CHAPTER 10

THE MANNICH REACTION

F. F. BLICKE

University of Michigan

CONTENTS

INTRODUCTION

The Mannich reaction consists in the condensation of ammonia or a primary or secondary amine, usually as the hydrochloride, with formaldehyde and a compound containing at least one hydrogen atom of pronounced reactivity. The essential feature of the reaction is the replacement of the active hydrogen atom by an aminomethyl or substituted aminomethyl group. The product from acetophenone, formaldehyde, and a secondary amine salt is an example. In the equation the reactive hydrogen atoms are underlined.

$$C_6H_5COC\underline{H}_3 + CH_2O + R_2NH\cdot HCl \rightarrow C_6H_5COC\underline{H}_2CH_2NR_2\cdot HCl + H_2O$$

The product from a methyl ketone contains reactive hydrogen atoms, and in some cases it is possible to carry the reaction one step further, yielding a compound with two basic groups.

$$C_6H_5COC\underline{H}_2NR_2\cdot HCl + CH_2O + R_2NH\cdot HCl \rightarrow C_6H_5COCH(CH_2NR_2\cdot HCl)_2 + H_2O$$

If the substance used in the condensation contains reactive hydrogen atoms on two or more different carbon atoms, then substituted aminomethyl groups may appear at different points in the molecule, leading to a mixture of isomers.

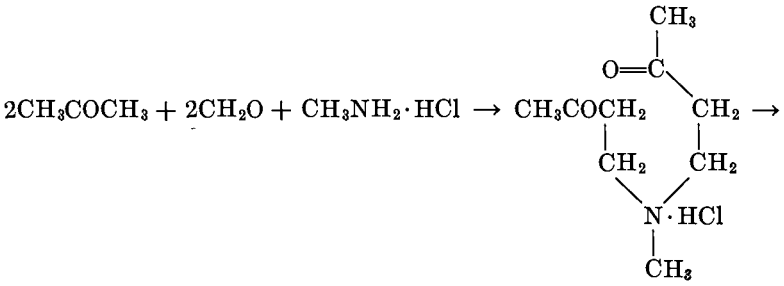
If the condensation is effected with a primary amine or its salt, the product is a secondary amine.

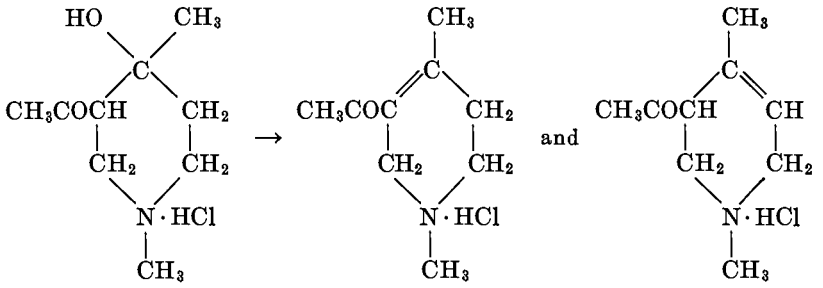
$$C_6H_5COCH_3 + CH_2O + RNH_2 \cdot HCl \rightarrow C_6H_5COCH_2CH_2NHR \cdot HCl + H_2O$$

In many cases the resulting secondary amine reacts further to yield a tertiary amine.

$$C_6H_5COCH_3 + CH_2O + C_6H_5COCH_2CH_2NHR \cdot HCl \rightarrow (C_6H_5COCH_2CH_2)_2NR \cdot HCl + H_2O$$

Frequently such products, derived from two molecules of ketone, two molecules of formaldehyde, and one molecule of primary amine, are unstable and readily undergo cyclization. The compounds obtained from acetone, formaldehyde, and methylamine are illustrative.[1]



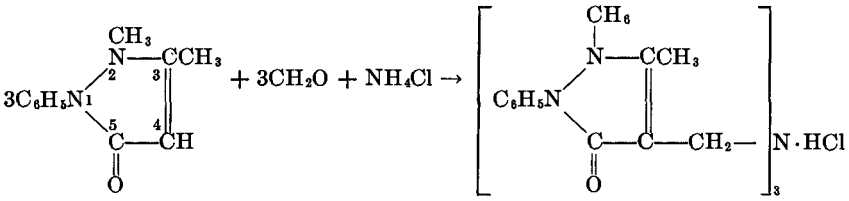


The product to be expected from a Mannich reaction involving an ammonium salt is a primary amine. In many cases, the primary amine so produced reacts further, as above, to form a secondary amine, a tertiary amine, or a cyclic substance. The situation is further complicated by the fact that methylamine, produced from the ammonium salt and formaldehyde, also takes part in the reaction. For example, the compounds shown above as products of acetone, formaldehyde, and

[1](a) Mannich and Ball, *Arch. Pharm.*, **264**, 65 (1926); (b) Mannich and Ritsert, *ibid.*, **264**, 164 (1926).

methylamine hydrochloride are also obtained from acetone, formaldehyde, and ammonium chloride.[1b]

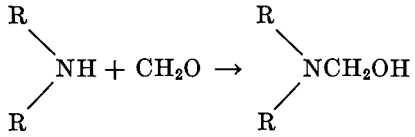
The first observation of a condensation of the type now known as the Mannich reaction was made by Tollens,[2, 3] who isolated the tertiary amine from ammonium chloride, formaldehyde, and acetophenone. Later Petrenko-Kritschenko [4] and his students studied condensations of this kind but failed to recognize the reaction as a general one. The detailed study by Mannich, begun in 1917, was initiated by the observation that antipyrine salicylate, formaldehyde, and ammonium chloride reacted to form a tertiary amine.[5]



Antipyrine

Since Aminopyrine (Pyramidon, 4-dimethylaminoantipyrine) failed to react, it was evident that the reaction involved the hydrogen atom of carbon 4 of antipyrine.

The mechanism of the Mannich reaction has not been established. The addition of the amine to formaldehyde has been considered as a possible primary step.



The fact that, in the case of antipyrine, the reaction of dimethylaminomethanol gives a poorer yield of condensation product than either formaldehyde and the amine or formaldehyde and the amine hydrochloride indicates that this view is not correct.[6] The possibility that the initial step is the formation of the methylol from the ketone has been examined.

$$RCOCH_3 + CH_2O \rightarrow RCOCH_2CH_2OH$$

[2] van Marle and Tollens, *Ber.*, **36**, 1351 (1903).

[3] Schäfer and Tollens, *Ber.*, **39**, 2181 (1906).

[4] Petrenko-Kritschenko and co-workers: (*a*) *Ber.*, **39**, 1358 (1906); (*b*) *Ber.*, **41**, 1692 (1908); (*c*) *Ber.*, **42**, 2020 (1909); (*d*) *Ber.*, **42**, 3683 (1909).

[5] Mannich and Krösche, *Arch. Pharm.*, **250**, 647 (1912).

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

The methylols of acetone and cyclohexanone do condense with dimethylamine to give the expected products. However, the methylol from antipyrine does not react at all with dimethylamine.[6] Apparently neither of these processes represents the primary step of the Mannich reaction.

THE SCOPE OF THE MANNICH REACTION

The Use of Secondary Amines

The secondary amines which have been used successfully are listed in Table I.

TABLE I

SECONDARY AMINES IN THE MANNICH REACTION

Dimethylamine	Piperidine
Diethylamine	1,2,3,4-Tetrahydroisoquinoline
Diethanolamine	6-Methoxy-1,2,3,4-tetrahydroisoquinoline
Dipropylamine	Morpholine
Di-*n*-butylamine	Piperazine
Diisoamylamine	ω-Methylaminopropiophenone
Dibenzylamine	β-Acetylethylbenzylamine
Methyldiethylethylenediamine	Benzyl-(2-cyclohexanonylmethyl)-amine
Methylaniline	3,4-Methylenedioxybenzyl-(2-cyclohexanonylmethyl)-amine

Dimethylamine is very reactive and usually leads to excellent yields. Diethylamine appears to be less reactive; it has been reported [7] that the typical condensation does not take place with ethyl methyl ketone, diethylamine, and formaldehyde. On the other hand, formaldehyde and this amine do give normal products with acetone,[8] benzalacetone,[9] acetophenone,[10] and several derivatives of the last.[11, 12] It has been reported that 2-acetylfuran and formaldehyde react normally with salts of dimethylamine, dipropylamine, di-*n*-butylamine, and diethanolamine, but not with the salt of diethylamine.[13] In other cases where dimethylamine, diethylamine, and dipropylamine have given good results, di-*n*-butylamine and diethanolamine have failed to react.[13] The cyclic secondary amines mentioned above generally react about as well as dimethylamine. However, dicyclohexylamine [14] and tetrahydroquinoline [11, 15] are said not to take part in the reaction.

[7] Kermack and Muir, *J. Chem. Soc.*, 3089 (1931).
[8] du Feu, McQuillin, and Robinson, *J. Chem. Soc.*, 53 (1937).
[9] Mannich and Schütz, *Arch. Pharm.*, **265**, 684 (1927).
[10] Blicke and Burckhalter, *J. Am. Chem. Soc.*, **64**, 451 (1942).
[11] Mannich and Lammering, *Ber.*, **55**, 3510 (1922).
[12] Mannich and Dannehl, *Arch. Pharm.*, **276**, 206 (1938).
[13] Levvy and Nisbet, *J. Chem. Soc.*, 1053 (1938).
[14] Burger and Bryant, *J. Am. Chem. Soc.*, **63**, 1054 (1941).
[15] Burger and Mosettig, *J. Am. Chem. Soc.*, **58**, 1570 (1936).

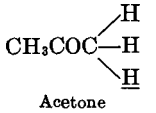
With Ketones. Saturated ketones, cycloalkanones, α,β-unsaturated ketones, aliphatic aromatic ketones, including those in which the aromatic ring is heterocyclic, and certain heterocyclic ketones containing a carbonyl group in the ring all undergo the Mannich reaction with secondary amines, usually in good yields.

In Table II are listed ketones which have been treated with formaldehyde and salts of secondary amines with the successful formation of a β-dialkylaminoketone. In the formulas the replaceable hydrogen atom is underlined. A detailed list of the Mannich reactions involving these ketones is given in Table V, p. 331.

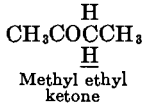
TABLE II

KETONES IN THE MANNICH REACTION

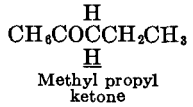
Aliphatic Ketones



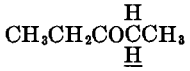
Acetone



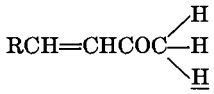
Methyl ethyl ketone



Methyl propyl ketone

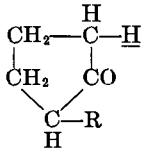


Diethyl ketone

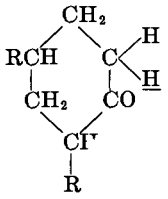


R = phenyl, substituted phenyl or α-furyl

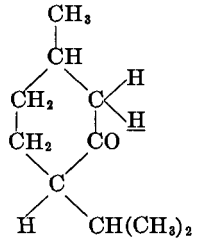
Cycloalkanones



R = H or CH_3
Cyclopentanone
2-Methylcyclopentanone

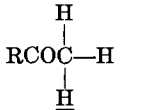


R = H or CH_3
Cyclohexanone
2-Methylcyclohexanone
4-Methylcyclohexanone

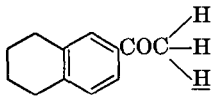


Menthone

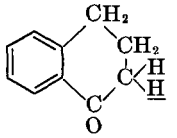
Aliphatic Aromatic Ketones



R = phenyl, substituted phenyl, β-naphthyl, 2-, 3-, or 9-phenanthryl, α-furyl, α-thienyl, or 2-(9-methylcarbazyl)



β-Acetotetralin

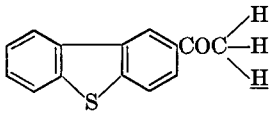


α-Tetralone
6-Methoxy-α-tetralone
6-Acetoxy -α-tetralone
7-Methoxy-α-tetralone
7-Acetoxy -α-tetralone

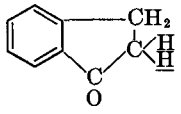
TABLE II—*Continued*

KETONES IN THE MANNICH REACTION—*Continued*

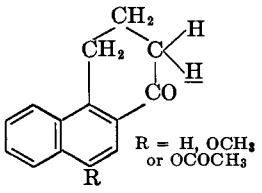
Aliphatic Aromatic Ketones—Continued



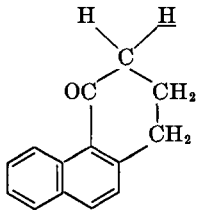
2-Acetyldibenzothiophene
4-Acetyldibenzothiophene



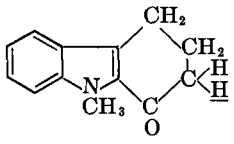
α-Hydrindone
5,6-Dimethoxy-α-hydrindone



1-Keto-1,2,3,4-tetrahydrophenanthrene, 1-keto-9-methoxy-1,2,3,4-tetrahydrophenanthrene and 1-keto-9-acetoxy-1,2,3,4-tetrahydrophenanthrene

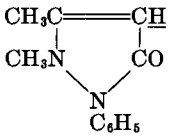


4-Keto-1,2,3,4-tetrahydrophenanthrene

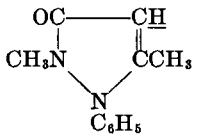


1-Keto-9-methyl-1,2,3,4-tetrahydrocarbazole

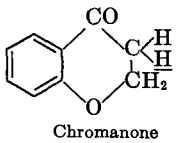
Heterocyclic Ketones



Antipyrine



Isoantipyrine



Chromanone

The following ketones have proved to be unreactive: *o*-aminoacetophenone and its acetyl and benzoyl derivatives;[12] *m*-aminoacetophenone (the acetyl and benzoyl derivatives do react in this case [12]); *p*-acetoaminoacetophenone;[11] and β-tetralone.[16] 1-Phenyl-3-methylpyrazolone-5,[17] 1-phenyl-5-methylpyrazolone-3,[17] and barbituric acid [17] do not react.

With Aldehydes. The behavior of aldehydes in the Mannich reaction is similar to that of ketones. The α-hydrogen atom of the aldehyde is substituted by a dialkylaminomethyl group. A secondary reaction which sometimes occurs involves the simultaneous introduction of a methylol group on the α-carbon atom.[18]

[16] Mosettig and May, *J. Org. Chem.*, **5**, 528 (1940).
[17] Mannich and Kather, *Arch. Pharm.*, **257**, 18 (1919).
[18] Mannich, Lesser, and Silten, *Ber.*, **65**, 378 (1932).

$$(CH_3)_2CHCH_2CHO + (CH_3)_2NH\cdot HCl + CH_2O \rightarrow$$

$$(CH_3)_2CHCHCHO \quad + \quad (CH_3)_2CHCCHO$$
$$\qquad\quad | \qquad\qquad\qquad\quad | \quad\quad |$$
$$\qquad CH_2N(CH_3)_2 \qquad\qquad CH_2OH \quad CH_2N(CH_3)_2$$

In the case of acetaldehyde the only product isolated is one of more complicated nature in which two dimethylaminomethyl groups and one methylol group have entered the molecule.[18]

$$(CH_3)_2NCH_2$$
$$\qquad\quad \diagdown$$
$$\qquad\quad CCHO$$
$$\qquad\quad \diagup \quad |$$
$$(CH_3)_2NCH_2 \quad CH_2OH$$

The aldehydes have been less extensively studied than the ketones and there are recorded merely the condensations of acetaldehyde, propionaldehyde, butyraldehyde, isobutyraldehyde, isovaleraldehyde, and hexahydrobenzaldehyde with dimethylamine or piperidine hydrochloride. The products from the reactions are shown in Table V, p. 331.

With Acids and Esters. A number of acids containing highly active hydrogen atoms in the α-position can be used instead of aldehydes or ketones. When an acid is employed the free secondary amine, rather than its salt, is used. The acids which have given satisfactory results are listed in Table III. The replaceable hydrogen atoms are underlined.

TABLE III

ACIDS IN THE MANNICH REACTION

$CNC\underline{H}_2CO_2H$	$CH_3COC\underline{H}(R)CO_2H$
p-$NO_2C_6H_4C\underline{H}_2CO_2H$	$C\underline{H}_2(CO_2H)_2$
$C_6H_5COC\underline{H}_2CO_2H$	$RC\underline{H}(CO_2H)_2$
o-$NO_2C_6H_4C\underline{H}(OH)CO_2H$	$RC\underline{H}(CO_2R)CO_2H$
$C\underline{H}_3COCO_2H$	$C_6H_5COCH_2C\underline{H}(CO_2H)_2$
$CH_3COC\underline{H}_2CO_2H$	$HO_2CCH_2C\underline{H}(CO_2H)_2$

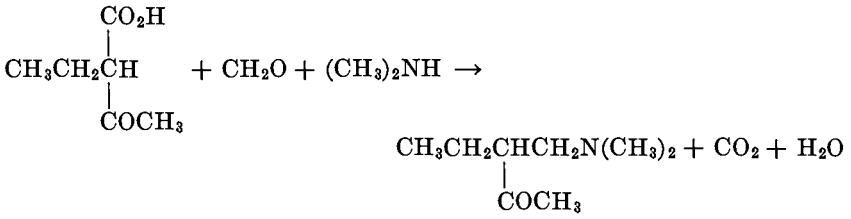
The replacement of a lone active hydrogen atom is illustrated by the reaction of ethylmalonic acid, formaldehyde, and dimethylamine.[19]

$$CH_3CH_2CH(CO_2H)_2 + CH_2O + (CH_3)_2NH \rightarrow CH_3CH_2C(CO_2H)_2CH_2N(CH_3)_2 + H_2O$$

A side reaction which often occurs involves the decarboxylation of

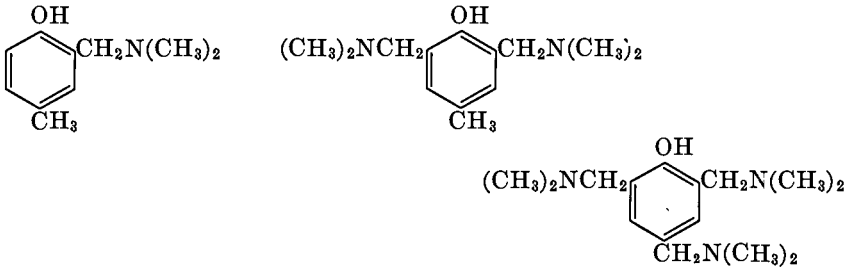
[19] Mannich and Ganz, *Ber.*, **55**, 3486 (1922).

the acid, as in the condensation of ethylacetoacetic acid with formaldehyde and dimethylamine [20]



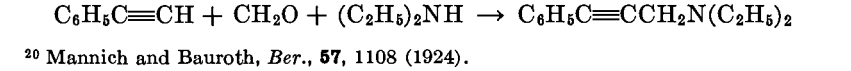
In those cases where two dialkylamino groups enter the molecule, carbon dioxide is invariably eliminated.

With Phenols. The *o*- and *p*-hydrogens in phenols are sufficiently active to enter into the Mannich reaction. Thus, products from phenol,[21, 22, 23] 4-acetaminophenol,[21] *o*- and *p*-cresol,[22] *m*-cresol,[23] 3,5-dimethylphenol,[24] 2-methyl-4-ethylphenol,[22] 2- and 4-methoxyphenol,[25] β-naphthol,[25] and 8-hydroxyquinoline [21] with formaldehyde and dimethylamine or piperidine or morpholine, have been reported. From *p*-cresol a mono- and a di-substitution product are obtained, and from phenol and *m*-cresol, trisubstitution products.



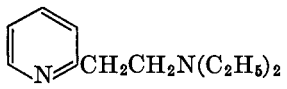
Interaction of 2-methyl-6-ethylphenol, formaldehyde, and dimethylamine is reported to yield a mixture of methylenedi-(2-methyl-6-ethylphenol) and 1-(dimethylaminomethoxy)-2-methyl-6-ethylbenzene.[22]

With Acetylenes. Phenylacetylene and certain substituted phenylacetylenes, such as the 2-nitro, 2-amino, and 4-methoxy derivatives, react readily with formaldehyde and secondary amines.[26]



[20] Mannich and Bauroth, *Ber.*, **57**, 1108 (1924).
[21] Ger. pat., 92,309; *Frdl.*, 4, 103 (1899).
[22] Décombe, *Compt. rend.*, **196**, 866 (1933).
[23] Bruson and MacMullen, *J. Am. Chem. Soc.*, **63**, 270 (1941).
[24] Caldwell and Thompson, *J. Am. Chem. Soc.*, **61**, 765 (1939).
[25] Décombe, *Compt. rend.*, **197**, 258 (1933).
[26] Mannich and Chang, *Ber.*, **66**, 418 (1933).

With α-Picolines and Quinaldines. Since an α-methyl group in a pyridine or quinoline nucleus has hydrogens of about the same activity as those in the methyl group of a methyl ketone, the Mannich reaction might be expected to take place with such molecules. α-Picoline,[27] 2-methylquinoline [7, 27, 28] (quinaldine), 2-methyl-4-hydroxyquinoline,[28] 2-methyl-8-nitroquinoline,[28] and 2-ethoxy-4-methylquinoline [28] have been condensed with dimethylamine, diethylamine, methyldiethylenediamine, piperidine, and methylaniline, either as the free amine or as the amine hydrochloride. Thus, α-picoline, formaldehyde, and diethylamine yield 2-(β-diethylaminoethyl)-pyridine.[27]



The Use of Primary Amines

The primary amines listed in Table IV have been used successfully in the Mannich condensation.

TABLE IV

PRIMARY AMINES IN THE MANNICH REACTION

Methylamine	β-Phenylethylamine
Ethylamine	Ethylenediamine
β-Hydroxyethylamine	Ethyl aminoacetate
β-Chloroethylamine	ω-Aminoacetophenone
Allylamine	Tetrahydro-β-naphthylamine
Benzylamine	Aniline *

3, 4-Methylene-dioxybenzylamine

Hydrazine [17] and guanidine,[17] have failed to react.

* Reacts only in certain instances.

With Ketones. When a primary amine or its salt is used in a Mannich reaction the first product is a secondary amine, but this often reacts with more of the reagents to give a tertiary amine. Aliphatic ketones and primary amines give rise to a number of products; for example, four substances have been isolated from the reaction of formaldehyde, diethylketone, and methylamine hydrochloride.[29] The structures of some of them are still in doubt (see also the reaction of acetone, methylamine, and formaldehyde, p. 305).

[27] Tseou Héou-Féo, *Compt. rend.*, **192**, 1242 (1931).
[28] Ger. pat., 497,907; *Frdl.*, **16**, 2669 (1931).
[29] Mannich, *Arch. Pharm.*, **255**, 261 (1917).

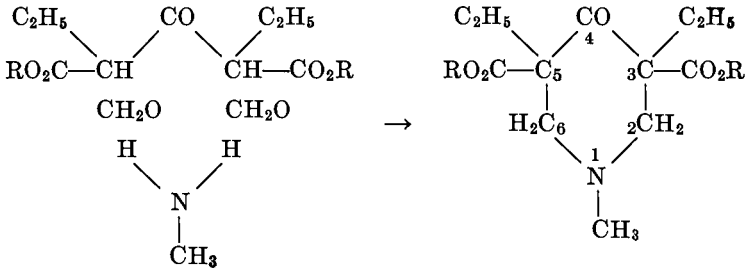
With Aldehydes. Apparently the only known reaction involving an aldehyde, a primary amine, and formaldehyde is that of isobutyraldehyde and methylamine.[30]

$$(CH_3)_2CHCHO + CH_2O + CH_3NH_2 \rightarrow (CH_3)_2\underset{\displaystyle CH_2NHCH_3}{\overset{\displaystyle |}{C}}CHO$$

With Acids and Esters. The Mannich reaction of primary amines with acids containing active hydrogen atoms leads to the same types of compounds as described above in connection with secondary amines. As might be expected, the first product often undergoes further condensation to form a tertiary amine. The reaction of methylmalonic acid, formaldehyde, and methylamine is an example.[31]

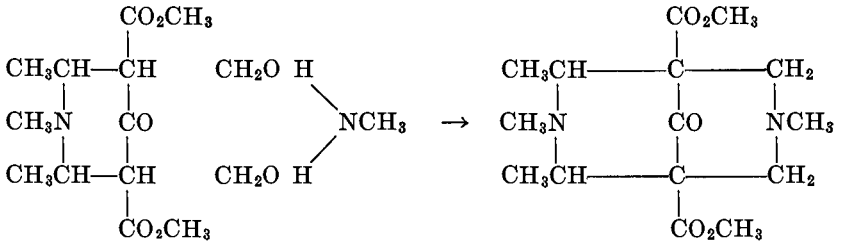
$$2CH_3\underset{\displaystyle CO_2H}{\overset{\displaystyle CO_2H}{\overset{\displaystyle |}{\underset{\displaystyle |}{CH}}}} + 2CH_2O + CH_3NH_2 \rightarrow \left(CH_3\underset{\displaystyle CO_2H}{\overset{\displaystyle CO_2H}{\overset{\displaystyle |}{\underset{\displaystyle |}{C}}}}-\!\!-CH_2 \right)_2 NCH_3$$

When a primary amine is used with a polycarbonyl compound which contains reactive hydrogen atoms on carbon atoms located in the 1,3-positions with respect to each other, then cyclic products may be expected. Thus, esters of α,α-diethylacetonedicarboxylic acid react with formaldehyde and methylamine to give pyridones.[32]



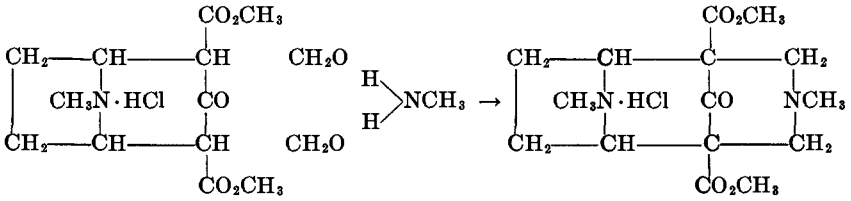
If the pyridone contains hydrogen atoms on the 3- and 5-carbon atoms, the condensation may be carried one step further and a bicyclic system may be produced. For example, the pyridone obtained by a reaction of the Mannich type from methyl acetonedicarboxylate, acetaldehyde, and methylamine can be condensed with formaldehyde and methylamine.[33]

[30] Mannich and Wieder, *Ber.*, **65**, 385 (1932).
[31] Mannich and Kather, *Ber.*, **53**, 1368 (1920).
[32] Mannich and Schumann, *Ber.*, **69**, 2299 (1936).
[33] Mannich and Viet, *Ber.*, **68**, 506 (1935).

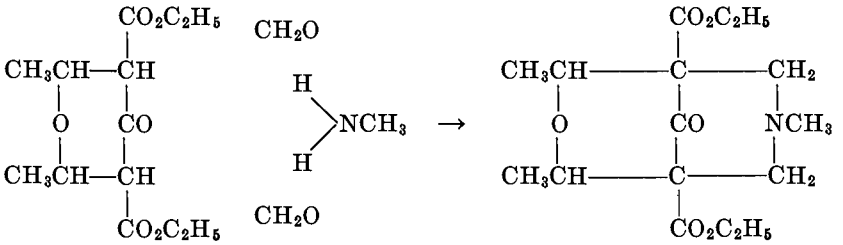


The name "bispidin" has been suggested for the bicyclic ring system produced in such reactions.[33, 34]

This reaction can be used to build up tricyclic systems. Thus, the hydrochloride of methyl tropanone-2,4-dicarboxylate reacts in the same way as the pyridone above.[33]



A similar reaction occurs when a tetrahydropyrone[35] derivative is used in place of the pyridone. For example, a bicyclic product is obtained from ethyl dimethyltetrahydropyronedicarboxylate, formaldehyde, and methylamine.



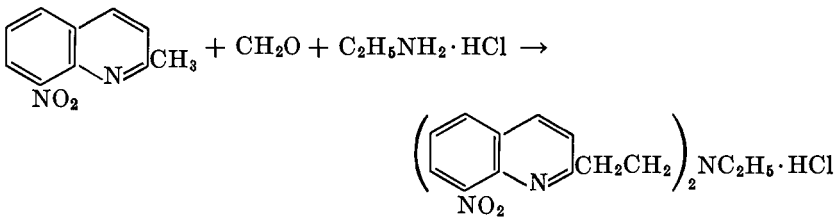
It has been suggested that the bicyclic ring system so formed be termed the "pydin" nucleus.

With Phenols and Acetylenes. No Mannich reactions involving primary amines and either phenols or acetylenes have been reported.

With α-Picolines and Quinaldines. Of the compounds containing a methyl group in the 2-position of a pyridine nucleus only 2-methyl-8-nitroquinoline has been treated with a primary amine and formalde-

[34] Mannich and Mohs, *Ber.*, **63**, 608 (1930).
[35] Mannich and Mück, *Ber.*, **63**, 604 (1930).

hyde. The amine used was ethylamine, and the product was a tertiary amine.[28]



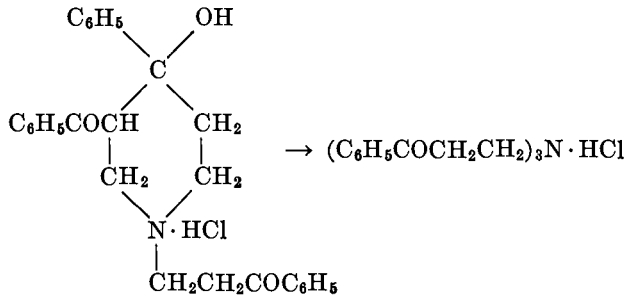
The Use of Ammonia

With Ketones. A primary amine is the first product to be expected from a Mannich reaction in which ammonia or an ammonium salt and formaldehyde react with a compound containing an active hydrogen atom. With the simple ketones subsequent reaction of the primary amine so formed usually leads to the production of tertiary amines. Salts of certain of these primary and secondary amines have been isolated and found to be stable, but the free bases change to the tertiary amines. The disproportionation of the primary and secondary amines obtained from acetophenone, formaldehyde, and ammonia is an example.[36]

$$3C_6H_5COCH_2CH_2NH_2 \rightarrow (C_6H_5COCH_2CH_2)_3N + 2NH_3$$

$$3(C_6H_5COCH_2CH_2)_2NH \rightarrow 2(C_6H_5COCH_2CH_2)_3N + NH_3$$

In some instances cyclic products are obtained from ketones, ammonia, and formaldehyde. From acetophenone, ammonium chloride, and formaldehyde there has been isolated a substance which is believed to be a substituted piperidine.[36] It readily changes to the salt of tri-(β-benzoylethyl)-amine.[3]

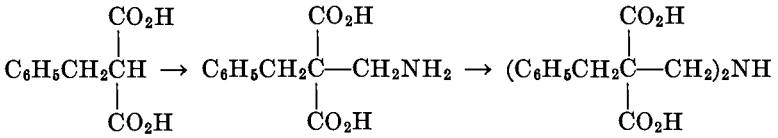


[36] Mannich and Abdullah, *Ber.*, **68**, 113 (1935).

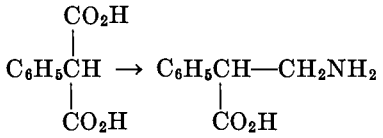
With cyclohexanone the tertiary amine is obtained directly,[5] in analogy with the reaction of antipyrine [5, 37] (p. 306).

The formation of cyclic products derived from methylamine, by reaction of acetone, formaldehyde, and ammonium chloride, has been mentioned (p. 305). The reaction with diethyl ketone takes a similar course, producing a trimethylpiperidone.[29] Presumably, methylamine is first formed from ammonium chloride and formaldehyde.

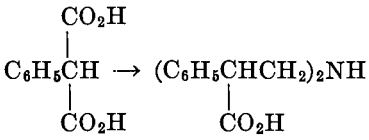
With Acids. From the reaction of benzylmalonic acid, ammonia, and formaldehyde both a primary amine and a secondary amine have been isolated.[19]



In the case of phenylmalonic acid a primary amine is produced and decarboxylation occurs when ammonia is used.[19]



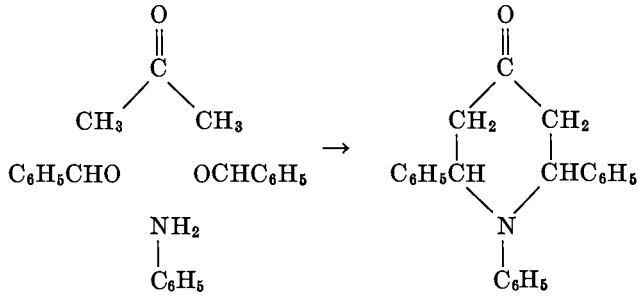
When ammonium chloride is employed the decarboxylated secondary amine is obtained.[19]



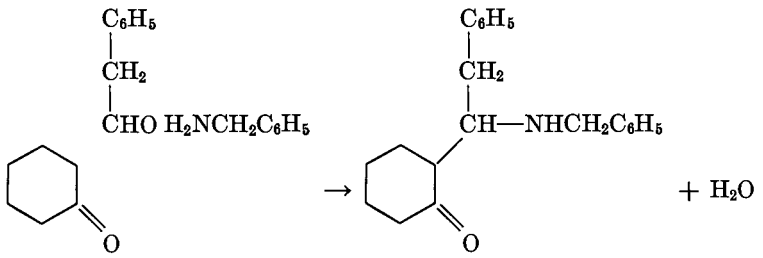
RELATED REACTIONS

Aldehydes other than formaldehyde may be used in certain condensations of the Mannich type. Those which have been studied are acetaldehyde, phenylacetaldehyde, benzaldehyde, and anisaldehyde. These have been employed successfully with acetone, cyclohexanone, and esters of acetonedicarboxylic acid. The reactions appear to be limited to ammonia and primary amines and their salts. With acetone, aniline, and benzaldehyde a piperidone is obtained.[4d]

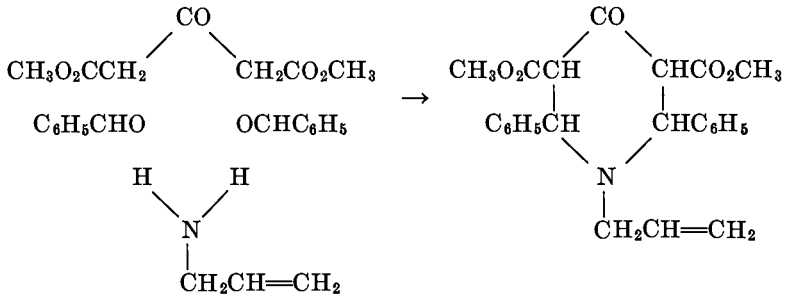
[37] Mannich and Braun, *Ber.*, **53**, 1874 (1920).



An open-chain product is formed from cyclohexanone, phenylacetaldehyde, and benzylamine.[38]



Substituted piperidones are always produced when esters of acetonedicarboxylic acid are employed, as in the reaction of the methyl ester with allylamine and benzaldehyde.[34]



Similar piperidones have been obtained by substituting for allylamine the following: ammonia,[4a] methylamine,[34] ethylamine,[4d] and β-hydroxyethylamine;[34] by employing acetaldehyde, instead of benzaldehyde, with ammonium bromide,[39] methylamine,[39] benzylamine,[39] and β-phenylethylamine;[39] and by using allylamine, anisaldehyde, and methyl acetonedicarboxylate.[34]

[36] Otto Hieronimus, Dissertation, Berlin, 1938.

[39] Peter Peckelhoff, Dissertation, Stuttgart, 1933; Ger. pat., 510,184.

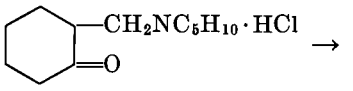
THE APPLICATION OF THE MANNICH REACTION IN SYNTHESIS

Unsaturated Compounds

Preparation of Ethylenic Compounds. The most characteristic property of many of the products obtained in the Mannich reaction, especially those derived from secondary amines, is the decomposition into the amine and an unsaturated compound. The various condensation products exhibit widely different stabilities. Some can be distilled under diminished pressure,[40] but most of them undergo decomposition when heated or subjected to steam distillation.

$$C_6H_5COCH_2CH_2N(CH_3)_2\cdot HCl \rightarrow C_6H_5COCH{=}CH_2 + (CH_3)_2NH\cdot HCl \quad \text{(Ref. 41)}$$

$$(C_6H_5COCH_2CH_2)_2NCH_3\cdot HCl \rightarrow C_6H_5COCH{=}CH_2 + C_6H_5COCH_2CH_2NHCH_3\cdot HCl \quad \text{(Ref. 41)}$$



$+ C_5H_{11}N\cdot HCl$ (Ref. 40)

$$CH_3CHCHO \quad (CH_2N(CH_3)_2\cdot HCl) \rightarrow CH_3CCHO \quad (CH_2) + (CH_3)_2NH\cdot HCl \quad \text{(Ref. 42)}$$

In a few cases the products from Mannich reactions decompose spontaneously. Thus, from monoethyl ethylmalonate, formaldehyde, and diethylamine there is obtained directly ethyl α-ethylacrylate; undoubtedly, this is formed by elimination of carbon dioxide and diethylamine from the primary reaction product.[43]

$$C_2H_5CH(COOH)COOC_2H_5 + H_2CO + (C_2H_5)_2NH \rightarrow \left[C_2H_5C(COOH)(CH_2N(C_2H_5)_2)COOC_2H_5\right]$$

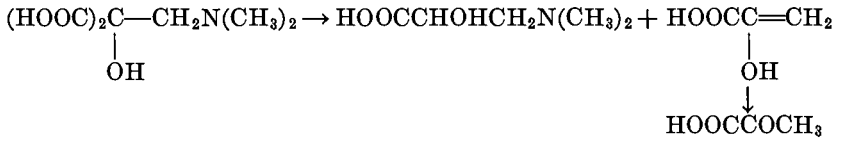
$$+ H_2O \rightarrow C_2H_5CCOOC_2H_5 \quad (CH_2) + H_2O + CO_2 + (C_2H_5)_2NH$$

Other β-dimethylaminoketones are sufficiently unstable that they decompose in the presence of sodium ethylate or dilute alkaline solu-

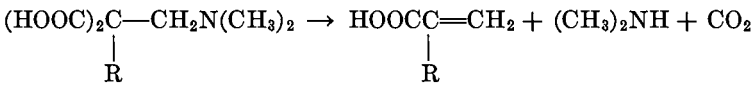
[40] Mannich and Hönig, *Arch. Pharm.*, **265**, 598 (1927).
[41] Mannich and Heilner, *Ber.*, **55**, 356 (1922).
[42] Mannich and Bauroth, *Ber.*, **55**, 3504 (1922).
[43] Mannich and Ritsert, *Ber.*, **57**, 1116 (1924).

tions. Addition of sodium carbonate to an aqueous solution of 2-nitro-β-dimethylaminopropiophenone hydrochloride or 3-acetylamino-β-dimethylaminopropiophenone hydrochloride results in an immediate liberation of dimethylamine.[12]

In some cases, when two carboxyl groups are present one is eliminated during the decomposition.[42]

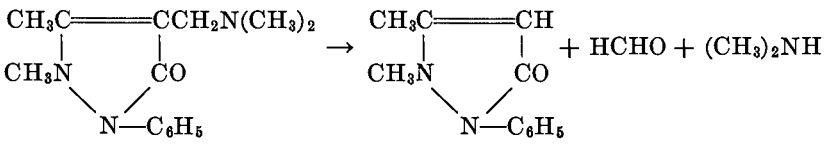


This process, when a monosubstituted malonic acid is employed, serves as a satisfactory method for synthesizing various α-aryl- or α-alkylacrylic acids.[42]



Carter and Jones,[44] in the preparation of α-benzylacrylic acid, found refluxing the Mannich base in neutral aqueous solution to be an excellent method for the decomposition.

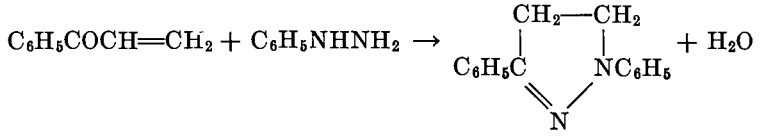
When the active hydrogen atom in the compound reacting with formaldehyde and a dialkylamine is a tertiary one, the product cannot decompose to an ethylenic substance and hence, presumably, may decompose under hydrolytic conditions to the dialkylamine, formaldehyde, and the original compound. This is illustrated by the decomposition of dimethylaminomethylantipyrine to antipyrine, dimethylamine, and formaldehyde, when treated with an aqueous solution of sodium sulfite and sulfurous acid.[17]



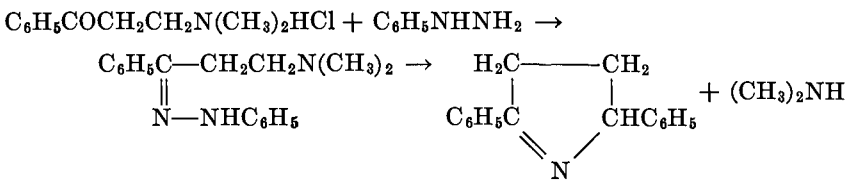
Preparation of Pyrazolines. Another reaction that may depend on intermediate formation of an ethylenic compound is the production of pyrazolines by the action of phenylhydrazine. Kohler [45] demonstrated

[44] H. E. Carter and R. C. Jones, private communication.
[45] Kohler, *Am. Chem. J.*, **42**, 375 (1909).

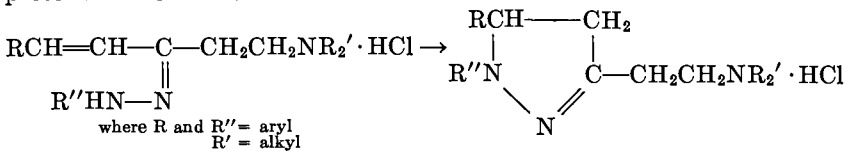
that phenyl vinyl ketone and phenylhydrazine react with surprising ease to yield 1,3-diphenylpyrazoline.



When β-dimethylaminopropiophenone hydrochloride and phenylhydrazine react in the presence of sodium acetate, 1,3-diphenylpyrazoline is formed.[13, 20, 40, 46, 47, 48] In some cases, the intermediate products must be treated with ethanolic hydrogen chloride to effect the cyclization.



It is not impossible that the initial phenylhydrazone decomposes to the phenylhydrazone of the phenyl vinyl ketone, which then cyclizes to the 1,3-diphenylpyrazoline. Such a mechanism is supported by the work of Nisbet,[49, 50, 51, 52] who observed that the phenylhydrazones of β-dialkylaminoketones derived from α,β-unsaturated ketones isomerize readily to pyrazolines and in so reacting make use of the double bond already present in the molecule.

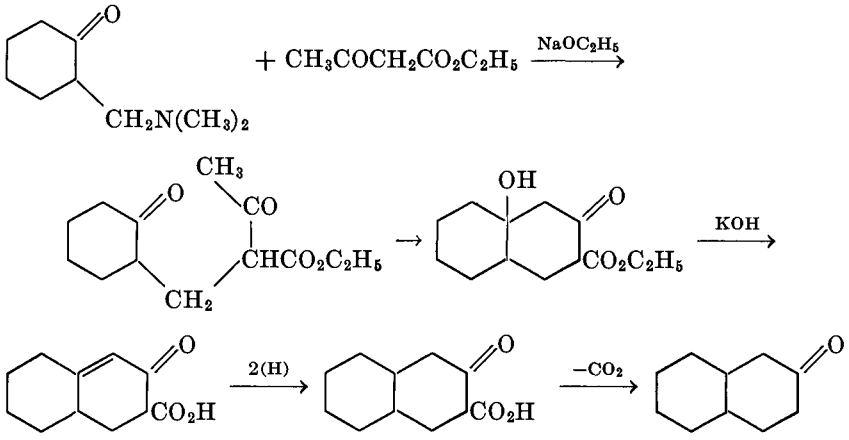


Some of the 1,5-diaryl-3-(β-dialkylaminoethyl)-pyrazoline salts were shown by Nisbet [50, 51, 52] to be local anesthetics.

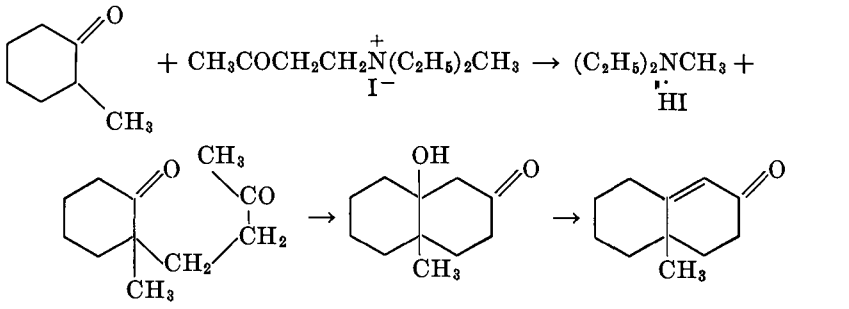
The Use of a Mannich Base as a Source of Unsaturated Ketone for Condensations with an Active Methylene Compound. A reaction which offers many possibilities in synthetic work is the condensation of β-dialkylaminoketones with active methylene compounds in the presence

[46] Jacob and Madinaveitia, *J. Chem. Soc.*, 1929 (1937).
[47] Harradence and Lions, *J. Proc. Roy. Soc. N. S. Wales*, **72**, 233 (1938).
[48] Harradence and Lions, *J. Proc. Roy. Soc. N. S. Wales*, **73**, 14 (1939).
[49] Nisbet and Gray, *J. Chem. Soc.*, 839 (1933).
[50] Nisbet, *J. Chem. Soc.*, 1237 (1938).
[51] Nisbet, *J. Chem. Soc.*, 1568 (1938).
[52] Levvy and Nisbet, *J. Chem. Soc.*, 1572 (1938).

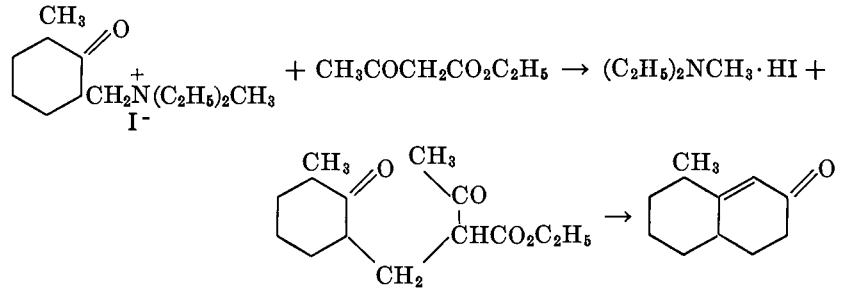
of sodium ethoxide. Apparently a gradual formation of α,β-unsaturated ketone results in a smoother addition reaction than is possible when the α,β-unsaturated ketone is used directly in the Michael condensation. For example, by a condensation with acetoacetic ester Mannich [53] converted 2-dimethylaminomethylcyclohexanone to a β-decalone derivative in excellent yield; the product was subsequently degraded to β-decalone.



Robinson [8] has employed a modification of this procedure for the synthesis of a variety of compounds which are otherwise inaccessible. The modification consists in treating the Mannich base with methyl iodide. A solution of the methiodide, which need not be isolated, is allowed to react with the active methylene compound in the presence of sodium amide or sodium ethoxide. The advantage of the methiodide over the Mannich base presumably lies in the liberation of the α,β-unsaturated ketone at lower concentration and greater reactivity. The following two syntheses illustrate Robinson's modification.



[53] Mannich, Koch, and Borkowsky, *Ber.*, **70**, 355 (1937).

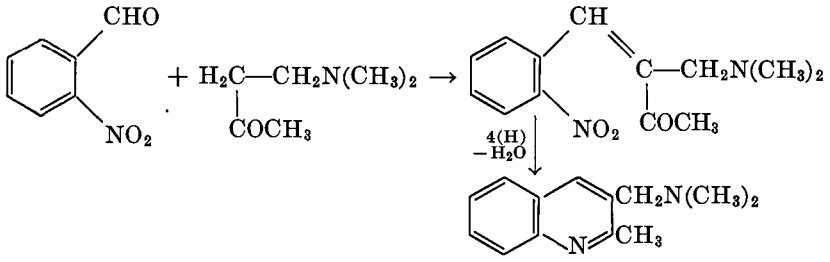


Conversion of a Ketone to Its Next Higher Homolog. Reduction of the unsaturated ketone obtained by decomposition of a Mannich base leads to a ketone with one more methylene group than that used in the preparation of the Mannich base.[11]

$$(p)\ CH_3OC_6H_4COCH_3 \rightarrow (p)\ CH_3OC_6H_4COCH_2CH_2N(CH_3)_2 \cdot HCl \rightarrow$$
$$(p)\ CH_3OC_6H_4COCH{=}CH_2 \rightarrow (p)\ CH_3OC_6H_4COCH_2CH_3$$

Syntheses Dependent on the Active Methylene Group in the Aminoketone

Advantage can be taken of the active methylene group in the β-dialkylamino carbonyl compounds for the synthesis of products otherwise inaccessible. Thus β-dimethylaminoethyl methyl ketone and *o*-nitrobenzaldehyde react to give a product which upon reduction loses water to form a substituted quinoline.[54]

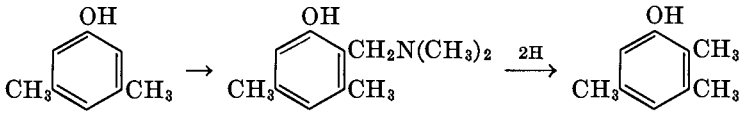


An analogous reaction may be used for the preparation 2-(β-piperidinethyl)-6,7-methylenedioxyquinoline.[55]

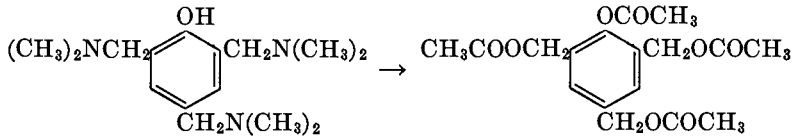
[54] Mannich and Reichert, *Arch. Pharm.*, **271**, 116 (1933).
[55] Mannich and Schilling, *Arch. Pharm.*, **276**, 582 (1938).

Syntheses Dependent on the Activity of the Dimethylamino Group in Dimethylaminomethylphenols

The products obtained by the Mannich reaction with phenols have possible synthetic uses in the introduction of methyl groups into the phenolic ring. Thus, β-dimethylaminomethylxylenol is readily hydrogenolyzed to 2,3,5-trimethylphenol.[24]



It has also been demonstrated that when these phenolic substances are treated with acetic anhydride the dimethylamino groups are replaced by acetoxy groups.[23] 2,4,6-Tri-(dimethylaminomethyl)-phenol is converted into 2,4,6-tri-(acetoxymethyl)-phenyl acetate.



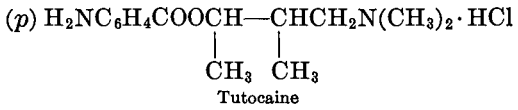
Reduction to Aminoalcohols

The β-substituted aminoketones or aldehydes can be reduced readily to the corresponding γ-substituted aminoalkanols,[11, 12] which are much more stable than the corresponding ketones. This procedure provides an unusually good source of such aminoalcohols. When the ketone contains an asymmetric carbon atom a second one is introduced when the carbinol is formed, and in several cases the two diastereoisomeric modifications have been isolated.[1, 18, 32, 56, 57, 58, 59, 60]

The γ-aminoalcohols, in the form of their benzoates and *p*-aminobenzoates, find application as local anesthetics, and many such physiologically active compounds have been prepared through the Mannich reaction.[9, 11, 18, 37, 40, 41, 56, 57, 61, 62, 63] The commercial local anesthetic Tutocaine is made from the alcohol obtained by reduction of the Mannich base from dimethylamine, formaldehyde, and ethyl methyl ketone;

[56] Mannich and Curtaz, *Arch. Pharm.*, **264**, 741 (1926).
[57] Mannich, *Arch. Pharm.*, **265**, 251 (1927).
[58] Mannich, Borkowsky, and Lin, *Arch. Pharm.*, **275**, 54 (1937).
[59] Mannich and Salzmann, *Ber.*, **72**, 506 (1939).
[60] Mannich and Stein, *Arch. Pharm.*, **264**, 77 (1926).
[61] Mannich and Schaller, *Arch. Pharm.*, **276**, 575 (1938).
[62] Mannich and Hof, *Arch. Pharm.*, **265**, 589 (1927).
[63] Mannich and Horkheimer, *Arch. Pharm.*, **264**, 167 (1926).

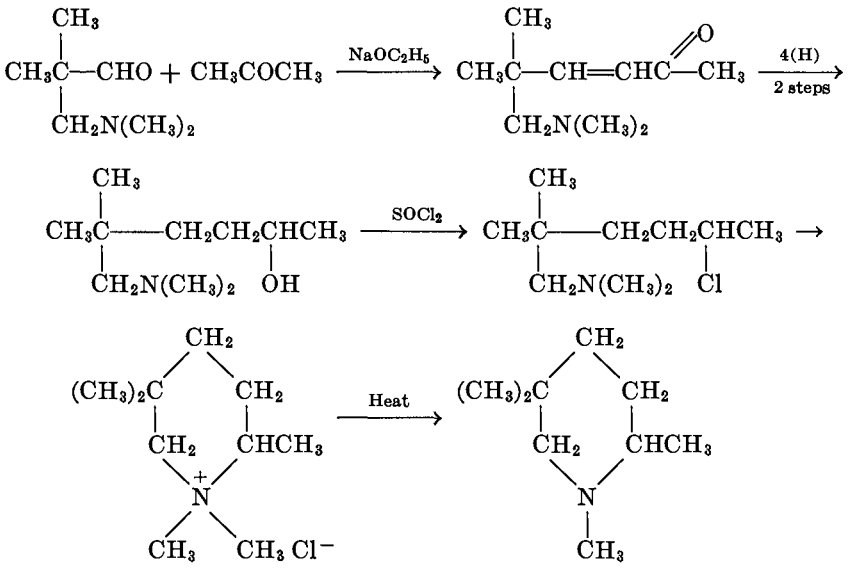
the alcohol is converted to the *p*-aminobenzoate, and the latter is used as the hydrochloride.



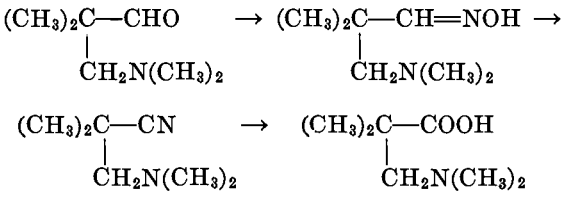
Tutocaine

Products Derived by Transformation of the Aldehyde Group in β-Dialkylaminoaldehydes

Certain of the β-dialkylaminoaldehydes can be transformed into piperidine derivatives. Thus, α,α-dimethyl-β-dimethylaminopropionaldehyde is converted into 1,2,5,5-tetramethylpiperidine.[38]

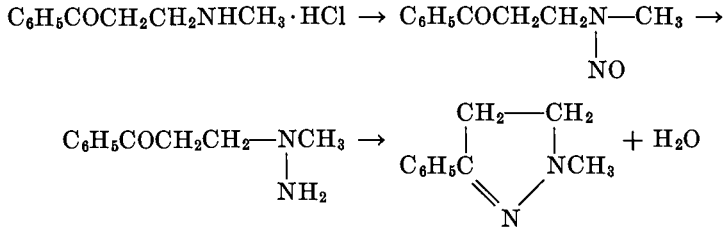


The aminoaldehyde also may be transformed into the corresponding amino acids [18] by the following series of reactions.

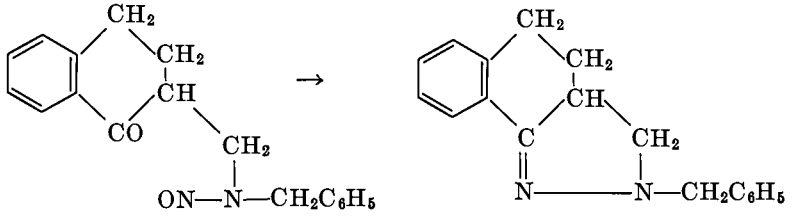


β-Monoalkylaminoketone Condensation Products

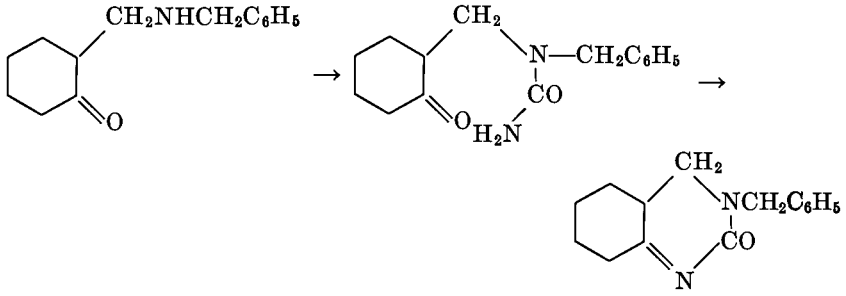
The Mannich bases from one molecule of a primary amine, one of formaldehyde, and one of ketone have been used in a variety of condensations involving both the ketone group and the secondary amine group. The nitroso derivative of β-methylaminopropiophenone is readily reduced to the corresponding β-hydrazinoketone, which cyclizes to 1-methyl-3-phenylpyrazoline.[64]



A similar cyclization occurs in the formation of 2-benzyltetrahydronaphthindazole[38] by reduction of 2-(benzylnitrosaminomethyl)-α-tetralone.

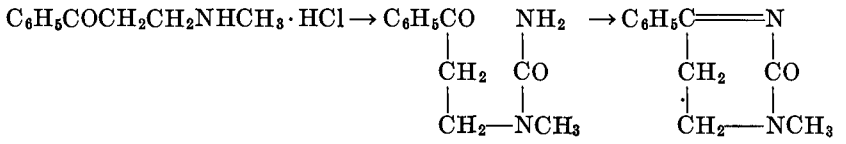


Other types of cyclic compounds may result if properly constructed molecules and appropriate reagents are used. Thus the compound from benzylamine hydrochloride, formaldehyde, and cyclohexanone reacts with potassium cyanate to form a urea which undergoes dehydration to an octahydroquinazoline.[38]



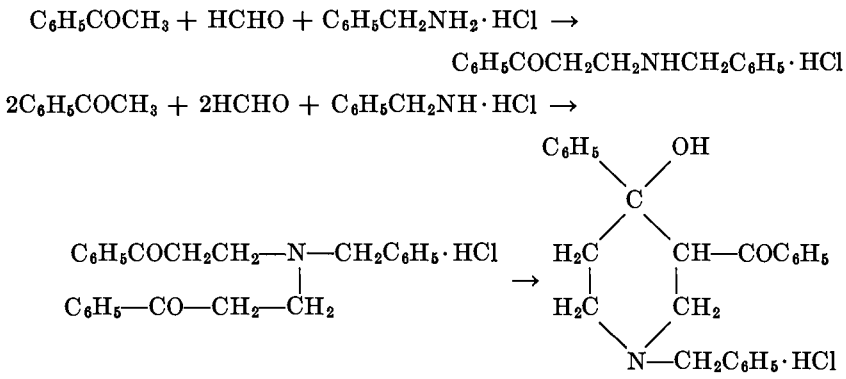
[64] Mannich and Heilner, *Ber.*, **55**, 365 (1922).

An analogous reaction has been used for the synthesis of 1-methyl-2-keto-4-phenyl-1,2,5,6-tetrahydropyrimidine from β-methylaminopropiophenone.[64]

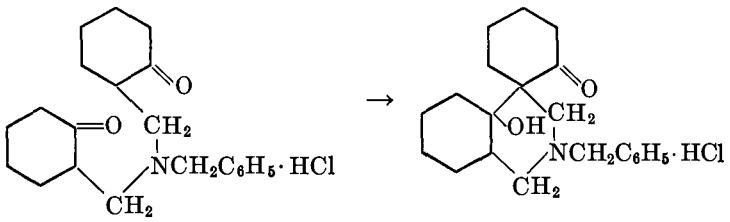


Condensation Products from One Mole of a Primary Amine, Two Moles of Formaldehyde, and Two Moles of a Ketone

Benzylamine hydrochloride, formaldehyde, and acetophenone react to form a mixture of products:[38] the first from one mole of benzylamine, one of acetophenone, and one of formaldehyde; and the second from one mole of benzylamine, two of acetophenone, and two of formaldehyde. The second is unstable and cyclizes to a piperidine derivative.

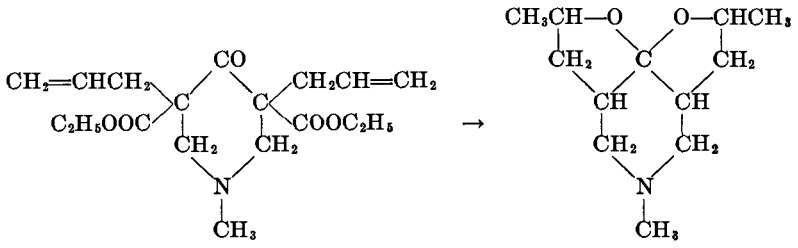


Benzylamine hydrochloride condenses similarly with cyclohexanone,[38] and the product involving two moles of cyclohexanone is converted to a reduced isoquinoline derivative during the reaction.



A tricyclic ring system is formed when the diethyl ester of 1-methyl-3,5-diallyl-4-piperidone-3,5-dicarboxylic acid (obtained from the diethyl

ester of α,α'-diallylacetonedicarboxylic acid, two moles of formaldehyde, and one of methylamine) is hydrolyzed and decarboxylated.[32]



EXPERIMENTAL CONDITIONS AND PROCEDURES

Solvents

When aqueous formaldehyde is used the condensation is ordinarily carried out by shaking or stirring the reactants in the absence of an organic solvent; in some cases[34] methanol has been added to such mixtures. When paraformaldehyde is used an organic solvent is required. If the ketone component is a liquid, such as acetone,[38] cyclopentanone,[47] or cyclohexanone,[47] an excess of it may be used as the solvent. In other cases ethanol (95% or absolute) is added as the solvent. In condensations involving 2-, 3-, or 9-acetylphenanthrene, paraformaldehyde, and salts of secondary amines, isoamyl alcohol is recommended as the solvent.[65] The condensations proceed much faster in the higher-boiling solvent, and the formation of certain by-products, obtained by prolonged heating in ethanol, is avoided. On the other hand, it is stated that, although in ethanol the condensation between 3-acetyl-9-methylcarbazole, formaldehyde, and a secondary amine salt proceeds more slowly than in isoamyl alcohol, it is less subject to side reactions associated with instability of the aminoketone salts at the higher temperature.[66]

Nature of Formaldehyde and Time of Reaction

Formaldehyde is used in the form of a 20–40% aqueous solution or as paraformaldehyde. In certain reactions, such as the condensation of α-tetralone, formaldehyde, and tetrahydroisoquinoline hydrochloride, aqueous formaldehyde is said to be superior to paraformaldehyde.[16]

In a few cases[12, 38, 47] enough concentrated hydrochloric acid is added at the beginning of the reaction to make the mixture acidic to Congo red;

[65] van de Kamp and Mosettig, *J. Am. Chem. Soc.*, **58**, 1568 (1936).
[66] Ruberg and Small, *J. Am. Chem. Soc.*, **63**, 736 (1941).

in other instances[11, 15, 65] the mixture is acidified at the end of the reaction in order to depolymerize unchanged paraformaldehyde and bring it into solution.

The time required for a Mannich reaction depends upon the nature of the ketone and of the amine salt and upon the boiling point of the solvent employed. The reaction between furfuralacetone, paraformaldehyde, and dimethylamine hydrochloride in alcoholic solution is said to be complete after the mixture has been boiled for a few minutes.[49] When 3-acetyl-9-methylcarbazole, paraformaldehyde, and diethylamine hydrochloride are heated in absolute ethanolic solution for five hours the yield of reaction product is 59% but is increased to 83% when the mixture is heated for eight hours.[66]

Relative Amounts of Components

In the preparation of Mannich products, various investigators have mixed the components in the calculated quantities or they have employed an excess of the amine salt and formaldehyde or an excess of the ketone. It is common practice to use 1.00 molecular equivalent of the carbonyl compound, 1.05–1.10 molecular equivalents of the amine salt, and 1.5–2.0 molecular equivalents of formaldehyde. Excellent yields of the basic ketone are obtained by the interaction of cyclohexanone, aqueous formaldehyde, and dimethylamine hydrochloride,[37] or morpholine hydrochloride,[47] when five times the calculated quantity of ketone is allowed to react. When excess formaldehyde is used, the material is added in several portions during the course of the reaction. Part of the formaldehyde reacts with ethanol, when this is used as a solvent, to form methylene diethyl ether.[9]

Due consideration should be given to the manner in which unchanged amine salt and formaldehyde can be separated from the desired product at the termination of the reaction. If difficulties are anticipated in such separations, the advantage to be gained by the employment of any of the components in excess may be questioned. If more than one reaction product is possible, the relative amounts of amine salt and formaldehyde may or may not influence the nature and yield of the product.[18, 19]

Isolation of Product

In a number of cases the salt of the desired product precipitates when the reaction mixture is cooled. Ether may be added to facilitate separation of the product. Occasionally the solvent is removed and crystallization of the residue brought about by washing it with ether or acetone. Sometimes it is advantageous to liberate the basic product from its salt

and purify the former by distillation, provided that the material can be distilled without decomposition.

By-Products

By-products of the reaction have been identified in some instances. They may be formed by some change of the reaction product itself, or they may be produced by condensation of the formaldehyde with the amine or ketone. Thus, diethylamine may be converted to N,N′-tetraethylmethylenediamine,[43] and piperidine to methylenedipiperidine.[56] From reactions involving cyclohexanone, there have been isolated 2-methylene cyclohexanone [37] and di-(2-cyclohexanonylmethyl) ether.[37] Similarly, methylenedi-β-naphthol [25] and methylenediantipyrine [17] have been produced in reactions involving β-naphthol and antipyrine, respectively.

Procedures

Preparation of Phenyl β-Piperidinoethyl Ketone Hydrochloride.[11] A mixture of 12.2 g. (0.1 mole) of piperidine hydrochloride, 0.25 cc. of concentrated hydrochloric acid, 4.5 g. (0.15 mole) of paraformaldehyde, 30 cc. of absolute ethanol, and 12.0 g. (0.1 mole) of acetophenone is heated to reflux. After one hour, 3 g. (0.1 mole) of paraformaldehyde is added to the solution and refluxing is continued for two hours. To the hot mixture is added 250 cc. of boiling acetone, and the resulting solution is cooled slowly, finally in ice water. The white crystalline product is collected on a filter; it weighs 21.5 g. (85%) and melts at 185–189°. For purification it is dissolved in 95% ethanol (4 cc. per g.), and the hot solution is diluted with a fourfold volume of boiling acetone. The recovery of material melting at 192–193° is about 80%.

1-Keto-2-(1,2,3,4-tetrahydroisoquinolinomethyl)-1,2,3,4-tetrahydronaphthalene.[16] A mixture of 5.0 g. (0.034 mole) of α-tetralone, 4.0 g. (0.041 mole) of 30% aqueous formaldehyde, and 6.1 g. (0.036 mole) of tetrahydroisoquinoline hydrochloride is prepared in a small (preferably 50-cc.) three-necked flask equipped with a mechanical stirrer, a reflux condenser, and a tube for admission of nitrogen. A slow stream of nitrogen is passed through the apparatus while the mixture is stirred and heated on the steam bath for one and one-half hours. The brown viscous mass is dissolved in water, and the solution is freed of neutral substances by extraction with ether. Concentrated ammonium hydroxide is then added to the aqueous solution until no further separation of water-insoluble material occurs. The product is collected by extraction with ether. The residue obtained by distillation of the ether solidifies upon washing with cold ethanol. Recrystallization of the crude material

(7.4 g.) from the minimum quantity of ethanol yields 6.6 g. (66%) of the pure aminoketone, m.p. 90–91°.

2,4,6-Tri-(dimethylaminomethyl)-phenol.[23] A mixture of 94 g. (1 mole) of phenol and 720 g. (4 moles) of 25% aqueous dimethylamine solution is cooled to 20° in a 2-l. three-necked flask fitted with a stirrer, a thermometer for reading the internal temperature, and an addition funnel. The mixture is stirred while 350 g. of 30% aqueous formaldehyde is added dropwise over a period of about one-half hour, the reaction mixture being maintained at 25–30°. Stirring at this temperature is continued for one hour after completion of the addition. The addition funnel is then replaced by a reflux condenser, and the solution is stirred and heated on a steam bath for two hours. To the hot solution is added 200 g. of sodium chloride, and stirring and heating are continued for about twenty minutes.

The organic layer is separated from the hot solution and transferred to a 500-cc. Claisen flask. It is distilled under diminished pressure; the fraction boiling at 130–150°/1-2 mm. weighs 228 g. (86%). The slight red color can be removed by redistillation (b.p. 130–135°/1 mm.) with almost no loss.

EXAMPLES OF THE MANNICH REACTION

The reactions summarized in Table V are classified according to the complexity of the basic component of the reaction mixture. Thus, reactions involving ammonia or its salts are listed first, and those involving secondary amines or their salts, last. Only the name or formula of the aminoketone is given in the product column; in reactions involving amine or ammonium salts it is to be understood that the product is also a salt. The yields are those given in the literature; sometimes they refer to purified products, sometimes to crude materials. Undoubtedly, many of the yields could be improved by a thorough study of optimum reaction conditions and processes of isolation and purification.

TABLE V *

EXAMPLES OF THE REACTION

Reactants	Product (Yield)
Ammonia, formaldehyde, and	
Tartronic acid [42]	$HOC(COOH)_2CH_2NH_2$ (39%)
Benzylmalonic acid [19]	$C_6H_5CH_2C(COOH)_2CH_2NH_2$ (65%)
	$[C_6H_5CH_2C(COOH)_2CH_2]_2NH$ (53%)
Phenylmalonic acid [19]	$C_6H_5CH(COOH)CH_2NH_2$ (63%)
Ammonia, benzaldehyde, and	
Dimethyl (and diethyl) acetonedicarboxylate [4a]	Dimethyl (and diethyl) 2,6-diphenyl-4-piperidone-3,5-dicarboxylate (good)
Ammonium chloride, formaldehyde, and	
Acetone [1b, 29]	1,4-Dimethyl-3-acetyl-4-hydroxypiperidine (—)
Diethyl ketone [29]	1,3,5-Trimethyl-4-piperidone (29) (—)
Acetophenone [3, 36]	$(C_6H_5COCH_2CH_2)_3N$ (23–31%)
	1-(β-Benzoylethyl)-3-benzoyl-4-hydroxy-4-phenylpiperidine (27%)
Cyclohexanone [37]	Tri-(2-cyclohexanonylmethyl)-amine (—)
Antipyrine [5]	Tri-(4-antipyrylmethyl)-amine (86%)
p-Tolypyrine [5]	Tri-(*p*-tolypyrylmethyl)-amine (72%)
Homoantipyrine [5]	Tri-(homoantipyrylmethyl)-amine (70%)
Phenylmalonic acid [19]	$[C_6H_5CH(COOH)CH_2]_2NH$ (63%)
Ammonium bromide,† acetaldehyde, and	
Diethyl acetonedicarboxylate [39]	Diethyl 2,6-dimethyl-4-piperidone-3,5-dicarboxylate (46 5%)
Methylamine, formaldehyde, and	
Tartronic acid [42]	$HOC(COOH)_2CH_2NHCH_3$ (33%)
Methylmalonic acid,‡ [31]	$[CH_3C(COOH)_2CH_2]_2NCH_3$ (34%)
Ethylmalonic acid [19]	$CH_3CH_2C(COOH)_2CH_2NHCH_3$ (—)
Benzylmalonic acid [19]	$C_6H_5CH_2C(COOH)_2CH_2NHCH_3$ (very good)
Phenacylmalonic acid [19]	$C_6H_5COCH_2C(COOH)_2CH_2NHCH_3$ (good)
4-Nitrophenylacetic acid [67]	(4) $NO_2C_6H_4CH(COOH)CH_2NHCH_3$ (20%)
Diethyl α,α′-diethylacetonedicarboxylate [32]	Diethyl 1-methyl-3,5-diethyl-4-piperidone-3,5-dicarboxylate (40%)
Diethyl α,α′-diallylacetonedicarboxylate [32]	Diethyl 1-methyl-3,5-diallyl-4-piperidone-3,5-dicarboxylate (65–70%)
Diethyl 2,6-dimethyltetrahydropyrone-3,5-dicarboxylate [35]	A "pydin" § (64%)
Diethyl 2,6-diphenyltetrahydropyrone-3,5-dicarboxylate [35]	A "pydin" (>80%)
Dimethyl 1-methyl-2,6-diphenyl-4-piperidone-3,5-dicarboxylate [34]	A "bispidin" § (74%)
Dimethyl 1-allyl-2,6-diphenyl-4-piperidone-3,5-dicarboxylate [34]	A "bispidin" § (70%)
Dimethyl tropanone-2,4-dicarboxylate [33]	A tricyclic compound § (45–50%)
Methylamine, benzaldehyde, and	
Dimethyl (and diethyl) acetonedicarboxylate [34, 4d]	Dimethyl (and diethyl) 1-methyl-2,6-diphenyl-4-piperidone-3,5-dicarboxylate (65%)

* References 67–74 appear on p 341

† The piperidone was obtained in smaller amount when ammonium chloride was used in place of ammonium bromide, the yield was still lower when ammonia was substituted for an ammonium salt

‡ Malonic acid yielded an unidentified product

§ See p 314

TABLE V *—*Continued*

EXAMPLES OF THE REACTION

Reactants	Product (Yield)
Methylamine hydrochloride, formaldehyde, and	
Acetone [29, 1a]	$(CH_3COCH_2CH_2)_2NCH_3$ (56%)
	1,4-Dimethyl-3-acetyl-4-hydroxypiperidine (—)
Diethyl ketone [29]	$CH_3CH_2COCH(CH_3)CH_2NH(CH_3)$ (—)
	1,3,5-Trimethyl-4-piperidone (—)
	$CH_3CH[CH_2NH(CH_3)]COCH[CH_2NH(CH_3)]CH_3$ or $CH_3CH_2COC[CH_2NH(CH_3)]_2CH_6$ (—)
	$[CH_3CH_2COCH(CH_3)CH_2]_2NCH_3$ (—)
Acetophenone [41, 10]	$C_6H_5COCH_2CH_2NHCH_3$ (70%)
	$(C_6H_5COCH_2CH_2)_2NCH_3$ (34%)
Cyclohexanone [37]	Methyldi-(2-cyclohexanonylmethyl)-amine (2.4%+)
2-Acetylthiophene [10]	Methyl di-[2-(α-thenoyl)-ethyl]-amine (61%)
Antipyrine [17]	Methyldi-(4-antipyrylmethyl)-amine (92%)
Isobutyraldehyde [30]	$(CH_3)_2C(CHO)CH_2NHCH_3$ (70%)
Dimethyl (and diethyl) 1,2,6-trimethyl-4-piperidone-3,5-dicarboxylate [33]	A "bispidin" (70%)
Methylamine hydrochloride, acetaldehyde, and	
Diethyl acetonedicarboxylate [39]	Diethyl 1,2,6-trimethyl-4-piperidone-3,5-dicarboxylate (—)
Ethylamine, benzaldehyde, and	
Diethyl acetonedicarboxylate [4d]	Diethyl 1-ethyl-2,6-diphenyl-4-piperidone-3,5-dicarboxylate (—)
Ethylamine hydrochloride, formaldehyde, and	
2-Methyl-8-nitroquinoline [26]	Ethyldi-[β-(8-nitro-2-quinolyl)-ethyl]-amine (—)
Antipyrine [17]	Ethyldi-(4-antipyrylmethyl)-amine (—)
β-Hydroxyethylamine, benzaldehyde, and	
Dimethyl acetonedicarboxylate [34]	Dimethyl 1-(β-hydroxyethyl)-2,6-diphenyl-4-piperidone-3,5-dicarboxylate (65%)
β-Chloroethylamine hydrochloride, formaldehyde, and	
Dimethyl 1,2,6-trimethyl-4-piperidone-3,5-dicarboxylate [33]	A "bispidin" (63%)
β-Phenylethylamine hydrochloride, formaldehyde, and	
Dimethyl 1,2,6-trimethyl-4-piperidone-3,5-dicarboxylate [33]	A "hispidin" (—)
β-Phenylethylamine hydrochloride, † acetaldehyde, and	
Dimethyl acetonedicarboxylate [39]	Dimethyl 1-(β-phenylethyl)-2,6-dimethyl-4-piperidone-3,5-dicarboxylate (—)
Allylamine, formaldehyde, and	
Benzylmalonic acid [19]	$C_6H_5CH_2C(COOH)_2CH_2NHCH_2CH{=}CH_2$ (good)
Dimethyl 1-methyl-2,6-diphenyl-4-piperidone-3,5-dicarboxylate [34]	A "bispidin" (75%)
Allylamine, benzaldehyde, and	
Dimethyl acetonedicarboxylate [34]	Dimethyl 1-allyl-2,6-diphenyl-4-piperidone-3,5-dicarboxylate (70%)

* References 67–74 appear on p. 341.

† Neither the racemic nor the dextro or levo modification of α-phenylethylamine hydrochloride could be made to react with acetaldehyde and the ester of acetonedicarboxylic acid.

TABLE V *—*Continued*

EXAMPLES OF THE REACTION

Reactants	Product (Yield)
Allylamine, anisaldehyde, and	
Dimethyl acetonedicarboxylate [34]	Dimethyl 1-allyl-2,6-di-*p*-anisyl-4-piperidone-3,5-dicarboxylate (70%)
Allylamine hydrochloride, formaldehyde, and	
Dimethyl 1,2,6-trimethyl-4-piperidone-3,5-dicarboxylate [33]	A "bispidin" (—)
Antipyrine [17]	Allyldi-(4-antipyrylmethyl)-amine (—)
ω-Aminoacetophenone hydrochloride, formaldehyde, and	
Antipyrine [17]	$C_6H_5COCH_2NR_2$; R = 4-antipyrylmethyl (98%)
Ethyl aminoacetate hydrochloride, formaldehyde, and	
Antipyrine [17]	$R_2NCH_2CO_2C_2H_5$; R = 4-antipyrylmethyl (—)
Benzylamine, phenylacetaldehyde, and	
Cyclohexanone [36]	$C_6H_5CH_2NHCH(CH_2C_6H_5)C_6H_9O$ (1.5%)
Benzylamine hydrochloride, formaldehyde, and	
Acetone [38]	$CH_3COCH_2CH_2NHCH_2C_6H_5$ (>3%)
Benzalacetone [36]	$C_6H_5CH{=}CHCOCH_2CH_2NHCH_2C_6H_5$ (20%)
	1-Benzyl-3-cinnamyl-4-styryl-4-hydroxypiperidine (10%)
Acetophenone [33]	$C_6H_5COCH_2CH_2NHCH_2C_6H_5$ (53%)
	1-Benzyl-3-benzoyl-4-phenyl-4-hydroxypiperidine (—)
Cyclopentanone [33]	Benzyl-(2-cyclopentanonylmethyl)-amine (—)
Cyclohexanone [36]	Benzyl-(2-cyclohexanonylmethyl)-amine (65%)
	A decahydroisoquinoline † (10–25%)
α-Tetralone [36]	β-(Benzylaminomethyl)-α-tetralone (55%)
Benzylamine hydrochloride, acetaldehyde, and	
Dimethyl acetonedicarboxylate [39]	Dimethyl 1-benzyl-2,6-dimethyl-4-piperidone-3,5-dicarboxylate (30%)
3,4-Methylenedioxybenzylamine hydrochloride, formaldehyde, and	
Acetone [36]	$CH_3COCH_2CH_2NHCH_2C_6H_3(O_2CH_2)(3,4)$ (20%)
Benzalacetone [36]	$C_6H_5CH{=}CHCOCH_2CH_2NHCH_2C_6H_3(O_2CH_2)(3,4)$ (52%)
Acetophenone [36]	$C_6H_5COCH_2CH_2NHCH_2C_6H_3(O_2CH_2)(3,4)$ (56%)
Cyclopentanone [36]	2-(3,4-Methylenedioxybenzylaminomethyl)-cyclopentanone (67%)
Cyclohexanone [36]	2-(3,4-Methylenedioxybenzylaminomethyl)-cyclohexanone (—)
	A decahydroisoquinoline † (—)
α-Tetralone [36]	β-(3,4-Methylenedioxybenzylaminomethyl)-α-tetralone (70%)
Aniline, benzaldehyde, and	
Acetone [4d]	1,2,6-Triphenyl-4-piperidone (—)
Tetrahydro-β-naphthylamine hydrochloride, formaldehyde, and	
Antipyrine [17]	Tetrahydro-β-naphthyldi-(4-antipyrylmethyl)-amine (—)
Ethylenediamine hydrochloride, formaldehyde, and	
Antipyrine [17]	Tetra-(4-antipyrylmethyl)-ethylenediamine (77%)

* References 67–74 appear on p. 341.
† See p. 326.

TABLE V *—*Continued*

EXAMPLES OF THE REACTION

Reactants	Product (Yield)
Dimethylamine, formaldehyde, and	
Cyanoacetic acid [19]	$CNCH_2CH_2N(CH_3)_2$ † (—)
4-Nitrophenylacetic acid [67]	(4) $NO_2C_6H_4CH(COOH)CH_2N(CH_3)_2$ (67%)
2,4-Dinitrophenylacetic acid [67]	(2,4) $(NO_2)_2C_6H_3CH[CH_2N(CH_3)_2]_2$ (52%)
Benzoylacetic acid [56]	$C_6H_5COCH_2CH_2N(CH_3)_2$ (—)
Pyruvic acid [20]	$(CH_3)_2NCH_2CHCOCOOCH_2$ ‡ (56%)
Acetoacetic acid [56]	$CH_6COCH_2CH_2N(CH_3)_2$ (42%)
	$CH_6COCH[CH_2N(CH_3)_2]_2$ (28%)
Methylacetoacetic acid [56]	$CH_3COCH(CH_3)CH_2N(CH_6)_2$ (—)
Ethylacetoacetic acid [20]	$CH_3COCH(C_2H_5)CH_2N(CH_6)_2$ ‡ (30%)
Allylacetoacetic acid [56]	$CH_6COCH(CH_2CH{=}CH_2)CH_2N(CH_3)_2$ (38%)
Levulinic acid [20]	$(CH_3)_2NCH_2CH_2COCH_2CH_2COOH$ ‡ (21%)
Malonic acid [31]	$CH(COOH)[CH_2N(CH_3)_2]_2$ (47%)
Methylmalonic acid [31]	$CH_3C(COOH)_2CH_2N(CH_3)_2$ (55%)
Ethylmalonic acid [19]	$CH_3CH_2C(COOH)_2CH_2N(CH_3)_2$ (70%)
Allylmalonic acid [19]	$CH_2{=}CHCH_2C(COOH)_2CH_2N(CH_3)_2$ (90%)
Benzylmalonic acid [19]	$C_6H_5CH_2C(COOH)_2CH_2N(CH_3)_2$ (90%)
Phenylmalonic acid [19]	$C_6H_5CH(COOH)CH_2N(CH_3)_2$ (60%)
γ-Phenylpropylmalonic acid [19]	$C_6H_5CH_2CH_2CH_2C(COOH)_2CH_2N(CH_3)_2$ (90%)
Phenacylmalonic acid [19]	$C_6H_5COCH_2C(COOH)_2CH_2N(CH_3)_2$ (45%)
Tartronic acid [42]	$HOC(COOH)_2CH_2N(CH_3)_2$ (54%)
Ethanetricarboxylic acid [19]	$(HOOC)_2C(CH_2COOH)CH_2N(CH_3)_2$ (46%)
Phenylacetylene [26]	$C_6H_5C{\equiv}CCH_2N(CH_3)_2$ (—)
2-Aminophenylacetylene [26]	(2) $NH_2C_6H_4C{\equiv}CCH_2N(CH_3)_2$ (—)
Antipyrine [6]	4-Dimethylaminomethylantipyrine (60%)
Phenol [21, 22, 23]	2-(Dimethylaminomethyl)-phenol (—)
	2,6-Di-(dimethylaminomethyl)-phenol (poor)
	2,4,6-Tri-(dimethylaminomethyl)-phenol (86%)
4-Acetylaminophenol [21]	2-(Dimethylaminomethyl)-4-acetylaminophenol (—)
o-Cresol [22]	2-(Dimethylaminomethyl)-6-methylphenol (—)
m-Cresol [23]	2,4,6-Tri-(dimethylaminomethyl)-3-methylphenol (—)
p-Cresol [22]	2-(Dimethylaminomethyl)-4-methylphenol (—)
	2,6-Di-(dimethylaminomethyl)-4-methylphenol (—)
2-Methoxyphenol [25]	2-Methoxy-6-(dimethylaminomethyl)-phenol (—)
4-Methoxyphenol [25]	4-Methoxy-6-(dimethylaminomethyl)-phenol (—)
3,5-Dimethylphenol [24]	2-(Dimethylaminomethyl) 3,5-dimethylphenol (34%)
2-Methyl-4-ethylphenol [22]	2-Methyl-4-ethyl-6-(dimethylaminomethyl)-phenol (—)
Catechol [25]	Dimethylaminomethylcatechol (—) ‡
Resorcinol [25]	Dimethylaminomethylresorcinol (—) ‡
Hydroquinone [24, 25]	2,5-*bis*-(Dimethylaminomethyl)-hydroquinone (almost quantitative) ‡
Phloroglucinol [25]	Dimethylaminomethylphloroglucinol (—) ‡
	bis-(Dimethylaminomethyl)-phloroglucinol (—) ‡
Indole [74]	3-Dimethylaminomethylindole (almost quantitative)
β-Naphthol [25]	Dimethylaminomethyl-β-naphthol (—)
Dimethylamine hydrochloride, formaldehyde, and	
Acetone [29, 59]	$CH_3COCH_2CH_2N(CH_3)_2$ § (—) (14%)
	$CH_6COCH[CH_2N(CH_3)_2]_2$ § (—) (58%)
Methyl ethyl ketone [62]	$CH_3COCH(CH_3)CH_2N(CH_3)_2$ (—)
	$CH_3CH_2COCH_2CH_2N(CH_3)_2$ (—)
Methyl propyl ketone [62]	$CH_3COCH(C_2H_5)CH_2N(CH_3)_2$ (—)

* References 67–74 appear on p 341
† The product could not be obtained in crystalline form
‡ In this instance the amine salt was employed
§ The amine base was used

TABLE V *—*Continued*

EXAMPLES OF THE REACTION

Reactants	Product (Yield)
Diethyl ketone [29]	$CH_3CH_2COCH(CH_3)CH_2N(CH_3)_2$ (31%)
Acetophenone [41]	$C_6H_5COCH_2CH_2N(CH_3)_2$ (60%)
2-Nitroacetophenone [12]	(2)$NO_2C_6H_4COCH_2CH_2N(CH_3)_2$ (80–90%)
3-Nitroacetophenone [12]	(3)$NO_2C_6H_4COCH_2CH_2N(CH_3)_2$ (80–90%)
3-Acetylaminoacetophenone [12]	(3)$(CH_3CONH)C_6H_4COCH_2CH_2N(CH_3)_2$ (55%)
3-Benzoylaminoacetophenone [12]	(3)$(C_6H_5CONH)C_6H_4COCH_2CH_2N(CH_3)_2$ (79%)
Acetoanisone [11]	(4)$CH_3OC_6H_4COCH_2CH_2N(CH_3)_2$ (—)
Acetoveratrone [11]	(3,4)$(CH_3O)_2C_6H_3COCH_2CH_2N(CH_3)_2$ (—)
Benzalacetone [50, 54]	$C_6H_5CH{=}CHCOCH_2CH_2N(CH_3)_2$ (25%)
4-Anisalacetone [50]	(4)$CH_3OC_6H_4CH{=}CHCOCH_2CH_2N(CH_3)_2$ (63%)
Piperonalacetone [51]	(3,4)$(CH_2O_2)C_6H_3CH{=}CHCOCH_2CH_2N(CH_3)_2$ (—)
3-Methoxy-4-ethoxybenzalacetone [51]	(3,4)$(CH_3O)(C_2H_5O)C_6H_3CH{=}CHCOCH_2CH_2N(CH_3)_2$ (—)
3-Ethoxy-4-methoxybenzalacetone [51]	(3,4)$(C_2H_5O)(CH_3O)C_6H_3CH{=}CHCOCH_2CH_2N(CH_3)_2$ (—)
6-Nitropiperonalacetone [55]	(3,4)(6)$(CH_2O_2)(NO_2)C_6H_2CH{=}CHCOCH_2CH_2N(CH_3)_2$ (—)
6-Nitroveratralacetone [55]	(3,4,6)$(CH_3O)_2(NO_2)C_6H_2CH{=}CHCOCH_2CH_2N(CH_3)_2$ (20–25%)
Methyl β-naphthyl ketone [68]	β-$C_{10}H_7COCH_2CH_2N(CH_3)_2$ (70%)
β-Acetotetralin [11]	β-(β-Dimethylaminopropionyl)-tetralin (—)
2-Acetylphenanthrene [65]	2-(β-Dimethylaminopropionyl)-phenanthrene (—)
3-Acetylphenanthrene [65]	3-(β-Dimethylaminopropionyl)-phenanthrene (—)
9-Acetylphenanthrene [65]	9-(β-Dimethylaminopropionyl)-phenanthrene (—)
Cyclopentanone [61]	2-(Dimethylaminomethyl)-cyclopentanone (—)
Cyclohexanone [37]	2-(Dimethylaminomethyl)-cyclohexanone (85%)
4-Methylcyclohexanone [40]	2-(Dimethylaminomethyl)-4-methylcyclohexanone (—)
Menthone [40]	Dimethylaminomethylmenthone † (54%)
α-Tetralone [58]	β-(Dimethylaminomethyl)-α-tetralone (70%)
1-Keto-1,2,3,4-tetrahydrophenanthrene [15]	1-Keto-2-dimethylaminomethyl-1,2,3,4-tetrahydrophenanthrene (65%)
4-Keto-1,2,3,4-tetrahydrophenanthrene [15]	4-Keto-3-dimethylaminomethyl-1,2,3,4-tetrahydrophenanthrene (77%)
2-Acetylfuran [13]	2-Furyl β-dimethylaminoethyl ketone (—)
Furfuralacetone [49]	$C_4H_3OCH{=}CHCOCH_2CH_2N(CH_3)_2$ (—)
2-Acetylthiophene [13, 10]	2-Thienyl β-dimethylaminoethyl ketone (47%)
2-Acetyldibenzothiophene [14]	β-Dimethylaminoethyl 2-dibenzothienyl ketone (41%) ‡
2-Propionylthiophene [10]	α-(Dimethylaminomethyl)-ethyl 2-thienyl ketone (60%)
2-Acetyl-4-phenylthiazole [13]	β-Dimethylaminoethyl 4-phenyl-2-thiazolyl ketone (—)
Antipyrine [17]	4-Dimethylaminomethylantipyrine (90%)
Isoantipyrine [17]	1-Phenyl-2,5-dimethyl-4-dimethylaminomethylpyrazolone-3 (74%)
2-Acetyl-9-methylcarbazole [69]	β-Dimethylaminoethyl 2-(9-methylcarbazyl) ketone (18%)
3-Acetyl-9-methylcarbazole [66]	β-Dimethylaminoethyl 3-(9-methylcarbazyl) ketone (61%) ‡
1-Keto-9-methyl-1,2,3,4-tetrahydrocarbazole [69]	1-Keto-2-dimethylaminomethyl-9-methyl-1,2,3,4-tetrahydrocarbazole (10–15%)
Acetaldehyde [16]	$[(CH_3)_2NCH_2]_2C(CH_2OH)CHO$ (practically quantitative)
Propionaldehyde [16]	$CH_3CH[CH_2N(CH_3)_2]CHO$ (15%)
	$CH_3C[CH_2N(CH_3)_2]_2CHO$ (—)

* References 67–74 appear on p. 341.
† A mixture of isomers seems to be formed.
‡ Yield based on the amount of original ketone not recovered from the reaction mixture.

TABLE V *—*Continued*

EXAMPLES OF THE REACTION

Reactants	Product (Yield)
Butyraldehyde [18]	$CH_3CH_2CH[CH_2N(CH_3)_2]CHO$ (—)
	$CH_3CH_2C(=CH_2)CHO$ (—)
Isobutyraldehyde [16]	$(CH_3)_2C[CH_2N(CH_3)_2]CHO$ (70–80%)
Isovaleraldehyde [18]	$(CH_3)_2CHCH[CH_2N(CH_3)_2]CHO$ (—)
	$(CH_3)_2CH(CH_2OH)[CH_2N(CH_3)_2]CHO$ (—)
Hexahydrobenzaldehyde [18]	1-Dimethylaminomethylhexahydrobenzaldehyde (—)
2-Methylquinoline [26]	2-(β-Dimethylaminoethyl)-quinoline (—)
2-Methyl-4-hydroxyquinoline [26]	2-(β-Dimethylaminoethyl)-4-hydroxyquinoline (—)
2-Ethoxy-4-methylquinoline [23]	2-Ethoxy-4-(β-dimethylaminoethyl)-quinoline (—)
Diethylamine, formaldehyde, and	
2,4-Dinitrophenylacetic acid [67]	$(2,4)(NO_2)_2C_6H_3CH[CH_2N(C_2H_5)_2]_2$ (52%)
Benzylacetoacetic acid [56]	$CH_3COCH(CH_2C_6H_5)CH_2N(C_2H_5)_2$ (46%)
Monoethylmalonate [43]	$C_2H_5OOCCH_2CH_2N(C_2H_5)_2$ (21%)
	$C_2H_5OOCCH[CH_2N(C_2H_5)_2]_2$ (—)
Monoethyl methylmalonate [43]	$C_2H_5OOCC(=CH_2)CH_3$ (88%)
Monoethyl ethylmalonate [43]	$C_2H_5OOCC(=CH_2)CH_2CH_3$ (63%)
Monoethyl allylmalonate [43]	$C_2H_5OOCC(=CH_2)CH_2CH=CH_2$ (quantitative)
Monoethyl benzylmalonate [43]	$C_2H_5OOCC(=CH_2)CH_2C_6H_5$ (73%)
Diethyl 2,6-dimethyltetrahydropyrone-3,5-dicarboxylate [35]	Diethyl 2,6-dimethyl-3-diethylaminomethyltetrahydropyrone-3,5-dicarboxylate (30%)
Phenylacetylene [26]	$C_6H_5C\equiv CCH_2N(C_2H_5)_2$ (80%)
2-Nitrophenylacetylene [26]	$(2)NO_2C_6H_4C\equiv CCH_2N(C_2H_5)_2$ (—)
4-Nitrophenylacetylene [26]	$(4)NO_2C_6H_4C\equiv CCH_2N(C_2H_5)_2$ (—)
4-Methoxyphenylacetylene [26]	$(4)CH_3OC_6H_4C\equiv CCH_2N(C_2H_5)_2$ (—)
α-Picoline [27]	2-(β-Diethylaminoethyl)-pyridine (80%)
Quinaldine [7, 27]	2-(β-Diethylaminoethyl)-quinoline (33%)
Diethylamine hydrochloride, formaldehyde, and	
Acetone [6]	$CH_3COCH_2CH_2N(C_2H_5)_2$ (66%)
Acetophenone [10]	$C_6H_5COCH_2CH_2N(C_2H_5)_2$ (45%)
2-Nitroacetophenone [12]	$(2)NO_2C_6H_4COCH_2CH_2N(C_2H_5)_2$ (80–90%)
3-Nitroacetophenone [12]	$(3)NO_2C_6H_4COCH_2CH_2N(C_2H_5)_2$ (80–90%)
Acetoveratrone [11]	$(3,4)(CH_3O)_2C_6H_3COCH_2CH_2N(C_2H_5)_2$ (—)
Benzalacetone [9]	$C_6H_5CH=CHCOCH_2CH_2N(C_2H_5)_2$ (60%)
4-Anisalacetone [50]	$(4)CH_3OC_6H_4CH=CHCOCH_2CH_2N(C_2H_5)_2$ (60%)
2-Butoxybenzalacetone [52]	$(2)C_4H_9OC_6H_4CH=CHCOCH_2CH_2N(C_2H_5)_2$ (5–10%)
Methylenedioxybenzalacetone [9]	$(3,4)(CH_2O_2)C_6H_6CH=CHCOCH_2CH_2N(C_2H_5)_2$ (60%)
3,4-Dimethoxybenzalacetone [9, 51]	$(3,4)(CH_6O)_2C_6H_3CH=CHCOCH_2CH_2N(C_2H_5)_2$ (60%)
3-Ethoxy-4-methoxybenzalacetone [51]	$(3,4)(C_2H_5O)(CH_3O)C_6H_3CH=CHCOCH_2CH_2N(C_2H_5)_2$ (—)
6-Nitropiperonalacetone [55]	$(3,4,6)(CH_2O_2)(NO_2)C_6H_2CH=CHCOCH_2CH_2N(C_2H_5)_2$ (50%)
6-Nitroveratralacetone [55]	$(3,4,6)(CH_3O)_2(NO_2)C_6H_2CH=CHCOCH_2CH_2N(C_2H_5)_2$ (40%)
2-Acetylphenanthrene [65]	2-(β-Diethylaminopropionyl)-phenanthrene (—)
3-Acetylphenanthrene [65]	3-(β-Diethylaminopropionyl)-phenanthrene (—)
9-Acetylphenanthrene [65]	9-(β-Diethylaminopropionyl)-phenanthrene (—)
2-Methylcyclopentanone [8]	2-Methyl-5-diethylaminomethylcyclopentanone (71%)
Cyclohexanone [40]	2-Diethylaminomethylcyclohexanone (83%)
2-Methylcyclohexanone [6]	2-Methyl-6-diethylaminomethylcyclohexanone (60–65%)
1-Keto-1,2,3,4-tetrahydrophenanthrene [15]	1-Keto-2-diethylaminomethyl-1,2,3,4-tetrahydrophenanthrene (59%)

* References 67–74 appear on p. 341.

TABLE V *—*Continued*

EXAMPLES OF THE REACTION

Reactants	Product (Yield)
4-Keto-1,2,3,4-tetrahydrophenanthrene [15]	4-Keto-3-diethylaminomethyl-1,2,3,4-tetrahydrophenanthrene (51%)
1-Keto-9-methoxy-1,2,3,4-tetrahydrophenanthrene [70]	1-Keto-2-diethylaminomethyl-9-methoxy-1,2,3,4-tetrahydrophenanthrene (41%)
1-Keto-9-acetoxy-1,2,3,4-tetrahydrophenanthrene [70]	1-Keto-2-diethylaminomethyl-9-acetoxy-1,2,3,4-tetrahydrophenanthrene (20%)
Furfuralacetone [49]	$C_4H_3OCH{=}CHCOCH_2CH_2N(C_2H_5)_2$ (—)
Chromanone [71]	3-Diethylaminomethyl-4-chromanone (—)
2-Acetylthiophene [10]	β-Diethylaminoethyl 2-thienyl ketone (39%)
2-Acetyldibenzothiophene [14]	β-Diethylaminoethyl 2-dibenzothienyl ketone (40%)
Antipyrine [17]	4-Diethylaminomethylantipyrine (—)
2-Acetyl-9-methylcarbazole [69]	β-Diethylaminoethyl 2-(9-methylcarbazyl) ketone (20–25%)
3-Acetyl-9-methylcarbazole [66]	β-Diethylaminoethyl 3-(9-methylcarbazyl) ketone (83%)†
2-Acetyl-4-phenylthiazole [13]	β-Diethylaminoethyl 4-phenyl-2-thiazolyl ketone (—)
Isobutyraldehyde [16]	$(CH_3)_2C[CH_2N(C_2H_5)_2]CHO$ (—)
Diethanolamine hydrochloride, formaldehyde, and	
2-Acetylfuran [13]	Di-β-(β-hydroxyethyl)-aminoethyl 2-furyl ketone (—)
Dipropylamine, formaldehyde, and	
Ethylacetoacetic acid [56]	$CH_3COCH(C_2H_5)CH_2N(C_6H_7)_2$ (40%)
Dipropylamine hydrochloride, formaldehyde, and	
Anisalacetone [50]	(4)$CH_3OC_6H_4CH{=}CHCOCH_2CH_2N(C_3H_7)_2$ (85%)
2-Acetylfuran [13]	β-Dipropylaminoethyl 2-furyl ketone (—)
2-Acetyl-4-phenylthiazole [13]	β-Dipropylaminoethyl 4-phenyl-2-thiazolyl ketone (—)
Dibutylamine hydrochloride, formaldehyde, and	
2-Acetylfuran [13]	β-Dibutylaminoethyl 2-furyl ketone (—)
Anisalacetone [50]	(4)$CH_3OC_6H_4CH{=}CHCOCH_2CH_2N(C_4H_9)_2$ (16%)
Diisoamylamine hydrochloride, formaldehyde, and	
Acetophenone [63]	$C_6H_5COCH_2CH_2N(C_5H_{11})_2$ (54%)
Methyldiethylethylenediamine hydrochloride, formaldehyde, and	
2-Methyl-4-hydroxyquinoline [28]	Methyldiethyl-β-(4-hydroxy-2-quinolyl)-ethylethylenediamine (—)
ω-Methylaminopropiophenone hydrochloride, formaldehyde, and	
Antipyrine [64]	$C_6H_5COCH_2CH_2N(CH_3)R$; R = 4-antipyrylmethyl (—)
β-Acetylethylbenzylamine hydrochloride, formaldehyde, and	
Acetone [38]	1-Benzyl-3-(α-hydroxyethyl)-4-methyl-4-hydroxypiperidine (—)
Dibenzylamine hydrochloride, formaldehyde, and	
Anisalacetone [50]	(4)$CH_6OC_6H_4CH{=}CHCOCH_2CH_2N(CH_2C_6H_5)_2$ (93%)

* References 67–74 appear on p. 341.
† Yield based on the amount of original ketone not recovered from the reaction mixture.

TABLE V *—*Continued*

EXAMPLES OF THE REACTION

Reactants	Product (Yield)
Benzyl-(2-cyclohexanonylmethyl)-amine hydrobromide, formaldehyde, and	
Acetone [36]	2-Benzyl-4-acetyl-10-hydroxydecahydroisoquinoline (73%)
Acetophenone [66]	2-Benzyl-4-benzoyl-10-hydroxydecahydroisoquinoline (7.5%)
3,4-Methylenedioxybenzyl-(2-cyclohexanonylmethyl)-amine hydrobromide, formaldehyde, and	
Acetone [38]	2-(3,4-Methylenedioxybenzyl)-4-acetyl-10-hydroxydecahydroisoquinoline (—)
Methylaniline, formaldehyde, and	
Quinaldine hydrochloride [7]	2-(β-Phenylmethylaminoethyl)-quinoline (—)
Methylaniline hydrochloride, formaldehyde, and	
Antipyrine [17]	4-(Phenylmethylaminomethyl)-antipyrine (49%)
Piperidine, formaldehyde, and	
Antipyrine [6]	4-Piperidinomethylantipyrine (44%)
Cyclohexanone [6]	2-Piperidinomethylcyclohexanone (37%)
4-Nitrophenylacetic acid [67]	(4) $NO_2C_6H_4CH(COOH)CH_2NC_5H_{10}$ (64%)
2,4-Dinitrophenylacetic acid [67]	(2,4) $(NO_2)_2C_6H_3CH(CH_2NC_5H_{10})_2$ (41%)
2-Nitromandelic acid [67]	(2) $NO_2C_6H_4C(OH)(COOH)CH_2NC_5H_{10}$ (75%)
Benzoylacetic acid [56]	$C_6H_5COCH_2CH_2NC_5H_{10}$ (90%)
Pyruvic acid [20]	$C_5H_{10}NCH_2CHCOCOOCH_2$ † (43%)
Methylacetoacetic acid [56]	$CH_3COCH(CH_3)CH_2NC_5H_{10}$ (60%)
Ethylacetoacetic acid [20]	$CH_3COCH(C_2H_5)CH_2NC_5H_{10}$ † (—)
Allylacetoacetic acid [56]	$CH_3COCH(CH_2CH{=}CH_2)CH_2NC_5H_{10}$ (30–45%)
Benzylacetoacetic acid [56]	$CH_3COCH(CH_2C_6H_5)CH_2NC_5H_{10}$ (46%)
Levulinic acid [20]	$CH_2(CH_2NC_5H_{10})COCH_2CH_2COOH$ (48%) †
Benzylmalonic acid [19]	$C_6H_5CH_2C(COOH)_2CH_2NC_5H_{10}$ (85%)
Tartronic acid [42]	$C(OH)(COOH)_2CH_2NC_5H_{10}$ (14%)
Diethyl 2,6-dimethyltetrahydropyrone-3,5-dicarboxylate [35]	Diethyl 2,6-dimethyl-3-(piperidinomethyl)-tetrahydropyrone-3,5-dicarboxylate (73%)
Phenylacetylene [26]	$C_6H_5C{\equiv}CCH_2NC_5H_{10}$ (—)
4-Methoxyphenylacetylene [26]	(4) $CH_3OC_6H_4C{\equiv}CCH_2NC_5H_{10}$ (—)
4-Acetylaminophenol [21]	2-Piperidinomethyl-4-acetylaminophenol (—)
β-Naphthol [25]	Piperidinomethyl-β-naphthol (—)
8-Hydroxyquinoline [21]	Piperidinomethyl-8-hydroxyquinoline (—)
Quinaldine hydrochloride [7]	2-(β-Piperidinoethyl)-quinoline (72%)
Indole [74]	3-Piperidinomethylindole (—)
Piperidine hydrochloride, formaldehyde, and	
Acetone [62]	$CH_6COCH_2CH_2NC_5H_{10}$ (good)
Methyl ethyl ketone [62]	$CH_3COCH(CH_3)CH_2NC_5H_{10}$ (—)
Pinacoline [62]	$(CH_3)_3CCOCH_2CH_2NC_5H_{10}$ (—)
Allylacetone [62]	$CH_2{=}CHCH_2CH_2COCH_2CH_2NC_5H_{10}$ (20%)
	$CH_2{=}CHCH_2CH(CH_2NC_5H_{10})COCH_3$ (—)
Acetophenone [11]	$C_6H_5COCH_2CH_2NC_5H_{10}$ (90%)
2-Nitroacetophenone [12]	(2) $NO_2C_6H_4COCH_2CH_2NC_5H_{10}$ (80–90%)
3-Nitroacetophenone [12]	(3) $NO_2C_6H_4COCH_2CH_2NC_5H_{10}$ (80–90%)
Acetoanisone [11]	(4) $CH_3OC_6H_4COCH_2CH_2NC_5H_{10}$ (—)

* References 67–74 appear on p. 341.
† In this instance the amine hydrochloride was used.

TABLE V *—*Continued*

EXAMPLES OF THE REACTION

Reactants	Product (Yield)
Desoxybenzoin [11]	$C_6H_5COCH(C_6H_5)CH_2NC_5H_{10}$ (—)
Acetoveratrone [11]	$(3,4)(CH_3O)_2C_6H_6COCH_2CH_2NC_5H_{10}$ (—)
Benzalacetone [9, 49, 50]	$C_6H_5CH{=}CHCOCH_2CH_2NC_5H_{10}$ (60%)
2-Methoxybenzalacetone [52]	$(2)CH_3OC_6H_4CH{=}CHCOCH_2CH_2NC_5H_{10}$ (13%)
2-Ethoxybenzalacetone [52]	$(2)C_2H_5OC_6H_4CH{=}CHCOCH_2CH_2NC_5H_{10}$ (30%)
2-Propoxybenzalacetone [52]	$(2)C_3H_7OC_6H_4CH{=}CHCOCH_2CH_2NC_5H_{10}$ (26%)
2-Butoxybenzalacetone [52]	$(2)C_4H_9OC_6H_4CH{=}CHCOCH_2CH_2NC_5H_{10}$ (26%)
Anisalacetone [9, 50]	$(4)CH_3OC_6H_4CH{=}CHCOCH_2CH_2NC_5H_{10}$ (60%)
Piperonalacetone [9, 51]	$(3,4)(CH_2O_2)C_6H_3CH{=}CHCOCH_2CH_2NC_5H_{10}$ (60%)
3,4-Dimethoxybenzalacetone [9, 51]	$(3,4)(CH_3O)_2C_6H_3CH{=}CHCOCH_2CH_2NC_5H_{10}$ (60%)
Ethyl 4-anisyl ketone [11]	$(4)CH_3OC_6H_4COCH(CH_3)CH_2NC_5H_{10}$ (—)
3-Methoxy-4-ethoxybenzalacetone [51]	$(3,4)(CH_3O)(C_2H_5O)C_6H_3CH{=}CHCOCH_2CH_2NC_5H_{10}$ (—)
3-Ethoxy-4-methoxybenzalacetone [51]	$(3,4)(C_2H_5O)(CH_6O)C_6H_3CH{=}CHCOCH_2CH_2NC_5H_{10}$ (—)
6-Nitropiperonalacetone [55]	$(3,4,6)(CH_2O_2)(NO_2)C_6H_2CH{=}CHCOCH_2CH_2NC_5H_{10}$ (60–65%)
6-Nitroveratralacetone [55]	$(3,4,6)(CH_3O)_2(NO_2)C_6H_2CH{=}CHCOCH_2CH_2NC_5H_{10}$ (55–60%)
2-Acetylphenanthrene [65]	2-(β-Piperidinopropionyl)-phenanthrene (—)
3-Acetylphenanthrene [65]	3-(β-Piperidinopropionyl)-phenanthrene (—)
9-Acetylphenanthrene [65]	9-(β-Piperidinopropionyl)-phenanthrene (—)
Methyl β-naphthyl ketone [66]	$(\beta)C_{10}H_7COCH_2CH_2NC_5H_{10}$ (60%)
β-Acetotetralin [11]	β-(β-Piperidinopropionyl)-tetralin (—)
Cyclopentanone [61]	2-Piperidinomethylcyclopentanone (90%)
Cyclohexanone [40]	2-Piperidinomethylcyclohexanone (62%)
4-Methylcyclohexanone [40]	2-Piperidinomethyl-4-methylcyclohexanone (93%)
α-Tetralone [56]	β-Piperidinomethyl-α-tetralone (75%)
1-Keto-1,2,3,4-tetrahydrophenanthrene [15]	1-Keto-2-piperidinomethyl-1,2,3,4-tetrahydrophenanthrene (—)
4-Keto-1,2,3,4-tetrahydrophenanthrene [15]	4-Keto-3-piperidinomethyl-1,2,3,4-tetrahydrophenanthrene (—)
1-Keto-9-methoxy-1,2,3,4-tetrahydrophenanthrene [70]	1-Keto-2-piperidino-9-methoxy-1,2,3,4-tetrahydrophenanthrene (63%)
2-Acetylfuran [13]	β-Piperidinoethyl 2-furyl ketone (—)
Furfuralacetone [49]	$C_4H_6OCH{=}CHCOCH_2CH_2NC_5H_{10}$ (—)
2-Acetylthiophene [10, 13]	β-Piperidinoethyl 2-thienyl ketone (74%)
2-Acetyldibenzothiophene [14]	β-Piperidinoethyl 2-dibenzothienyl ketone (55%) †
4-Acetyldibenzothiophene [14]	β-Piperidinoethyl 4-dibenzothienyl ketone (40%) †
2-Acetyl-4-phenylthiazole [13]	β-Piperidinoethyl 4-phenyl-2-thiazolyl ketone (—)
Antipyrine [6, 17]	4-Piperidinomethylantipyrine (70%)
Chromanone [71]	3-Piperidinomethyl-4-chromanone (28%)
Isobutyraldehyde [18]	$(CH_6)_2C(CH_2NC_5H_{10})CHO$ (—)
Isovaleraldehyde [16]	$(CH_3)_2CHCH(CH_2NC_5H_{10})CHO$ (—)
	$(CH_3)_2CHC(CH_2OH)(CH_2NC_5H_{10})CHO$ (70%)
Hexahydrobenzaldehyde [18]	1-Piperidinomethylhexahydrobenzaldehyde (—)
Tetrahydroisoquinoline hydrochloride, formaldehyde, and Acetophenone [11]	2-(β-Benzoylethyl)-1,2,3,4-tetrahydroisoquinoline (—)
2-Acetylphenanthrene [65]	2-(β-1,2,3,4-Tetrahydroisoquinolinopropionyl)-phenanthrene (—)

* References 67–74 appear on p. 341.
† Yield based on the amount of original ketone not recovered from the reaction mixture.

TABLE V *—*Continued*

EXAMPLES OF THE REACTION

Reactants	Product (Yield)
3-Acetylphenanthrene [65]	3-(β-1,2,3,4-Tetrahydroisoquinolinopropionyl)-phenanthrene (—)
9-Acetylphenanthrene [65]	9-(β-1,2,3,4-Tetrahydroisoquinolinopripionyl)-phenanthrene (—)
Cyclohexanone [40]	2-(1,2,3,4-Tetrahydroisoquinolinomethyl)-cyclohexanone (—)
α-Tetralone [16]	1-Keto-2-(1,2,3,4-tetrahydroisoquinolinomethyl)-1,2,3,4-tetrahydronaphthalene (66%)
1-Keto-6-methoxy-1,2,3,4-tetrahydronaphthalene [16]	1-Keto-2-(1,2,3,4-tetrahydroisoquinolinomethyl)-6-methoxy-1,2,3,4-tetrahydronaphthalene (63%)
1-Keto-6-acetoxy-1,2,3,4-tetrahydronaphthalene [16]	1-Keto-2-(1,2,3,4-tetrahydroisoquinolinomethyl)-6-acetoxy-1,2,3,4-tetrahydronaphthalene (81%)
1-Keto-7-methoxy-1,2,3,4-tetrahydronaphthalene [16]	1-Keto-2-(1,2,3,4-tetrahydroisoquinolinomethyl)-7-methoxy-1,2,3,4-tetrahydronaphthalene (76%)
1-Keto-7-acetoxy-1,2,3,4-tetrahydronaphthalene [16]	1-Keto-2-(1,2,3,4-tetrahydroisoquinolinomethyl)-7-acetoxy-1,2,3,4-tetrahydronaphthalene (61%)
1-Keto-1,2,3,4-tetrahydrophenanthrene [15]	1-Keto-2-(1,2,3,4-tetrahydroisoquinolinomethyl)-1,2,3,4-tetrahydrophenanthrene (61%)
4-Keto-1,2,3,4-tetrahydrophenanthrene [15]	4-Keto-3-(1,2,3,4-tetrahydroisoquinolinomethyl)-1,2,3,4-tetrahydrophenanthrene (34%)
1-Keto-9-methoxy-1,2,3,4-tetrahydrophenanthrene [70]	1-Keto-2-(1,2,3,4-tetrahydroisoquinolinomethyl)-9-methoxy-1,2,3,4-tetrahydrophenanthrene (46%)
1-Keto-9-acetoxy-1,2,3,4-tetrahydrophenanthrene [70]	1-Keto-2-(1,2,3,4-tetrahydroisoquinolinomethyl)-9-acetoxy-1,2,3,4-tetrahydrophenanthrene (72%)
2-Acetyldibenzothiophene [14]	β-(1,2,3,4-Tetrahydroisoquinolino)-ethyl 2-dibenzothienyl ketone (30%)
2-Acetyl-9-methylcarbazole [69]	β-(1,2,3,4-Tetrahydroisoquinolino)-ethyl 2-(9-methyloarbazyl) ketone (37%)
3-Acetyl-9-methylcarbazole [66]	β-(1,2,3,4-Tetrahydroisoquinolino)-ethyl 3-(9-methylcarbazyl) ketone (78%)
6-Methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, formaldehyde, and α-Tetralone [16]	1-Keto-2-(6-metnoxy-1,2,3,4-tetrahydroisoquinolinomethyl)-1,2,3,4-tetrahydronaphthalene (68%)
1-Keto-6-methoxy-1,2,3,4-tetrahydronaphthalene [16]	1-Keto-2-(6-methoxy-1,2,3,4-tetrahydroisoquinolinomethyl)-6-methoxy-1,2,3,4-tetrahydronaphthalene (88%)
1-Keto-6-acetoxy-1,2,3,4-tetrahydronaphthalene [16]	1-Keto-2-(6-methoxy-1,2,3,4-tetrahydroisoquinolinomethyl)-6-acetoxy-1,2,3,4-tetrahydronaphthalene (74%)
1-Keto-7-methoxy-1,2,3,4-tetrahydronaphthalene [16]	1-Keto-2-(6-methoxy-1,2,3,4-tetrahydroisoquinolinomethyl)-7-methoxy-1,2,3,4-tetrahydronaphthalene (68%)

* References 67–74 appear on p. 341.

TABLE V—*Continued*

EXAMPLES OF THE REACTION

Reactants	Product (Yield)
1-Keto-7-acetoxy-1,2,3,4-tetrahydronaphthalene [16]	1-Keto-2-(6-methoxy-1,2,3,4-tetrahydroisoquinolinomethyl)-7-acetoxy-1,2,3,4-tetrahydronaphthalene (64%)
Morpholine, formaldehyde, and	
Phenol [23]	2,4,6-Tri-(morpholinomethyl)-phenol (—)
Morpholine hydrochloride, formaldehyde, and	
Acetone [47]	β-Morpholinoethyl methyl ketone (73%)
Diethyl ketone [48]	α-(Morpholinomethyl)-ethyl ethyl ketone (50%)
Acetophenone [47]	β-Morpholinoethyl phenyl ketone (excellent)
Acetoveratrone [47]	β-Morpholinoethyl 3,4-dimethoxyphenyl ketone (56%)
2-Acetylphenanthrene [72]	β-Morpholinoethyl 2-phenanthryl ketone (73%)
3-Acetylphenanthrene [72]	β-Morpholinoethyl 3-phenanthryl ketone (76%)
Cyclopentanone [47]	2-Morpholinomethyl cyclopentanone (90%)
	2,5-Dimorpholinomethyloyclopentanone (—)
Cyclohexanone [47]	2-Morpholinomethylcyclohexanone (practically quantitative)
2-Methylcyclohexanone [47]	2-Methyl-6-morpholinomethylcyclohexanone (—)
4-Methylcyclohexanone [47]	2-Morpholinomethyl-4-methylcyclohexanone (—)
α-Hydrindone * [76]	2-Morpholinomethyl-1-hydrindone (83%)
5,6-Dimethoxy-α-hydrindone [73]	2-Morpholinomethyl-5,6-dimethoxy-1-hydrindone (37%)
1-Keto-1,2,3,4-tetrahydrophenanthrene [72]	1-Keto-2-morpholinomethyl-1,2,3,4-tetrahydrophenanthrene (41%)
4-Keto-1,2,3,4-tetrahydrophenanthrene [72]	3-Morpholinomethyl-4-keto-1,2,3,4-tetrahydrophenanthrene (30%)
2-Acetylthiophene [47]	β-Morpholinoethyl 2-thienyl ketone (46%)
Antipyrine [47]	4-Morpholinomethylantipyrine (46%)
Chromanone [71]	3-Morpholinomethyl-4-chromanone (37%)
Piperazine hydrochloride, formaldehyde, and	
Acetophenone [11]	N,N′-Di-(β-benzoylethyl)-piperazine (—)
Acetoanisone [11]	N,N′-Di-(β-4-methoxybenzoylethyl)-piperazine (—)
Acetoveratrone [11]	N,N′-Di-(β-3,4-dimethoxybenzoylethyl)-piperazine (—)
Malonic acid [19]	$(HOOC)_2CHCH_2NCH_2CH_2N(CH_2CH_2COOH)CH_2CH_2$ † (17%)
	$HOOCCH_2CH_2NCH_2CH_2N(CH_2CH_2COOH)CH_2CH_2$ (19%)
Antipyrine [17]	N,N′-Di-(antipyrylmethyl)-piperazine (—)

* A gummy product was obtained when β-hydrindone was used.
† The piperazine base was used.

[67] Mannich and Stein, *Ber.*, **58**, 2659 (1925).
[68] Blicke and Maxwell, *J. Am. Chem. Soc.*, **64**, 428 (1942).
[69] Ruberg and Small, *J. Am. Chem. Soc.*, **60**, 1591 (1938).
[70] Burger, *J. Am. Chem. Soc.*, **60**, 1533 (1938).
[71] Harradence, Hughes, and Lions, *J. Proc. Roy. Soc. N. S. Wales*, **72**, 273 (1938).
[72] Mosettig, Shaver, and Burger, *J. Am. Chem. Soc.*, **60**, 2464 (1938).
[73] Harradence and Lions, *J. Proc. Roy. Soc. N. S. Wales*, **72**, 284 (1938).
[74] Kühn and Stein, *Ber.*, **70**, 567 (1937).