity of the Mannich condensation procedure in the successful cases should not lead anyone to believe that the process is not indeed complicated and one frequently beset with pitfalls. The author sincerely hopes that this review will serve a useful purpose and that it will aquaint those in the field with more of the work which has been published in other languages.

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Keyphrases

Mannich reaction—review
Mechanism, technology—Mannich reaction
Condensation, Mannich reaction—mechanism
Decomposition reactions—Mannich bases
Reversibility—Mannich reaction
Formaldehyde source—Mannich reaction

Research Articles

Electrolyte Alterations in Vascular Smooth Muscle and Hypotensive Activity of a New Chalcone Derivative

By GERALD P. SHERMAN, ELIAS W. PACKMAN, and G. VICTOR ROSSI

Chalcone R-2803 [2-(2-dimethylaminoethoxy)-3′,4′,5′-trimethoxy chalcone hydrochloride] is an effective and long-acting depressor agent when administered intravenously and orally to dogs and rats. In the intact animal, R-2803 is essentially devoid of adrenolytic or ganglioplegic activity. Cross-circulation studies indicate that R-2803 does not possess central hypotensive activity. A direct action at the vascular level is demonstrated by inhibition of norepinephrine- and angiotensin-induced contractions of isolated aortic muscle. Single intravenous doses increase the sodium and potassium content of rabbit aorta, but decrease serum sodium and potassium values, reflecting an apparent shift in the equilibrium of electrolytes between blood and vascular tissue. Although a decrease in hypotensive activity is not observed after administration of R-2803 for 3 days, the electrolyte changes are less than those observed after single intravenous doses. An equidepressor dose of hesperidin methyl chalcone produces similar elevations of aortic sodium and potassium levels. The electrolyte alterations are not a consequence of blood pressure reduction as evidenced by failure of other hypotensive agents to alter aortic electrolyte balance. Sodium and potassium changes in vascular muscle may play a role in the initial phase of the hypotensive effect of the chalcones.

PHARMACOLOGIC EVALUATION by Rossi and Packman (1) of 14 chalcone derivatives synthesized by Packman and Rubin (2) indicated 2-(2-dimethylaminoethoxy) chalcone to be the most active hypotensive compound in the series. Further modification of this molecule by Packman (3) resulted in a derivative, 2-(2-dimethylaminoethoxy)-3′,4′,5′-trimethoxy chalcone hydrochloride (compound R-2803), characterized by greater depressor potency and extended duration of action.

Based primarily on studies on isolated intestinal smooth muscle, Riedesel and Combs (4) postulated that hesperidin methyl chalcone, which

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