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* *Index Medicus* abbreviations were used for journals not listed in *Chemical Abstracts*.

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# ____Research Articles____

# Studies on the Mechanism of the Mannich Reaction

## By W. LEWIS NOBLES* and N. D. POTTI

**A study of the Mannich reaction has been carried out in which the importance of the nature of the amine component has been noted; with unsymmetrical bisamines, based on limited studies to date, the stronger base of the two amines involved in such a moiety appears to be always incorporated into the final Mannich product. Also, the importance of steric factors in the mechanism of the reaction has been noted.**

FOR MORE THAN 60 years the Mannich reaction has been studied by several groups of workers, especially in the field of medicinal chemistry, primarily because of its synthetic utility and the favorable pharmacological properties of the Mannich bases and their derivatives. The mechanism of this reaction has been the subject of considerable discussion (1–13). Yet, thus far, no single mechanism which will account for all the experimental facts has been suggested.
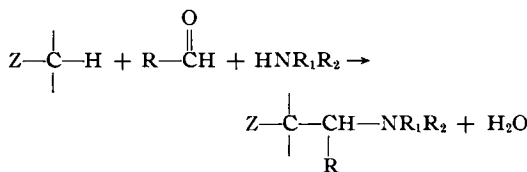
The reaction in its most generalized form may be represented as follows:

$$Z\!-\!\underset{|}{\overset{|}{C}}\!-\!H + R\!-\!\overset{\overset{\displaystyle O}{\|}}{C}H + HNR_1R_2 \rightarrow$$

$$Z\!-\!\underset{|}{\overset{|}{C}}\!-\!\underset{\underset{\displaystyle R}{|}}{C}H\!-\!NR_1R_2 + H_2O$$

Several investigators (2, 5, 7, 14, 15) have indicated the possibility of considering a methylenebisamine as the most probable intermediate under normal reactions. A quasi-six-membered hydrogen-bonded transition state has been offered, in the case of the Mannich reaction with phenols as a plausible mechanism for the selective

formation of the *ortho*-substituted phenols (8). A similar complex transition state has been indicated (5) in the case of the Mannich reaction of nitroalkanes. Further strong intramolecular hydrogen bonding is indicated in Mannich bases in general (10,16).

Methylenebispiperidine reacts faster than methylenebismorpholine in the Mannich reaction (5); since they are sterically quite similar, this has been attributed to their difference in basicity. One objective of the present investigation was to study the course of the Mannich reaction when an unsymmetrical methylenebisamine was used.

In previous mechanistic studies, there seems to have been little consideration of the steric effects of the reactants, even though there is a significant amount of published data available. The significance of this aspect is elaborated in this study to the point that it appears to account for several otherwise unexplained facts.

### DISCUSSION AND RESULTS

The formation of a methylenebisamine (II) as the primary step of the Mannich reaction has been suggested by Lieberman and Wagner (2) even though later kinetic studies (3, 4) proved their mechanism to be incorrect. Alexander and Underhill (3) held the view that an aminomethylol (I) is the intermediate of the reaction. The possibility of the formation of an aminomethyl ether (III) in alcoholic medium also has been suggested (8, 17). (Scheme I.)

To date, one may accept most of the intermediates that have been proposed in the mechanistic considerations of this reaction. This is essentially true since, according to the current view (4, 18, 19), in slightly acidic medium the carbonium ion (IV) which is obtainable from all the above intermediates, attacks the enol form (VI) of the ketone in an electrophilic attack to give the Mannich base (VII).
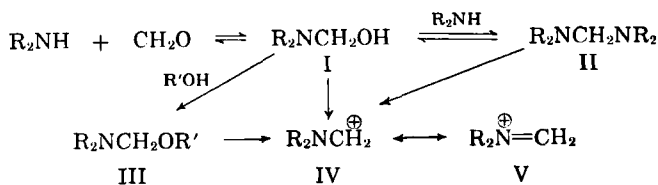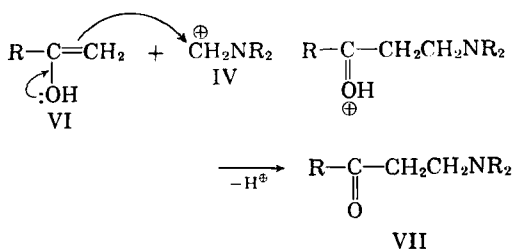
and formaldehyde are mixed. There is little evidence (17) to consider the aminomethyl ether as a possible intermediate in the normal Mannich reaction, since the rate of formation of this ether is very slow compared to the almost instantaneous formation of the methylenebisamine. Furthermore, Varma and Nobles (20), while attempting the Mannich reaction with indanedione, isolated a methylenebisamine dihydrochloride when the normal reaction failed. Fernandez and Fowler (5) have demonstrated the possibility of a six-membered hydrogen-bonded transition state in the Mannich reaction of nitroalkanes with a methylenebisamine. Burckhalter and Leib (8) offered a similar mechanism involving a chelated six-membered transition state in the Mannich reaction of phenol to account for the selective formation of the *ortho*-substituted derivative.

The present study extends the possibility of a similar six-membered (chelated) transition state to other types of Mannich reactions, especially those involving ketones and phenols as active hydrogen components. As a matter of fact, ketones, after enolization, appear to behave exactly as the phenols do from one mechanistic point of view.

Two unsymmetrical methylenebisamines,[1] 5-bromo-1-piperidinomethylisatin (VIII) and N,N-3-azabicyclo[3.2.2.] nonylmethylisatin (IX) have been reacted with β-naphthol and acetophenone, respectively. The products obtained have been identified by independent synthesis as shown in Scheme II. The selective incorporation of the piperidine and AZBN moieties in the final product is in good agreement with the observation of Fernandez and Fowler (5).



VIII                                                      XI
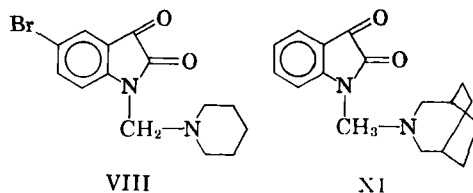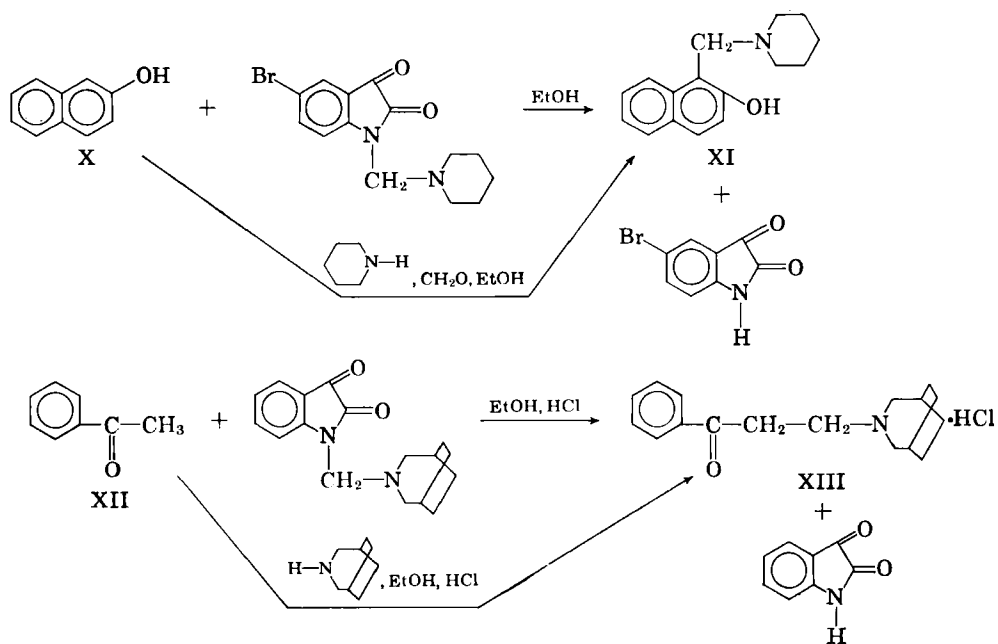


*Scheme I*



VII

A more recent study (14) indicates that at 30° practically the entire quantity of the amine exists as the methylenebisamine when the secondary amine

The possible significance of this particular study is limited by the realization that isatin acts as a weak acid in aqueous solution, being soluble in cold alkali and yielding 2-aminophenylpyruvic acid on warming with aqueous alkali. Nonetheless, the leveling effect in comparing the relative strengths of acids and bases in various solvents should be noted; the range of comparisons is limited by the strength of the solvent as an acid or base.

Participation of isatin to date in the Mannich reaction has been limited to the observation that N-Mannich bases may be prepared by the action of

[1] Isatin is a very weak base (21) and forms a crystalline perchlorate, $C_8H_5NO_2 \cdot 2H_2O$.

*Scheme II*

formaldehyde and a secondary amine with this lactam. Studies are currently underway in our laboratory to determine if it is possible to utilize the leveling effect of various solvents on amine strengths as bases in the utilization of isatin and related products as amine components in the Mannich reaction.

The stronger base should logically form a more effective hydrogen bond. The mechanism may be represented as in Scheme III; the primary step of the reaction is the formation of the methylenebisamine.

R′ and R″ may form a part of the ring in the case of cyclic ketones and phenols. In the case of phenols R‴ must necessarily be a hydrogen atom so that by enolization it can rearrange to the more stable phenol form.

Hitherto, it appears little attempt has been made to study the steric effects of the reactants. Diethylamine appears to behave quite differently in several situations (18, 22, 23) when compared with dimethylamine and piperidine. Dicyclohexylamine does not take part in the normal Mannich reaction (24). In the present study, an attempt has been made to condense dicyclopentylamine (XIV) both in acidic and basic media using acetophenone and β-naphthol, respectively, without success. Interestingly enough, heat is liberated when the amine is mixed with the formalin; this may indicate that the primary reaction, formation of the methylenebisamine, has taken place. Attempts to isolate the methylenebisamine dihydrochloride (XVI), however, have failed thus
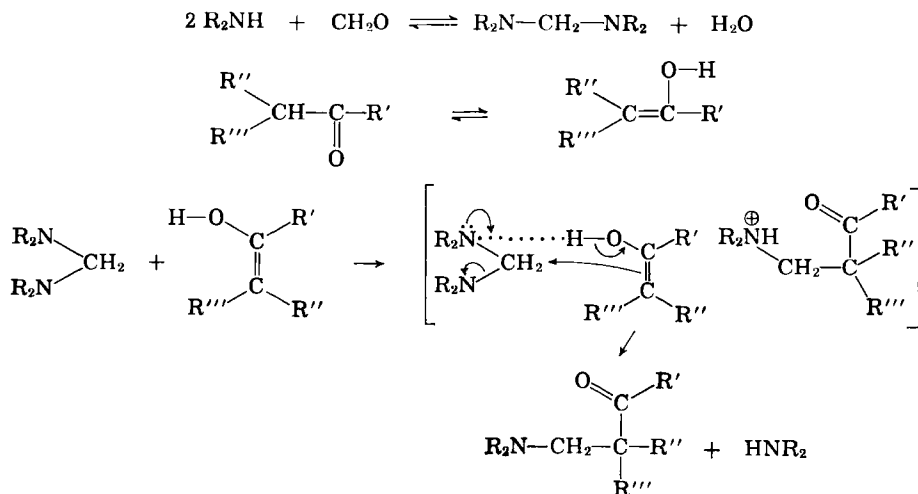


*Scheme III*

far. Instead, dicyclopentylamine (XIV) has been isolated; identity has been confirmed by independent synthesis. This is not surprising since the reaction is one of a reversible nature and a molecular model study indicates a considerable amount of steric hindrance would be involved in the formation of the methylenebisamine (XVI). But model studies would indicate no difficulty in forming the carbonium ion (XVII) from the aminomethylol (XV) and, according to the current view (4, 18, 19), XVII may result in the formation of the Mannich base (XIX) by an electrophilic attack on the enol form (XVIII) of the ketone.



XX



XIV                XV

XVI

XVIII

XVII

XIX
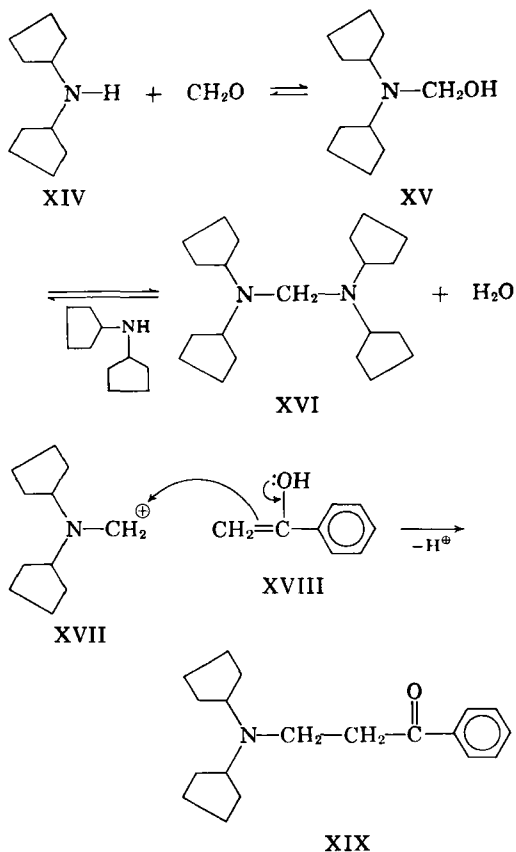
The total failure of the reaction is contrary to the current view, but is in full agreement with the mechanism proposed; the attainment of the suggested transition state (XX) is difficult on steric grounds even if the methylenebisamine (XVI) were to be formed.

The present consideration satisfactorily explains the apparent existing ambiguity (18, 25) with respect to the predominant Mannich condensation at the most highly substituted position or the least substituted postion (12, 13, 26) in 2-substituted cyclic and branched ketones. Apparently, that which determines the nature of the products will depend on the steric environment of the ketone and the ability of the methylenebisamine to form an effective hydrogen-bonded six-membered (chelated) transition state. The situation can be explained as indicated in Scheme IV. The proportion of isomer A or B may vary from 0% to 100% depending upon the
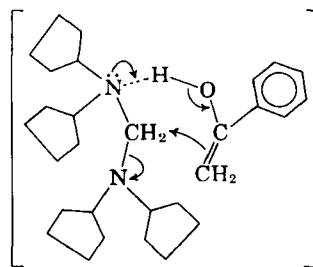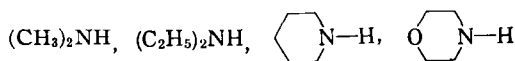
steric contribution of the substituents $R_1R_2$ and $R'$; route I is preferrred but II is followed when these groups become more bulky in nature.

The reaction is controlled both thermodynamically and kinetically. House and Trost (18) found the ratio of isomer A to B ($n = 3$; $R'$, $R_1$, $R_2 = CH_3$) to be 70 to 30% and 65 to 35% in acidic and basic media, respectively, indicating that variation of pH does not affect the ratio of the isomers considerably. The proportion of B ($n = 3$, $R' = CH_3$; $R_1 = R_2 = C_2H_5$) increases to about 42% when diethylamine is used (27) instead of dimethylamine as the former offers comparatively more resistance toward following route I.

2-Methylcyclohexanone appears to be a borderline case. Reichert and Mayr (28) report the formation of several Mannich bases of the general formula XXII in very good yields from 2-alkylcyclohexanones (XXI) having very large substituents at $C_2$. The reaction follows route II as shown in Scheme IV predominantly.



XXI                XXII

$$R^1 = -CH_2-\underset{\underset{CH_3}{|}}{CH}-(CH_2)_n-CH_3$$

$$n = 2, 3$$
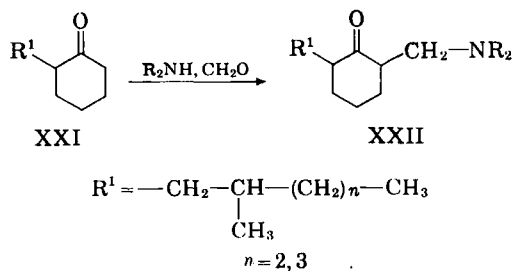
$R_2NH =$



$(CH_3)_2NH$, $(C_2H_5)_2NH$, 

Bachmann and Wick (29) have demonstrated a similar course for 2-arylcyclohexanones; the less stable enol undergoes the Mannich condensation. For example, 2-phenylcyclohexanone (XXIII) gives the Mannich base XXVII in 62% yield. (Scheme V)

The same reasoning is applicable to the behavior of menthone (XXVIII) in the Mannich reaction (12). Mention may be made that the Mannich base XXX is less strained as compared to XXIX on the basis of nonbonded interactions.

The proposed mechanism may be extended to explain the nature of the products obtained (22) from lawsone (XXXI). Contrary to expectation (12), the primary amine, instead of proceeding to the Mannich base XXXIII, gives the secondary amine, XXXII, which is the primary product of the reaction. When the complexity of the amine in-
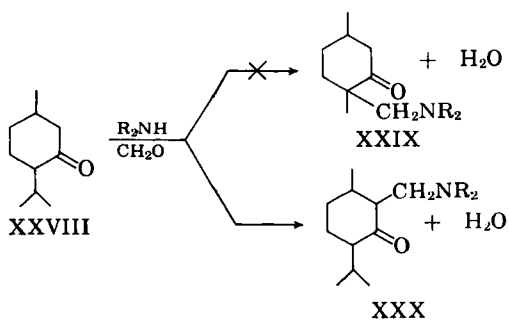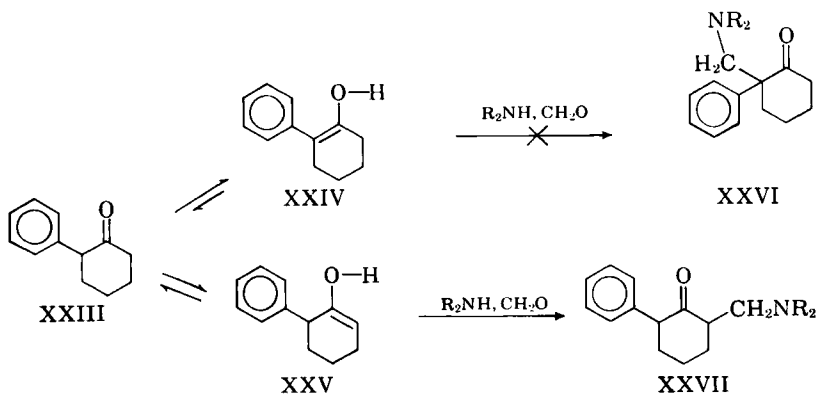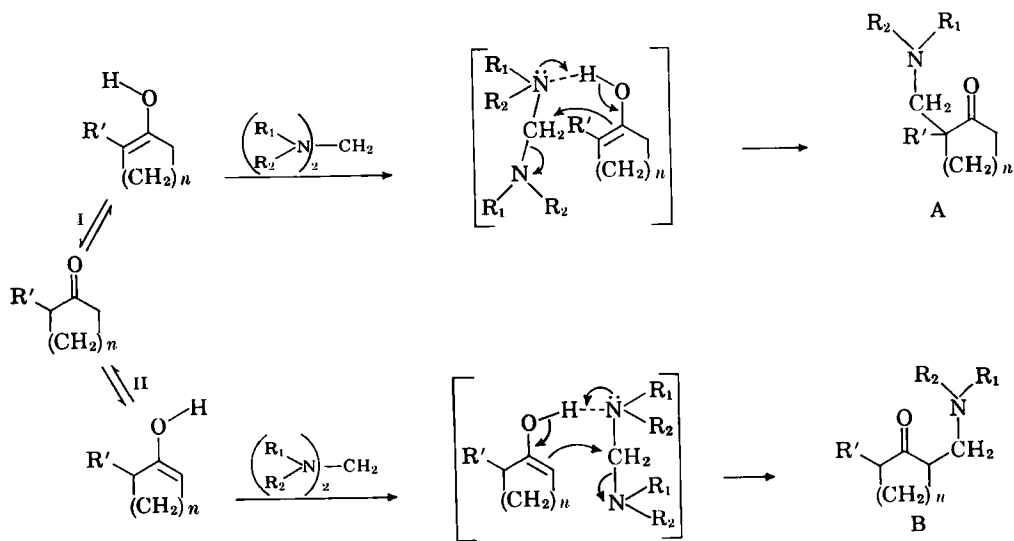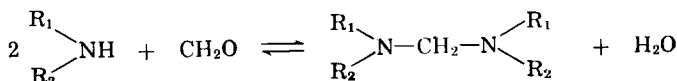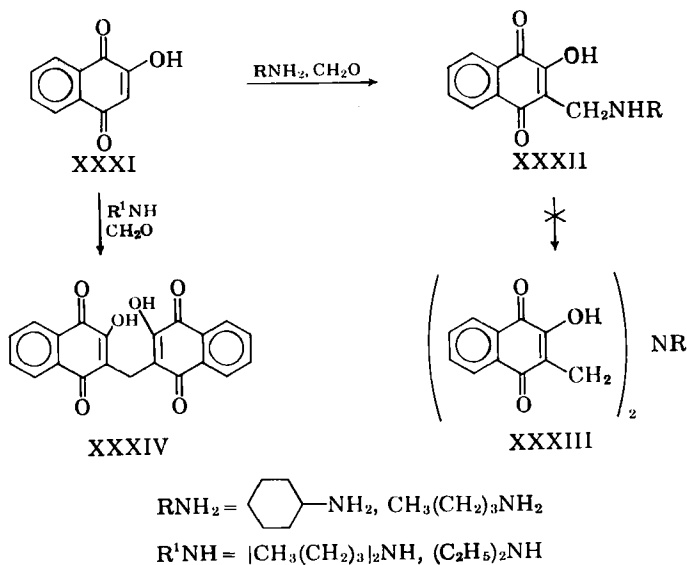
*Scheme IV*



*Scheme V*



creases, the side reaction predominates so as to give the bis compound, XXXIV (Scheme VI).

Existing views (4, 18, 19) do not appear to explain all these facts; nor do they satisfactorily explain the selective formation of the *ortho* isomer in the case of the Mannich reaction with phenols. The *ortho* substitution of the phenol may be comparable to that of Claisen rearrangement (30) of allylic ethers, rather than a simple electrophilic substitution by the car-

bonium ion, IV, which is free to attack either the *ortho* or *para* position or both.

*Para* substitution in the *ortho* substituted phenols may take place through the participation of a second molecule of the methylenebisamine as is shown in Scheme VII; this makes it a termolecular reaction, the frequency of which is considerably less than that of a bimolecular reaction under identical conditions. Thus, it also explains why *ortho* substitution takes place in unsubstituted phenols in good yields.

A considerable amount of confusion (4) exists as to the effect of pH on the Mannich reaction. Usually an acidic pH is not favorable for phenolic Mannich condensations. Too alkaline an environment also is not favorable since the sodium salt of naphthol (XXXV), under usual Mannich conditions, does not give the Mannich base XXXVI (Scheme VIII). Instead, it results in a resinous mass insoluble in both dilute alkali and dilute acid. The pH of the medium which affects unfavorably the formation and stability of the chelated transition state shown in Scheme III
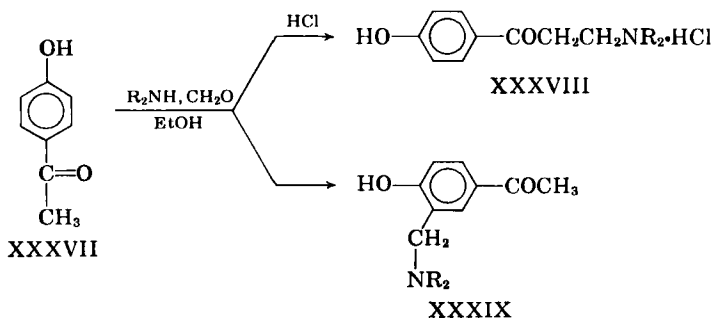
$RNH_2 = $ [cyclohexyl]$-NH_2$, $CH_3(CH_2)_3NH_2$

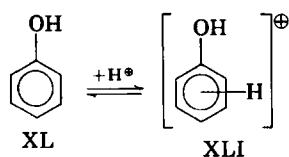$R^1NH = |CH_3(CH_2)_3|_2NH$, $(C_2H_5)_2NH$
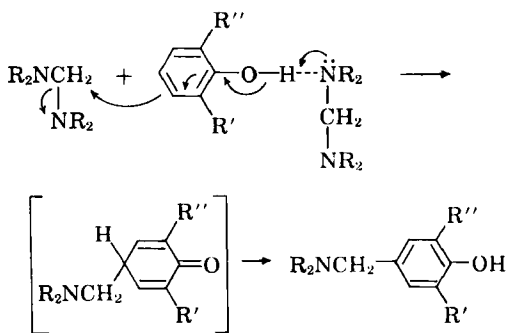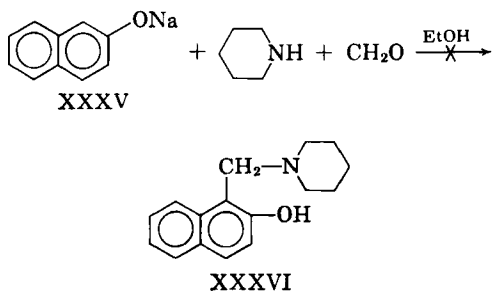
*Scheme VI*

*Scheme VII*

*Scheme VIII*

will delay the normal reaction and this in turn may result in the side reaction predominating.

Gautier and his associates (31) report the isolation of phenolic and ketonic Mannich bases from *p*-hydroxyacetophenone (XXXVII) with the reaction being carried out in basic and acidic media, respectively (Scheme IX). The products have been identified on the basis of the nuclear magnetic resonance spectra and also by chemical means. The acidic medium appears to deactivate the ring with respect to the Mannich condensation, whereas it will catalyze the enolization of the ketone, thus favoring the formation of the ketonic Mannich base, XXXVIII. This deactivation of the ring by acid may be attributed to the formation of a $\pi$-complex, XLI, between the phenol and the proton surrounding it. This results in the generation of a partial posi-

tive charge on the aromatic ring. It may be recalled that during the formation of the chelated transition state (Scheme III) the ring plays the role of a nucleophilic species and it is, therefore, evident that

*Scheme IX*

the aromatic ring carrying a partial positive charge will no longer effectively play the part of the nucleophilic species.

## EXPERIMENTAL[2]

Essentially, the method followed by Varma and Nobles (32) was utilized for the preparation of VIII and IX.

**5-Bromo-1-piperidinomethylisatin (VIII)**—A mixture of 4.25 Gm. (0.05 mole) of piperidine, 11.3 Gm. (0.05 mole) of 5-bromoisatin, 5 ml. (0.06 mole) of formalin, and 50 ml. of ethanol (95%) was heated on a water bath for 1 hr. and then chilled in an ice bath. The crude product was filtered and crystallized from ethanol; yield 13 Gm. (81%), m.p. 135–136° [lit. (32) m.p. 135–136°].

**N-N-3-Azabicyclo[3.2.2]nonylmethyl Isatin (IX)**—A mixture of 7.3 Gm. (0.05 mole) of isatin, 6.25 Gm. (0.05 mole) of 3-azabicyclo[3.2.2]nonane, 5 ml. (0.06 mole) of formalin, and 50 ml. of ethanol (95%) was heated on a water bath for 1 hr. and chilled in an ice bath. The crude product was filtered and crystallized from ethanol; yield 9.2 Gm. (64.3%), m.p. 101–102°. [Lit. (32) m.p. 103–105°.]

**2-Hydroxy-1-piperidinomethylnaphthalene (XI). Method A**—A mixture of 1.44 Gm. (0.01 mole) of β-naphthol, 0.85 Gm. (0.01 mole) of piperidine, 1 ml. (0.01 mole) of formalin, and 3 ml. of ethanol was refluxed for 2 hr. on a water bath and chilled in an ice bath. The crude product was filtered and crystallized from ethanol; yield 1.6 Gm. (66%), m.p. 94–95°. [Lit. (33) m.p. 96°.]

**Method B—From VIII**—A solution of 3.23 Gm. (0.01 mole) of VIII in 15 ml. of ethanol was refluxed with 1.44 Gm. (0.01 mole) of β-naphthol, on a water bath for 15 min.; a yellow precipitate (2.1 Gm.) separated and was removed by filtration. This was found to be 5-bromoisatin, m.p. 255–256°. The filtrate was concentrated and chilled in an ice bath until crude XI weighing 1.8 Gm. (73%) separated. Crystallization from ethanol gave a colorless product, m.p. 94–95°. A mixed melting point determination with the product from *Method A* showed no depression. The infrared spectra of the products from both methods were found to be identical.

**Phenyl-β-N-3-azabicyclo[3.2.2]nonylethyl Ketone Hydrochloride XIII. Method A**—In a 100-ml. flask 2.4 Gm. (0.02 mole) acetophenone, 2.5 Gm. (0.02 mole) of 3-azabicyclo[3.2.2]nonane, 0.9 Gm. (0.03 mole) of paraformaldehyde, and 5 ml. of ethanol (95%) were mixed; the pH was adjusted to 5 with concentrated hydrochloric acid. The mixture was refluxed for 3 hr. The volume was reduced to one-half of its original volume and 30 ml. of acetone was added by stirring. The product separated on crystallization from ethanol; yield 3.4 Gm. (68%), m.p. 199–200°. [Lit. (34) m.p. 199–200°.]

**Method B—From IX**—A mixture of 1.2 Gm. (0.01 mole) of acetophenone, 2.84 Gm. (0.01 mole) of IX, and 5 ml. of ethanol was refluxed on a water bath for 1 hr. after adjusting the pH to 5 with concentrated hydrochloric acid; a yellow precipitate

then appeared. It was filtered and identified as isatin, m.p. 197°. The filtrate was concentrated and 20 ml. of acetone was added; a light yellow precipitate, 1.9 Gm. (75%), separated; on crystallization from ethanol-acetone mixture this yielded colorless crystals, m.p. 198–199°. A mixture melting point determination with the sample from *Method A* showed no depression. The infrared spectra of both samples were found to be identical.

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◎⟶ *Keyphrases*

Mannich reaction—mechanism
Bisamines, unsymmetrical—reaction effect
Methylenebisamine—reaction intermediate
Steric factors—Mannich reaction mechanism
IR spectrophotometry—identity