REVIEWS

Advances in the Chemistry of Mannich Bases

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In this review, the progress in the chemistry of Mannich bases in the years 1960–1970 is reported in depth. The first part of the review deals with the synthesis of the bases and discusses separately the types of substrates undergoing the reaction. The second part contains a discussion of Mannich base reactions, whereby these bases are regarded as easily accessible intermediates for the synthesis of various products.

Der folgende Übersichtsartikel behandelt die Fortschritte in der Chemie der Mannich-Basen während des Jahrzehnts 1960–1970. Im ersten Teil wird die Synthese von Mannich-Basen unter Verwendung der verschiedenen Substrat-Typen eingehend besprochen. Im zweiten Teil werden präparativ interessante Reaktionen der Mannich-Basen in Einteilung nach Reaktionstypen abgehandelt. Das große praktische Interesse an der Chemie der Mannich-Basen beruht hauptsächlich auf der leichten Einführbarkeit einer basischen Funktion mittels der Mannich-Reaktion und der einfachen Quaternisierung dieser Funktion zu einer Aminium-Gruppierung, die das Molekül wasserlöslich machen kann, sowie auf der vielseitigen Reaktivität der Mannich-Verbindungen und ihren pharmakologischen Eigenschaften.

The chemistry of Mannich bases, first studied by Mannich, has been the subject of investigations by an ever increasing number of researchers. Several studies[1,2] which appeared before 1960 together with books by Reichert[3] and by Hellmann and Opitz[4], provide excellent coverage on practically the entire chemistry of Mannich bases up to 1960. In addition, in the last ten years many investigators have studied the numerous applications of the Mannich reaction (for some significant examples, see Ref.[5]), the problems of orientation and mechanism (for a recent comprehensive review, see Ref.[6]), and the reactivity of the bases which allows the synthesis of numerous other products.

This review represents a comprehensive documentation of the progress of this work during the period 1960–1970.

The great interest in the chemistry of Mannich bases has been essentially inspired by two facts:

- The Mannich synthesis introduces a basic function which can, e.g., render the molecule soluble in aqueous solvents when it is transformed into the aminium salt;
- Mannich bases are very reactive; in fact, they can easily be transformed into numerous other compounds. The reactivity of the bases accounts for several interesting properties (mainly pharmacological).

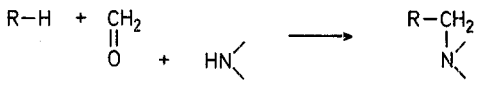
Studies on the chemistry of Mannich bases are of interest in various areas of application:

- A large number of aminoalkyl derivatives have been prepared in order to correlate their structure and reactivity with their pharmacological activity. Particularly noteworthy are some general studies such as those concerning cytostatic Mannich bases derived from, e.g., bis-[2-chloroethyl]-amine[7], melamine, or ethylenediamines[8], and those regarding Mannich base derivatives possessing antimicrobial[9,10] or cardiotonic[11] activity.
- Mannich bases represent easily obtainable intermediates for the synthesis of other compounds, such as heterocycles, amino-alcohols, etc. (see section 2.).
- Finally, Mannich bases have been investigated as potential biological agents, as dyes for synthetic fibres, as reactive dyes, and also as surface active compounds.

1. Synthesis of Mannich Bases

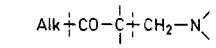
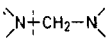
1.1. Structure

Mannich aminomethylation consists of the condensation of a *substrate* (R—H) possessing at least one active hydrogen (alkyl ketones, phenols, NH-heterocycles, etc.) with *formaldehyde* (or, occasionally, other aldehydes) and a primary or secondary *amine*[1,2] (or, occassionally, ammonia).



The general structures of Mannich bases described in this review are shown in Table 1, which also indicates the Sections in which the bases are discussed. The classification is based on the functional groups of the substrates.

Table 1. General Structures of Mannich Bases[a]

Section	Type of Bases	Section	Type of Bases
1.4.	*C*-Mannich bases	1.5.1	*N*-Mannich bases
1.4.1.			
1.4.2.	 (and cyclic derivatives)		
			
1.4.3.	 (or para)		
1.4.4.	 (and derivatives) X = -CN, -CO-R, $C_6H_4-NO_2$, $-SO_2-R$, etc.		 (Heterocycle)
		1.5.2.	*S*-Mannich bases
1.4.5.	 (Heterocycle)		
			
1.4.6.			
1.4.7.			
1.4.8.	Miscellaneous	1.5.3.	*Se*-Mannich bases
			
		1.5.4.	*P*-Mannich bases
			
			

[a] Mannich bases derived from

amino acids	see Sections 1.4.3., 1.4.4., 1.4.8., 1.5.1.
dyes	1.4.2., 1.4.4.
ferrocenes	1.4.8.
heterocyclics	1.4.1., 1.4.2., 1.4.3., 1.4.5., 1.4.6., 1.4.8., 1.5.2.
optically active compounds	1.6.
steroids	1.4.1., 1.4.3., 1.4.6.

1.2. Reactants and Reaction Conditions

Formaldehyde, either as aqueous solution ("formalin"), paraformaldehyde, or 1,3,5-trioxan (trioxymethylene), is the aldehyde most frequently used. The amines are employed either as free bases or as hydrochlorides.

The most widely used solvents are ethanol, other alcohols such as methanol and isopropanol, water, and acetic acid.

It is difficult to give general rules concerning the choice of reagents and reaction conditions (cf. Ref.[6]); however, the most widely and successfully used reaction conditions for several groups of substrates are as follows.

Alkyl Ketones: Substrate, amine hydrochloride, and paraformaldehyde (sometimes 1,3,5-trioxan or aqueous formaldehyde) are refluxed in alcoholic solvents for several hours.

Phenols: Substrate, amine, and aqueous formaldehyde (sometimes paraformaldehyde) in alcoholic solvents are heated for a short time (up to several hours), or are allowed to stand at room temperature for a longer time (up to a few days).

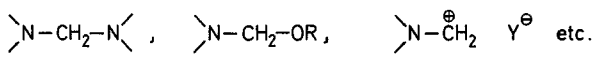
Carboxylic Acid Derivatives: Substrate, amine, and aqueous formaldehyde are allowed to react in water (sometimes in alcoholic solvents) at room temperature.

Heterocyclic Compounds: Substrate, amine, and aqueous formaldehyde are allowed to react in water or in alcoholic solvents at room temperature (sometimes with brief heating).

Alkynes: Various reaction conditions as above are used; the reaction is carried out in the presence of copper salts.

The reaction is generally carried out by mixing substrate, aldehyde, and amine in equimolar amounts. However, in several cases the amine and aldehyde are condensed first and then allowed to react with the substrate; sometimes, the initial condensation products are isolated.

[1] F. F. Blicke, "The Mannich Reaction", *Org. Reactions* **1**, 303 (1942).
[2] H. Hellmann, G. Opitz, *Angew. Chem.* **68**, 265 (1956).
[3] B. Reichert, *Die Mannich Reaktion*, Springer-Verlag, Berlin, 1959.
[4] H. Hellmann and G. Opitz, *α-Aminoalkylierung*, Verlag Chemie, Weinheim, Germany, 1960.
[5] M. Miocque, *Ann. Pharm. Franç.* **27**, 381 (1969).
[6] B. B. Thompson, *J. Pharm. Sci.* **57**, 715 (1968), and references cited therein.
see also L. W. Nobles, *J. Mississippi Acad. Sci.* **8**, 36 (1962).
[7] W. Werner, W. Jungstand, W. Gutsche, *Arzneimittelforschung* **20**, 246 (1970), and references cited therein.
[8] H. Schönenberger, A. Adam, *Arzneimittelforschung* **15**, 30 (1965).
[9] H. Schönenberger et al., *Pharm. Acta Helv.* **44**, 691 (1969).



In other cases, condensation between aldehyde and substrate (to give R—CH_2—OH) is allowed to take place before addition of the amine. These initial condensation products, usually obtained by use of amidic substrates, indoles, etc., have been investigated for cytostatic activity[13].

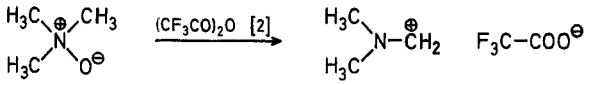
Mannich bases often crystallize from the reaction mixture (in some cases, concentration of the reaction mixture or addition of a solvent with low dissolving power for the product is necessary) or the bases can be separated by extraction with aqueous hydrochloric acid.

Some examples of particular reactions and of unusual reaction conditions are given below (see also Ref.[4,23]):

In some reactions involving weakly reactive substrates such as certain steroidal derivatives and 4-acetamidoacetophenone, 1,2-dimethoxyethane has been used as solvent [1]; the yields were nearly quantitative[14].

[1] Substrate, amine hydrochloride, and paraformaldehyde were refluxed in 1,2-dimethoxyethane for 30 hr[14].

Some easily degradeable compounds (e.g., certain steroids) have been condensed[15] with imonium salt **1**.

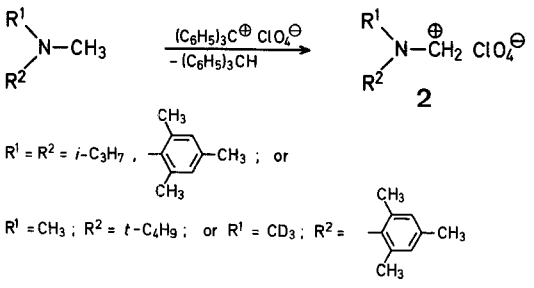


1

[2] *Preparation of the Reactant* (**1**): Trifluoroacetic anhydride (1 mmol) was added to a solution of trimethylamine oxide (1 mmol) in dichloromethane (5 ml) at 0°; the salt was then dried under reduced pressure at 100° and crystallized by cooling.

Mannich Reaction: The above reagent (**1**; 1 mmol) and the substrate (1 mmol) were dissolved in dichloromethane (10 ml) and the mixture allowed to stand at 40° for 2–8 days; yield: nearly quantitative[15].

Some methylenimonium perchlorates (**2**) derived from tertiary methylamines have been synthesized and isolated (90% yield); however, they have not yet been used as Mannich reagents. The synthesis was carried out in dichloromethane by allowing the amine to react with triphenylmethyl- or bis-[4-methoxyphenyl]-methyl perchlorate, followed by precipitation of the salt with carbon tetrachloride[16].



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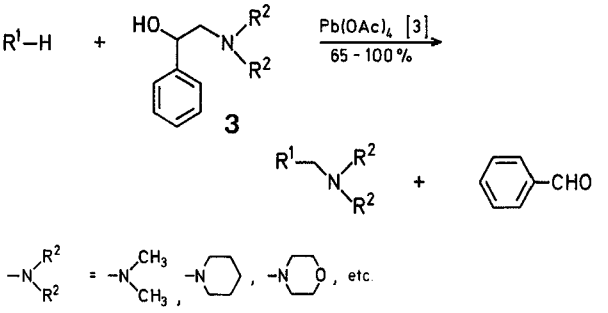
A great variety of substrates has been successfully aminomethylated by the reagent 2-amino-1-phenylethanol (**3**) in the presence of lead(IV) acetate[17].



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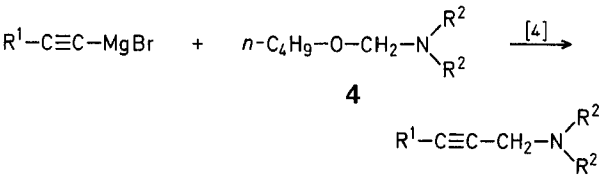
[3] The substrate (1 mmol) and compound **3** (1 mmol) were dissolved in anhydrous benzene, lead(IV) acetate (0.45 g) was added, and the mixture was warmed at 40° until the yellow color disappeared. The precipitate was separated by filtration and the filtrate evaporated under reduced pressure. The (solid) Mannich base was separated from benzaldehyde by washing, recrystallization, etc.[17].

Several acetylenic compounds in the form of their magnesium derivatives have been aminomethylated using aminomethyl butyl ethers[18] (**4**).



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[4] A solution of ethylmagnesium bromide was added in 30 min, with stirring, to a solution of phenylacetylene in tetrahydrofuran. The solution was stirred for 2 hr, aminomethyl butyl ether was added, and the mixture refluxed for 3 hr[18].

[10] H. Schönenberger, T. Bastug, D. Adam, *Arzneimittelforschung* **19**, 1082 (1969).
see also Y. K. Agarwal, J. N. Tayal, *Indian J. Pharm.* **29**, 46 (1967); *C. A.* **67**, 81894 (1967).

[11] K. von Thiele, U. Schimassek, A. von Schlichtegroll, *Arzneimittelforschung* **16**, 1064 (1966).
see also K. von Thiele, E. Koberstein, G. Nonnenmacher, *Arzneimittelforschung* **18**, 1255 (1968).

[12] For the analogous reaction with carboxamides, see:
H. Hellmann, "Amidomethylierungen", in: W. Foerst, *Neuere Methoden der präparativen organischen Chemie*, Band II, Verlag Chemie, Weinheim, 1960, p. 190.
H. Hellmann, "Amidomethylation", in: W. Foerst, *Newer Methods of Preparative Organic Chemistry*, Vol. 2, Academic Press, New York, 1963, p. 277.
H. E. Zaugg, W. B. Martin, "α-Amidoalkylation at Carbon", *Org. Reactions* **14**, 52 (1965).
H. E. Zaugg, *Synthesis* **1970**, 49.
For the analogous reaction with urea, guanidine, and related compounds, see H. Petersen, *Angew. Chem.* **76**, 909 (1964); *Synthesis* **1973**, 343.

[13] G. Weitzel et al., *Z. Physiol. Chem.* **334**, 1 (1963).

[14] S. Hirai, R. G. Harvey, E. V. Jensen, *Tetrahedron Lett.* **1963**, 1123.

[15] A. Ahond, A. Cavé, C. Kan-Fan, P. Potier, *Bull. Soc. Chim. France* **1970**, 2707.

[16] H. Volz, H. Kiltz, *Tetrahedron Lett.* **1970**, 1917.

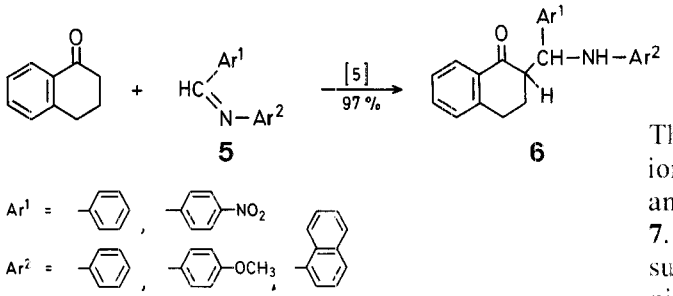
[17] H. J. Roth, *Arch. Pharm.* **294**, 623 (1961).

[18] I. Iwai, Y. Yura, *Chem. Pharm. Bull.* **11**, 1049 (1963); *C.A.* **59**, 13848 (1963).

High yields of Mannich bases have been obtained in the condensation of amines with 1-hydroxymethylindazole (Table 23) and 2,2-dinitroalkanols (Section 1.4.7.).

Successful aminomethylation of 2-naphthol has been achieved using several alkyl aminomethyl ethers (ethyl, allyl, propargyl, and 2-methoxyethyl)[19], and of tropolones by use of methylene-bis-amines (Section 1.4.8.).

Finally, the use of Schiff bases (**5**) in condensations with an aldehyde other than formaldehyde should be mentioned. The reaction is carried out in the presence of boron trifluoride as a catalyst; attempts to carry out the reaction without catalysis merely by mixing the three components (ketone, aldehyde, and amine) or benzylideneketones and amines were unsuccessful[20].



[5] Ether saturated with gaseous boron trifluoride at room temperature (10 g) was added dropwise to a solution of compound **5** (0.1 mol) in α-tetralone (0.12 mol). 95% Methanol was then added and the mixture cooled at −20° for several hr[20].

The ketonic Mannich bases derived from acetophenone, 1-acetylnaphthalene[21], β-tetralone[22], and indanone[20] have been obtained using the same reaction conditions.

1.3. Mechanism, Orientation, and By-products

The mechanism of the Mannich reaction has been well investigated, and a comprehensive review[6] covering studies up to 1968 has been published. Only a few of the main points will be covered here; the reader is referred to the cited review for a more complete discussion.

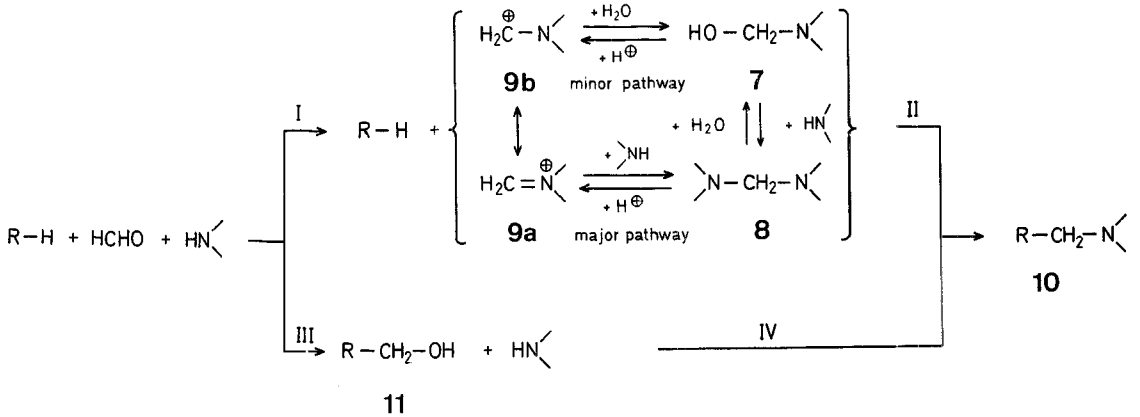
The Mannich reaction leads to products of the type **10**, bearing an unsymmetrically substituted methylene group connecting the substrate residue with an amino group.

The condensation reaction occurs in two steps: first, the amine reacts with formaldehyde to give condensation product **7**⇄**8**⇄**9** (step I), which then attacks the substrate R—H (step II). The reaction does not normally follow the other possible route (steps III and IV); however, some successful reactions between hydroxymethyl derivatives (**11**) and alkylamines to give Mannich bases (**10**) should be mentioned.

The reactive species in *acidic medium* is the imonium ion **9**, derived principally from methylene-bis-amine **8** and secondarily from hydroxymethylamine **7**. The electrophilic attack of **9** on alkylcarbonyl substrates is postulated to occur by an S_E2 mechanism on the enol, rather than on the carbanion.

In *basic medium*, the reactant is postulated to be hydroxymethylamine **7** or, more probably, methylene-bis-amine **8**; however, the participation of the *O*,*N*-acetal (Alkyl—O—CH_2—N<) in the reaction in alcoholic solvents cannot be excluded.

In the case of cycloalkanones, an S_N2 mechanism involving attack by the carbanion derived from the substrate has been postulated; however, a mechanism involving a hydrogen-bonded complex (**12**) has also been invoked for both carbonyl (enol form) and phenolic substrates. The latter mechanism could explain the preferred *o*-substitution in phenols (see Section 1.4.3.).



[19] J. E. Fernandez, C. Powell, J. S. Fowler, *J. Chem. Eng. Data* **8**, 600 (1963).

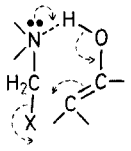
[20] H. J. Roth, F. Assadi, *Arch. Pharm.* **303**, 29 (1970).

[21] H. J. Roth, H. George, *Arch. Pharm.* **303**, 725 (1970).

[22] H. J. Roth, F. Assadi, *Arch. Pharm.* **303**, 149 (1970).

[23] M. Masul, K. Fujita, H. Ohmori, *Chem. Commun.* **1970**, 182

[24] N. D. Potti, *Diss. Abstr. (Chemistry)* **27**, 4335 (1967).



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A hydrogen-bonded complex also appears to be involved in the reaction between methylene-bis-amines and nitroalkanes, in which the reactive substrate is assumed to be present in the aci-nitro form (see Section 1.4.7.).

Further papers concerning mechanistic studies of the Mannich reaction were simultaneously and subsequently published to the above-mentioned review[6] (see also Ref.[424,425,426]).

The existence of cation **9** in aqueous solutions of amine and formaldehyde has been demonstrated by polarographic methods; the maximum concentration of **9** was reported[23] to occur at pH 10–11.

In Mannich reactions with unsymmetrical methylene-bis-amines, only the more basic of the two amino groups is incorporated into the condensation product; in addition, steric factors seem to be relevant to the course of the reaction[24,25]. The assumption of a cyclic hydrogen-bonded complex (**12**, X = —N<) is in accordance with the results obtained and suggests that the methylene-bis-amine is the principal reactant which determines the orientation of the reaction. The steric requirements of the methylene-bis-amine could explain the fact that the reaction, in certain cases (i.e. with unsymmetrical dialkyl ketones; see Section 1.4.1.), takes place on the electronically less favored but sterically less hindered position.

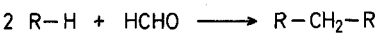
It is also worthwhile to mention studies on the mechanism of the de-aminomethylation reaction, which can be considered an inverse Mannich reaction (see discussion and references in Section 2.1.). In investigations concerning Mannich bases derived from nitroalkanes, the important role played by steric factors, including those of the imonium cation **9**, has been noted. In fact, cation **9** has been proposed to be the product of the rate-determining step in the de-aminomethylation reaction.

The orientation and by-products of the Mannich reaction will be discussed in the following Sections. Principally concerned are dialkyl ketones (attack on the more or the less substituted C-atom), phenols (attack on the *o*- or *p*-position), NH-heterocyclic compounds (attack on the N-atom or on a heterocyclic C-atom), and in general all compounds having two or more reactive groups (e.g., hydroxyindoles, acetylenic ketones, etc.).

[25] W. L. Nobles, N. D. Potti, *J. Pharm. Sci.* **57**, 1097 (1968).

Further, substitution of more than one H-atom on the same C-atom has been observed in the case of compounds containing activated methylene groups (e.g., carbonyl and nitro compounds).

Some side reactions often occurring in Mannich syntheses are the formation of methylene-bis-derivatives **13**, deamination, and decarboxylation.



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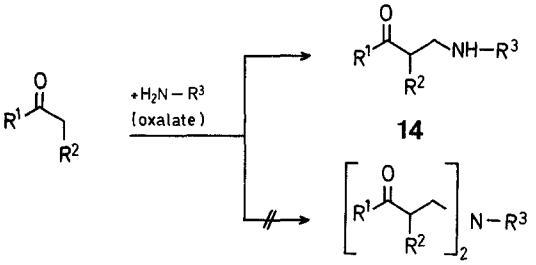
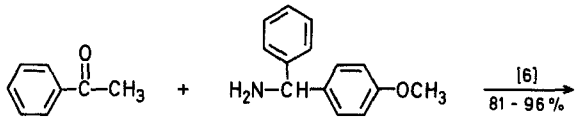
The choice of the amine used in the reaction is important in this context. For example, primary amines can react at both amine H-atoms and it is therefore difficult to obtain secondary Mannich bases **(14)** free from tertiary derivatives. However, use of the oxalate derivatives of the primary amines instead of the corresponding hydrochlorides makes possible the synthesis of secondary Mannich bases **(14)** in high yields even when excess formaldehyde is used[26,27].



14

R^1 = CH_3, C_2H_5, C_6H_5
R^2 = H, CH_3
R^3 = CH_3, C_2H_5, $-CH_2-C_6H_5$

Use of the sterically hindered amine **15**, or similar amines containing bulky groups (*t*-butyl, di- or triarylmethyl), can also prevent a substitution reaction involving the second amine H-atom of **16**. The bulky alkyl groups can subsequently be removed by hydrolysis to give the *N*-unsubstituted aminoketone **17**, which is not directly obtainable from ammonia and formaldehyde[27,28].



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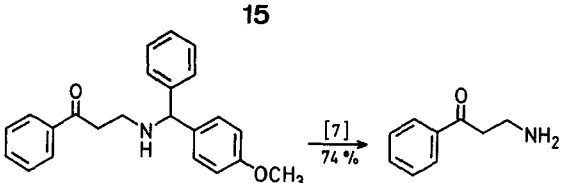


16 **17**

[26] H. G. O. Becker, W. Ecknig, E. Fanghänel, S. Rommel, *Wiss. Z. Techn.* **11**, 38 (1968); *C. A.* **71**, 60938 (1970).

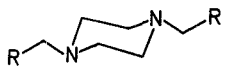
[27] H. Becker, E. Fanghänel, W. Ecknig, *Angew. Chem.* **72**, 633 (1960).

[28] H. Becker, E. Fanghänel, *J. Prakt. Chem.* [4] **26**, 58 (1964).

[6] Acetophenone (20 ml), amine hydrochloride (0.02 mol), and paraformaldehyde (0.022 mol) were heated for 30 min at 150°. In other cases, the mixture was refluxed in ethanol in the presence of hydrogen chloride for 8 hr (66–82% yield)[28].

[7] A mixture of compound **16**, formic acid, and 48% hydrobromic acid was refluxed for 3 hr. Alternatively, compound **16** was heated with conc. hydrochloric acid in a sealed tube for 2 hr at 150°; yield: 60%[28].

The use of secondary bifunctional amines such as piperazine always leads to symmetric Mannich bases (e.g. **18**), in which both of the amino groups have reacted. Attempts to restrict the reaction to only one amine function, or hydrolysis of the Mannich products obtained from mono-*N*-acyl-piperazines invariably leads to the formation of di-substituted piperazines **18**[29].



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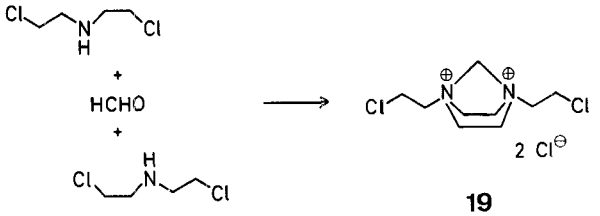
Mannich reaction of bis-[2-chloroethyl]-amine (the derivatives of which are widely used in cytostatic drugs) can give a bicyclic salt as by-product[30]. Two molecules of the amine thus condense with one molecule of formaldehyde to give **19**, which shows cytostatic properties as do halogenated derivatives of similar structure[31,32].



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[29] H. J. Roth, M. Mühlenbruch, *Arch. Pharm.* **303**, 156 (1970).
[30] G. R. Pettit, A. K. Das Gupta, *Chem. & Ind.* **1962**, 1016.
[31] G. R. Pettit, J. A. Settepani, *Chem. & Ind.* **1964**, 1085.
[32] H. Böhme, H. Orth, *Arch. Pharm.* **300**, 148 (1967).

1.4. *C*-Aminomethylation Reactions

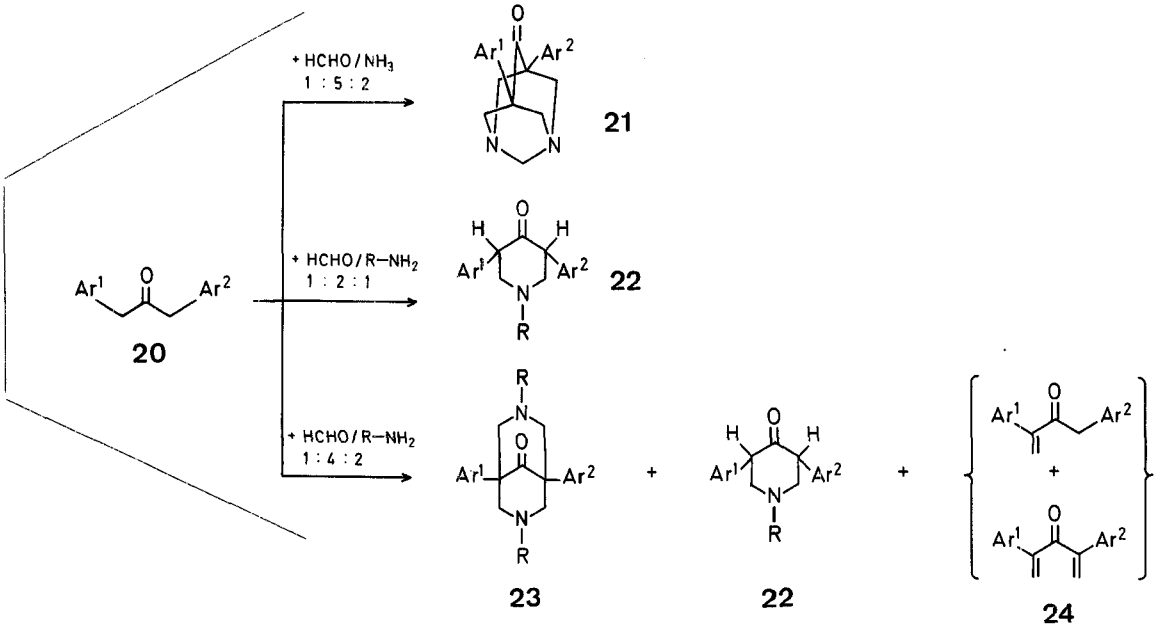
1.4.1. Aminomethylation of Dialkyl Ketones

Since dialkyl ketones and cycloalkanones have two reactive centers (the two positions α to the carbonyl group), they can undergo Mannich reaction to afford more than one product, i.e., α-monosubstitution-, or α,α′- and α,α,α′,α′-polysubstitution products. In the case of unsymmetric ketones, the question of preferred orientation arises.

Cyclic β-amino-ketones have been obtained from the reaction of a ketone, an aldehyde, and a primary amine (or ammonia) in a molar ratio of 1:2:1 or 1:4:2 (1:5:2 for ammonia).

1,3-Diazaadamantan-6-ones (**21**) have been obtained in good yields from the reaction of 1,1′-diaryl-acetones (**20**) with ammonia and formaldehyde[33,34].

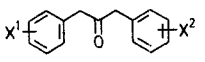
On the other hand, use of primary amine acetates in the reaction affords piperidin-4-ones (**22**) or 1,5-diaryl-9-oxo-3,7-diazabicyclo[3.3.1]nonanes ("bispidinones", **23**) (see Table 2).



Reactions involving derivatives of **20** in which Ar^1 and Ar^2 represent bulky *o*-substituted alkyl groups afford complex mixtures of products **22**, **23**, and **24**. In the case of highly sterically hindered ketones (e.g. **20**, $Ar^1 = Ar^2$ = 2,6-dimethylphenyl), the reaction is completely inhibited[34].

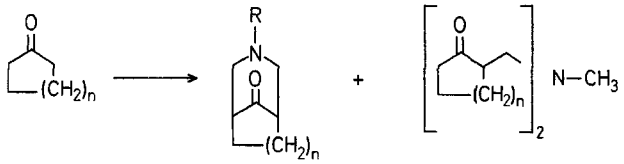
[33] S. Chiavarelli, F. Töffler, P. Mazzeo, L. Gramaccioni, *Il Farmaco, Ed. Sci.* **23**, 360 (1968).
[34] D. Misiti, G. Settimj, P. Mantovani, S. Chiavarelli, *Gazz. Chim. Ital.* **100**, 495 (1970).
[35] G. Settimj, R. Landi Vittory, F. Delle Monache, S. Chiavarelli, *Gazz. Chim. Ital.* **96**, 311 (1966).
[36] S. Chiavarelli, F. Töffler, R. Landi Vittory, P. Mazzeo, *Gazz. Chim. Ital.* **94**, 1021 (1964).

Table 2. Mannich Reactions of α,α'-Diarylacetones with Primary Amines

Ketones	Amines	Products	Yield (%)	References
 **20**				
$X^1 = X^2 = 2\text{-}CH_3$	$H_2N\text{-}CH_3$	**22**	60	34
$X^1 = 2\text{-}NO_2, 4\text{-}NO_2;$ $X^2 = H, 4\text{-}NO_2$	$H_2N\text{-}CH_3$, $H_2N\text{-}C_2H_5$	**22**	24–79	35
$X^1 = X^2 = H$	$H_2N\text{-}R$ $R = H_3C\text{-}(CH_2)_{6,7,9,16}$; $n\text{-}C_6H_{13}\text{-}CH(CH_3)\text{-}$, $H_3C\text{-}O\text{-}(CH_2)_{2,3}\text{-}$, $HO\text{-}(CH_2)_{2,5}$; $(H_3CO)_3C_6H_2\text{-}CH_2\text{-}CH_2\text{-}$	**23**	35–71 (Conditions [8])	36, 37
$X^1 = H;\ X^2 = 2\text{-}CH_3$	$H_2N\text{-}CH_3$	**23**	70	34
$X^1 = 2\text{-}NO_2, 4\text{-}NO_2;$ $X^2 = H, NO_2$	$H_2N\text{-}CH_3$, $H_2N\text{-}C_2H_5$, $H_2N\text{-}CH_2\text{-}C_6H_5$	**23**	51–92	35

[8] Compound **20**, amine acetate, and paraformaldehyde (or 1,3,5-trioxan) were refluxed for various times (5–6 hr[33,34] to 17–60 hr[36]) in alcoholic solvents.

Azabicyclic compounds of the type **26** have been obtained from cycloalkanones (**25**) via Mannich synthesis using primary amines. Although the yields are poor (the major products are the open-chain bases **27**), this synthesis[38] still represents the simplest route to compounds **26**.



25 **26** **27**

An analogous bicyclic ketone has been obtained from the reaction of 2,6-bis-[dimethylaminomethyl]-cyclohexanone[39].

Several publications concerning the orientation of aminomethylation in the reaction of unsymmetric dialkyl ketones with secondary amines[40,41,42,43,44] have appeared; a few previously assigned structures were corrected.

Aminomethylation reactions have been carried out on compounds **28** and **29**, and the positions of substitution determined. The rule that attack takes place on the C-atom bearing the least number of H-atoms, taking particular account of the pertinent enolization equilibria, has been discussed[45].

28 **29**

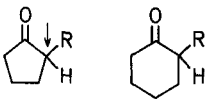
$R^1 = H;\ R^2 = C_2H_5, i\text{-}C_4H_9, C_6H_5$ $R^1 = H;\ R^2 = i\text{-}C_3H_7, -CH_2\text{-}COOH$

$R^1 = CH_3;\ R^2 = CH_3, C_2H_5$ $R^1 = R^2 = C_6H_5$

$R^1\text{-}R^2 = -CH_2\text{-}CH_2\text{-}$

Specifically, it was observed that ketone **28** ($R^1 = R^2 = CH_3$) is aminomethylated to give a mixture of bases[46] in which the product of attack at the C-atom bearing the least number of H-atoms is predominant (~3.5:1)[42,44]; furthermore, the latter product has been found to undergo thermal trans-aminomethylation to afford the product of reaction at the C-atom bearing more H-atoms[41].

The 2-alkylcyclopentanones and -cyclohexanones **30** and **31** undergo similar reactions. In the case of the cyclopentanones, the reaction was reported to occur either at the more substituted C-atom[47], or at both C^α-atoms to give a mixture of two aminomethylation products[44]. In all cases it was observed that the products undergo rearrangement, leading to migration of aminomethyl groups to the less substituted C-atom[41].



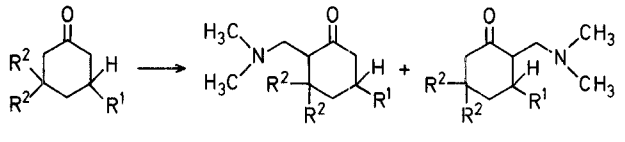
30 **31**

$R = CH_3$ $R = CH_3, C_2H_5, i\text{-}C_3H_7, C_6H_5$

[37] S. Chiavarelli, F. Töffler, R. Landy Vittory, P. Mazzeo, *Il Farmaco, Ed. Sci.* **20**, 421 (1965).
[38] H. O. House, P. P. Wickham, H. C. Müller, *J. Amer. Chem. Soc.* **84**, 3139 (1962).
[39] F. F. Blicke, F. J. McCarty, *J. Org. Chem.* **24**, 1379 (1959).
[40] M. Brown, W. S. Johnson, *J. Org. Chem.* **27**, 4706 (1962).
[41] G. L. Buchanan, A. C. W. Curran, *Chem. Commun.* **1966**, 773.
[42] G. L. Buchanan, A. C. W. Curran, *Chem. & Ind.* **1967**, 156
[43] T. A. Spencer, D. S. Watt, R. J. Friary, *J. Org. Chem.* **32**, 1234 (1967).
[44] G. L. Buchanan, A. C. W. Curran, R. T. Wall, *Tetrahedron* **25**, 5503 (1969).
[45] H. O. House, V. Kramar, *J. Org. Chem.* **28**, 3362 (1963).
[46] N. B. Haynes, C. J. Timmons, *J. Chem. Soc.* [C] **1966**, 224.
[47] H. O. House, B. M. Trost, *J. Org. Chem.* **29**, 1339 (1964).

In one study[47] it was claimed that aminomethylation of cyclohexanones **31** mainly takes place at the more-substituted C-atom. However, other authors reported that in the product mixtures obtained the products of attack at the less substituted C-atom were predominant[48,49]. Furthermore, longer reaction times were found to induce intermolecular rearrangement leading exclusively to Mannich bases formed by aminomethylation at the less substituted C-atom[48]. The influence of various reaction conditions and of steric factors on the transformation have been discussed[48,25].

In the case of 3-substituted cyclohexanones **32**, the reaction occurred mainly at the less hindered position[50].

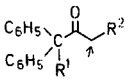
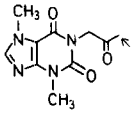


32 **33** **34**

R^1	R^2	% **33**	% **34**
CH_3	H	90	10
C_6H_5	H	88	12
CH_3	CH_3	5	95

Other Mannich syntheses involving dialkyl ketones **28**, **35**, **36**, and **37**, and cycloalkanones **30**, **31**, **38**, **39**, and **40** are reported in Tables 3 and 4.

Table 3. Mannich Reactions between Dialkyl Ketones and Secondary Amines

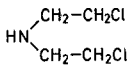
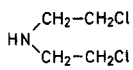
Ketones	Amines	Reaction Conditions	Yield (%)	References
 **28**				
R^1 = H; R^2 = H, CH_3, C_2H_5			50–91	51
R^1 = H, R^2 = C_6H_5			45	10
 **35**				
R^1 = H; R^2 = H, CH_3 or R^1 = CH_3, n-C_3H_7; R^2 = H		[9]		52
 **36**				
R^1 = OH, OCH_3; R^2 = H or R^1 = H; R^2 = CH_3		[10]	10–57	53
 **37**		[11]	31	54

[9] Substrate, amine hydrochloride, aqueous formaldehyde, and a few drops of conc. hydrochloric acid were heated at 100° for 2–10 hr[52].

[10] Compound **36**, amine hydrochloride, and paraformaldehyde (1/2 of the theoretical amount) in ethanediol or dimethylformamide were heated with stirring at 190–195° for 10 min; more formaldehyde (1/2 of the theoretical amount), suspended in ethanediol, and several drops of conc. hydrochloric acid were then added within 30 min and the mixture refluxed for another 30 min[53].

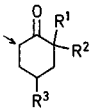
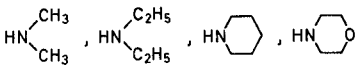
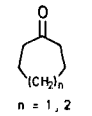
[11] The pH of a mixture of compound **37**, amine hydrochloride, and formic acid was adjusted to 3–4 with conc. hydrochloric acid. The mixture was concentrated under reduced pressure, made alkaline with potassium hydroxide, and extracted with chloroform[54].

Table 4. Mannich Reactions between Cycloalkanones and Secondary Amines

Ketones	Amines	Reaction Conditions	Yield (%)	References
 **30**		[12]	90	55
 **38**			30	56
 **31**		[12]	30–40	55, 57

[48] G. Descotes, S. Laurent, *C.R. Acad. Sci.* **264**, 714 (1967).
[49] A. N. Kost, I. P. Sugrobova, *Vestn. Mosk. Univ. Ser. II, Khim.* **18**, 75 (1963); *C.A.* **59**, 7459 (1963).
[50] G. Descotes, S. Laurent, *C.R Acad. Sci.* **265**, 1167 (1967).
[51] W. Schneider, H. J. Dechov, *Arch. Pharm.* **299**, 279 (1966).
[52] G. S. Mironov, M. I. Farberov, I. M. Orlova, *Zh. Obshch. Khim.* **33**, 1512 (1963); *C.A.* **60**, 5324 (1964).
[53] J. V. Greenhill, M. D. Metha, *J. Chem. Soc.* [C] **1970**, 1549.

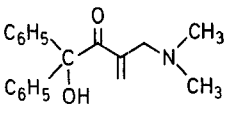
Table 4 (continued)

Ketones	Amines	Reaction Conditions	Yield (%)	References
 **39** $R^1 = R^2 = H$; $R^3 = CH_3$ or $R^1 = R^3 = H$; $R^2 = n\text{-}C_4H_9$, $-CH_2-CH(CH_3)-C_3H_7\text{-}n$, $-CH_2-CH(C_2H_5)-C_3H_7\text{-}n$		[13]	42–70	58
$R^1\text{-}R^2 = (CH_2)_5$; $R^3 = H$			80	59
 **40** n = 1, 2		[13]	good	29

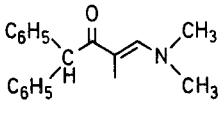
[12] Substrate, amine hydrochloride, aqueous formaldehyde, and water were mixed, the pH adjusted to 1, and the mixture heated at 95°, until precipitation began. For cyclohexanone, the pH was adjusted to 2, and the mixture heated for 4 hr[55].

[13] Substrate, amine hydrochloride, and paraformaldehyde in isopropanol (or aqueous formaldehyde in propanol[29]) were refluxed for 30 min to 5 hr[58].

Mannich bases derived from ketones **36** are of pharmaceutical interest; however, the synthesis is difficult and the use of high-boiling solvents is necessary in order to obtain satisfactory yields. Vinylic by-products **41** and **42**, probably formed via a deamination reaction[53], are often obtained together with the expected bases.



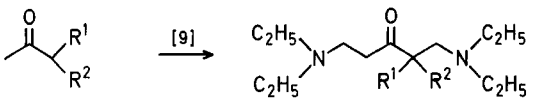
41



42

Reaction of ketones of the type **20** (Ar^1 = mesityl; Ar^2 = phenyl or 2-methylphenyl) with formaldehyde and dimethylamine affords[34] mixtures of vinyl ketones **24** instead of normal Mannich bases.

Mannich reaction of ketones of the type **28** directly affords[52] bis-bases (**43**).



28 **43**

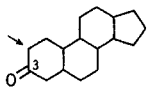
$R^1 = H$

$R^2 = H, CH_3, C_2H_5$

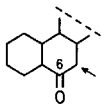
It is worthwhile mentioning several steroidal alkyl ketones and cycloalkanones which have been subjected to the Mannich reaction (see Table 5).

[54] G. Gräfe, *Arch. Pharm.* **300**, 874 (1967).

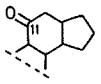
Table 5. Types of Steroidal Ketones which have been subjected to Mannich Reactions



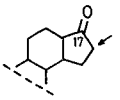
44 Ref.[15,60–63]



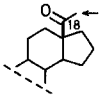
45 Ref.[15]



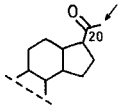
46[a]



47 Ref.[15]



48 Ref.[14]

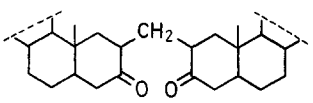


49 Ref.[15,60]

[a] Compound **46** failed to react[60].

The most satisfactory aminomethylation conditions for the compounds listed in Table 5 involve use of the amine hydrochloride (most widely used amines are dimethylamine and pyrrolidine) with paraformaldehyde in ethanol; the reaction mixture is allowed to reflux for 3–5 hr[61]. Alternatively, aqueous formaldehyde in water at room temperature (reaction time: 7 days)[62] or in acetic acid at 80° (1–2 hr)[60,63] can be used. In the case of weakly reactive molecules, it appears advisable to replace ethanol with 1,2-dimethoxyethane[14], whereas use of methylimonium trifluoroacetate (**1**) gives excellent results[15] in reactions with unstable substrates.

Under particularly forcing reaction conditions, methylene-bis-steroids (**50**) have sometimes been obtained[62].

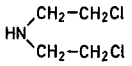
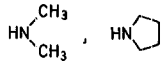
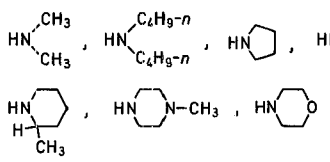
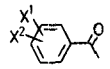
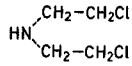
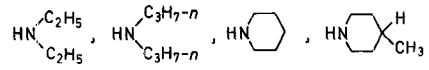
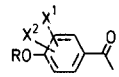
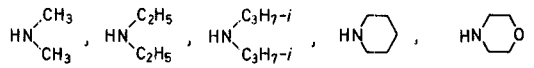
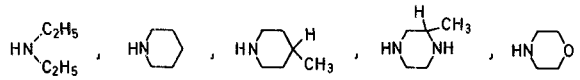
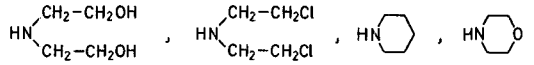
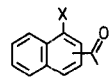
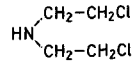
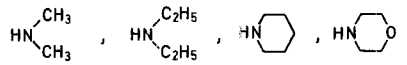


50

[55] W. Werner, M. Wunderval, W. Ozegowski, D. Krebs, *German Patent (DBP.)* 1161271 (1964), Deutsche Akademie der Wissenschaften, Berlin; *C.A.* **60**, 10604 (1964).

[56] K. Tonari, I. Ichimoto, H. Ueda, C. Tatsumi, *Nippon Nogei Kagaku Kaishi* **44**, 55 (1970); *C.A.* **72**, 100105 (1970).

Table 6. Mannich Reactions of Acetophenones and Acetylnaphthalenes with Primary and Secondary Amines

Ketones	Amines	Reaction Conditions	Yield (%)	References
 **51**				
X = H	$H_2N-C_2H_5$, $H_2N-C_3H_7-n$, $H_2N-C_4H_9-n$, $H_2N-CH_2-C_6H_5$		89–95[a]	64
X = H; 3- and 4-NH-Ac; 2-, 3-, and 4-NO_2; 4-OCH_3; 4-O-C_4H_9-n; 4-Cl		[14]	23–74	55, 57, 65
X = 4-NH-Ac		[1]	~100	14
X = H; 3-, 4-NO_2; 2-, 4-OH; 4-OAlk; 4-Hal			28–81	66, 67
 **52**				
X^1, X^2 = 2,4-di-CH_3; 3,4-di-CH_3 2,5-di-OCH_3		[14]	73–91	55, 65
X^1, X^2 = 2-OH, 4-OCH_3			good	68
X^1, X^2 = 2,4-di-OCH_3		[15]	56–72	69
 **53**				
R = H X^1, X^2 = 3,5-di-*t*-C_4H_9; 3,5-di-*t*-C_5H_{11}; 3,5-di-*c*-C_6H_{11}; 3-CH_3, 5-*t*-C_4H_9			30–70	70
R = CH_3 X^1, X^2 = 2,6-di-OCH_3		[15]	52–64	69
R = CH_3 X^1, X^2 = 3-H, 5-H; 3,5-di-OCH_3			14–74	71
 **54**				
X = H; 3- or 4-Ac		[14]	51–91	65
X = OH; 2- or 4-Ac		[16]	40–80	72

[a] Except for propylamine, tertiary Mannich bases are obtained.

[14] Ketone, amine hydrochloride, and aqueous formaldehyde were heated without solvent with stirring at 105° for several min; water was distilled azeotropically with chloroform and the residue was triturated with ether[65].

[15] Ketone, amine hydrochloride, paraformaldehyde (2/3 of the required amount), and several drops of conc. hydrochloric acid were refluxed in ethanol for 2 hr; the remaining paraformaldehyde (1/3) was then added and the mixture refluxed for 8–24 hr[69-93].

[16] Substrate, amine, and aqueous formaldehyde in ethanol were allowed to stand at room temperature or were refluxed for 1–2 hr[72].

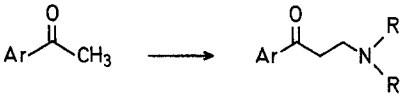
1.4.2. Aminomethylation of Alkyl Aryl Ketones

The Mannich bases described in this Section (see also Ref.[428-433]) have mainly been synthesized because of their pharmacological interest. The products will be divided into two main groups:

- Bases derived from "common" amines;
- Bases derived from "unusual" amines (often selected to obtain particular pharmacological properties).

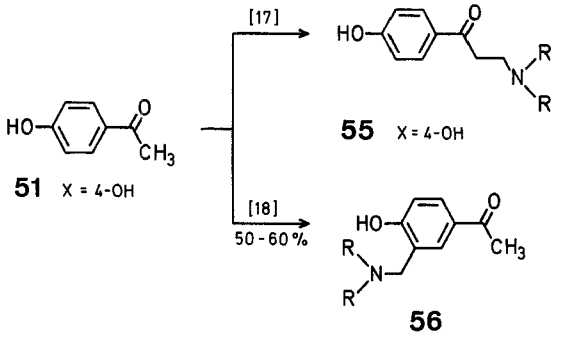
The most common substrates in the first group are acetophenones, acetylnaphthalenes, higher alkyl aryl ketones, alkyl heteroaryl ketones, aryl cycloalkyl ketones, methyl styryl ketones, and alkyl aryl ketones derived from aromatic azo compounds and anthraquinone dyes.

With only a few exceptions, acetophenones and acetylnaphthalenes (**51**–**54**) can be aminomethylated to give 2-aminoalkyl aryl ketones (**55**; Table 6).



51-54 **55**

In the Mannich reaction of 4-hydroxyacetophenone (**51**, X = 4-OH)[67] and 2-hydroxy-4-methoxyacetophenone (**52**, X^1 = 2-OH, X^2 = 4-OCH_3)[68], different products are obtained depending on the pH of the medium; at low pH, the acetyl group undergoes reaction, whereas in alkaline medium the position *ortho* to the hydroxy group is substituted to afford **56**.

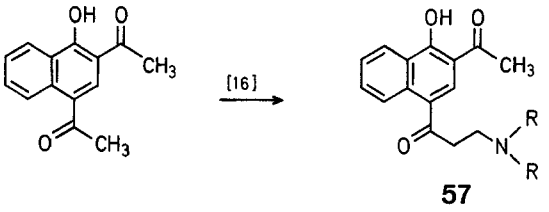


[17] Hydroxyacetophenone and amine hydrochloride were refluxed in ethanol in the presence of hydrogen chloride for several hours[67].

[18] A solution of aqueous formaldehyde (1 mol) in 75% ethanol was added to a solution of the ketone (1.5 mol) and the amine (1 mol) in aqueous ethanol; the mixture was then stirred for 24 hr[67].

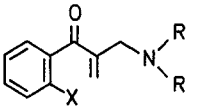
This rule does not, however, apply to acetyl-1-hydroxynaphthalenes (**54**, 2- or 4-Ac, X = OH), which are only converted into 2-aminoethyl naphthyl ketones[72].

The reaction of 2,4-diacetylnaphthol represents another interesting example of the problem of orientation; the 4-acetyl group first undergoes Mannich reaction leading to the base **57**, which subsequently can be further aminomethylated at the acetyl group in the 2-position[72].



57

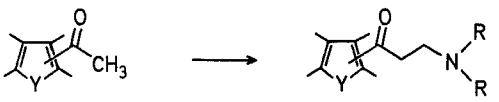
Acetophenones are also remarkable in that they can react to form Mannich bases of the type **58**, containing a vinyl-ketonic moiety. The reaction has in particular been carried out with 2-ethoxycarbonylamino-[73] and 2-nitroacetophenones[74].



58

X = -NH-$COOC_2H_5$, -NO_2

Several acetylfurans, acetylthiophenes, and acetylpyrroles (**59**) also undergo the Mannich reaction to afford the corresponding 2-aminoethyl ketones (**60**) (Table 7).



59 **60**

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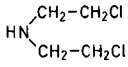
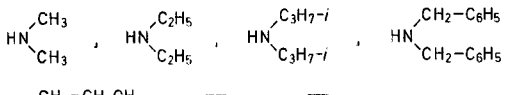
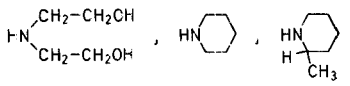
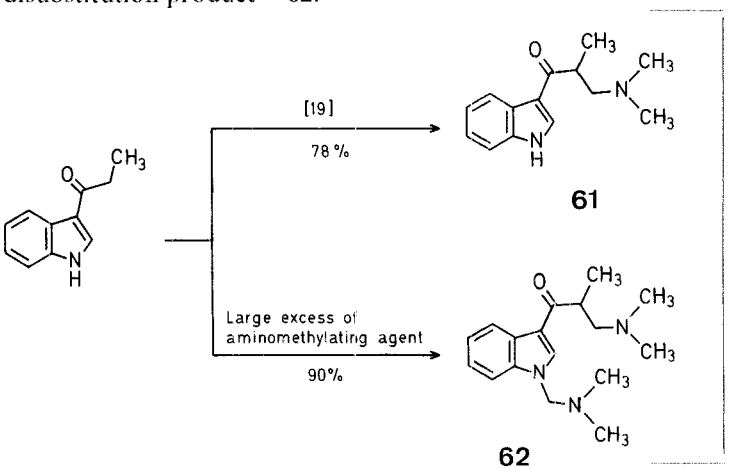
Table 7. Mannich Reactions of Acetylfurans, Acetylthiophenes, or Acetylpyrroles (**59**) and Primary or Secondary Amines

Ketone			Amines	Reaction Conditions	Yield (%)	References
 **59**						
Y	acetyl (position)	substituents				
NH	2	–				75
NH, N–CH_3, N–C_2H_5	3	4,5-benzo		[19]	54–87	76
O	2	none, or 5-NO_2	$H_2N-CH_2-C_6H_5$,  ,  [a]		15–60	77
S	2	4- or 5-CH_3		[14]	64–91	65
S	2	none, or 5-Cl	 		6–68	78, 75

[a] Bis-[dihydroxyethyl]-amine did not react.

[19] Substrate, amine hydrochloride, paraformaldehyde, and ethanol were refluxed for 24 hr[76].

Mannich reaction of 3-propanoylindole, which contains two potential reaction centers, can give (depending on the conditions) both **61** and the disubstitution product[76] **62**.



Alkyl aryl ketones **63** and alkyl heteroaryl ketones **64** react to afford Mannich bases **65** having an asymmetric center α to the carbonyl group (Table 8). Some of the amino-ketones **65** have been resolved into their optical antipodes (see Section 1.6.).

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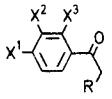
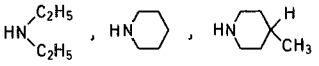
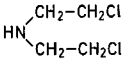
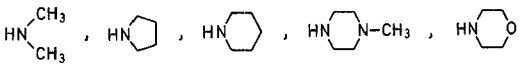
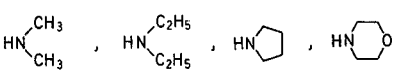
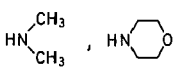
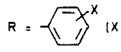
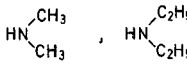
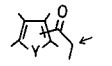
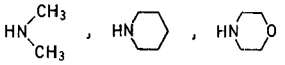
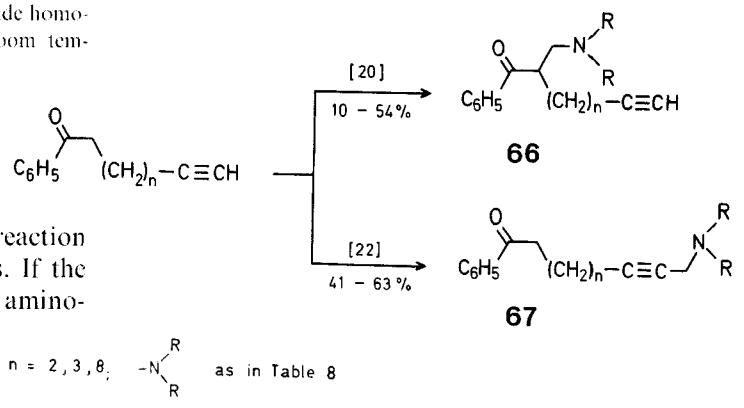
Table 8. Mannich Reactions of Alkyl Aryl Ketones or Alkyl Heteroaryl Ketones and Secondary Amines

Ketones	Amines	Reaction Conditions	Yield (%)	References
 **63**				
R = CH_3 $X^1 = X^3 = OCH_3$; $X^2 = H$		[15]	67–69	69
R = CH_3 $X^1 = OH$; $X^2 = X^3 = H$		[14]	50	65
R = n-C_3H_7, n-C_4H_9 $X^1 = X^2 = H$; $X^3 = H$, CH_3, OH				79
R = $-(CH_2)_n-C\equiv CH$ (n = 2, 3, 8) $X^1 = X^2 = X^3 = H$		[20]	10–54	80
R = $-CH_2-C_6H_4-X$ (X = H, OCH_3, Cl) $X^1 = X^2 = H$; $X^3 = H$, OCH_3			30–80	81
R =  (X = H, 3-OCH_3, 4-OCH_3, 3-Cl, 4-Cl) $X^1 = X^2 = H$; $X^3 = H$, OCH_3, Cl or $X^1 = X^3 = H$; $X^2 = OCH_3$, Cl			20–65	10
R = COOH $X^1 = X^2 = X^3 = H$		[21]	~100	82
 **64**				

Y	propanoyl (position)	substituent			
N-CH_3	3	4,5-benzo		[19]	32	76
O	2	none, or 5-CH_3			good	83
S	2	none			49–67	84

[20] Substrate, amine hydrochloride, paraformaldehyde, ethanol, and hydrochloric acid were refluxed[80].

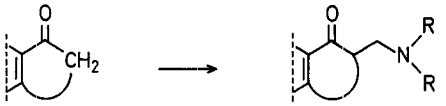
[21] Equimolar amounts of piperidine and aqueous formaldehyde were added to the acid. The mixture was made homogeneous by gently warming and then left at room temperature for 3–4 days[82].



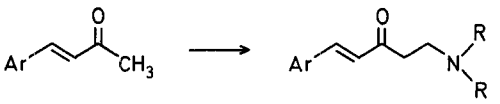
The problem of orientation in the Mannich reaction also arises in the case of acetylenic ketones. If the reaction is performed in acidic medium[80], aminomethylation α to the carbonyl group takes place to afford products **66**; in the presence of copper salts, attack occurs at the ethynyl group to give **67**.

[22] Substrate (0.035 mol), Mannich reagent (20 ml; from 10 g dimethylamine, 7.7 g trioxan, and 100 ml dioxan), and several crystals of copper(II) acetate in dioxan (10 ml) were heated for 65 hr at 70 °[80].

In the case of cyclic ketones such as benzo- and naphtho derivatives **68** and the heterocyclic compounds **69** and **70** (Table 9), the reaction occurs α to the carbonyl group, leading to the asymmetric β-aminoalkyl ketones **71**.



68, 69, 70 **71**



72 **73**

Aminomethylation of several aromatic azo compounds and anthraquinone derivatives containing one or more alkyl-ketonic groups constitutes an interesting application of the Mannich synthesis.

Table 9. Mannich Reactions of Aromatic- or Heteroaromatic-Condensed Cycloalkenones with Secondary Amines

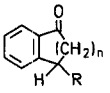
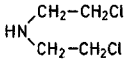
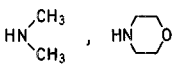
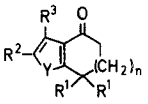
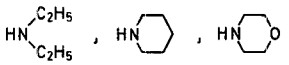
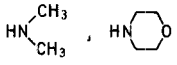
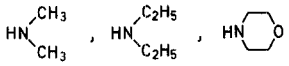
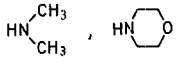
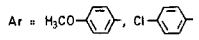
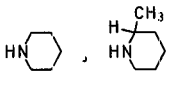
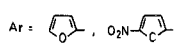
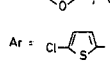
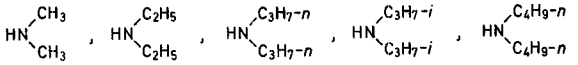
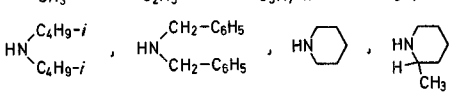
Ketones	Amines	Yield (%)	References
 **68**			
R = H, n = 1, 2, 3			85
R = H, n = 4		65	86
R = C_6H_5, n = 1 (=CH–CH_3)			81
 **69**			
Y = NH, R^1 = H, CH_3, R^2 = CH_3, C_2H_5, C_6H_5, R^3 = H, n = 1, 2			87
Y = O, R^1 = H, R^2 = H, CH_3, C_2H_5, R^3 = H, n = 1		8–74	83
Y = S, R^1 = H, R^2 = H, R^3 = H, n = 1			88
 **70**			83

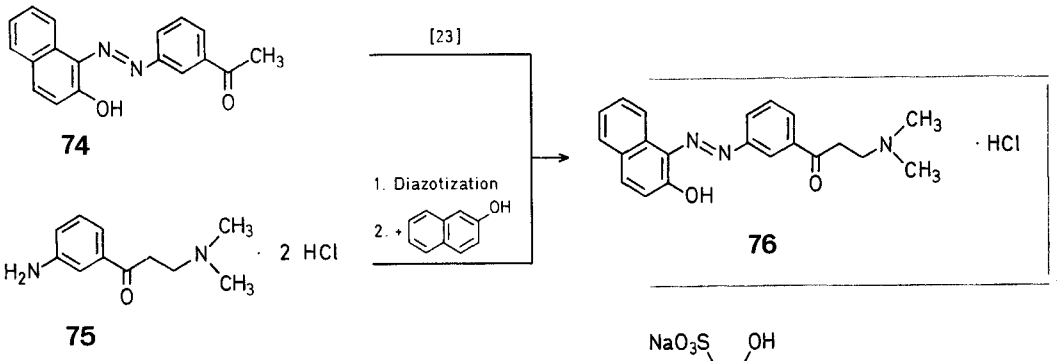
Table 10. Mannich Reactions of Methyl Styryl Ketones and Heterocyclic Analogs (**72**) with Primary or Secondary Amines

Ketones	Amines	Yield (%)	References
 **72**			
Ar = 		69–76	66
Ar = 	$H_2N-CH_2-C_6H_5$	15–30	77
Ar = 		9–56	78
			

Methyl styryl ketones (**72**) such as benzylidenacetone, and heterocyclic analogs, also undergo Mannich reaction at the methyl group to afford the corresponding 2-aminoethyl ketones (**73**); see Table 10.

Since the products have cationic properties (the quaternary aminium derivatives can also be easily obtained from the bases) they can be successfully used as dyes for textiles (including synthetic ones)[89,90] and as reactive dyes[91].

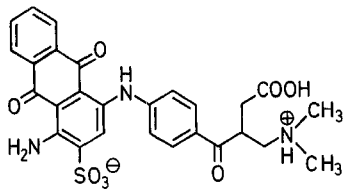
The synthesis of such aminomethylated azo compounds (e.g. **76**) can proceed either via Mannich reaction of the alkyl azoaryl ketones (**74**), or by starting from a previously aminomethylated aromatic amine (**75**).



74 **75** **76**

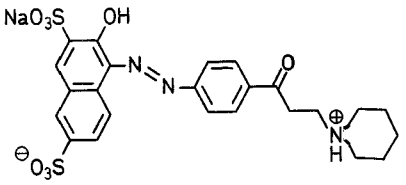
[23] Alkyl azoaryl ketone, amine hydrochloride, and paraformaldehyde (or aqueous formaldehyde) in acetic acid were refluxed until a sample was completely soluble in water; the solvent was then removed under reduced pressure and the residue was triturated with acetone or ethanol[89].

Similarly, anthraquinone derivatives (e.g. **77**) have been synthesized either by aminomethylation of an appropriate alkyl-ketonic anthraquinone, or by condensation of a previously aminomethylated arylamine [e.g. 3-(4-aminophenyl)-2-dimethylaminomethyl-3-oxopropanoic acid] with a bromoanthraquinone.



77

Mannich bases derived from disulfonated azo dyes[91] (e.g. **78**) display reactivity towards cellulose fibres. Deamination of such 2-aminoalkyl azoaryl ketones affords a vinyl-ketonic structure analogous to that present in other reactive dyes.

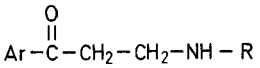


78 [24] 90%

[24] Alkyl azoaryl ketone, amine hydrochloride, and paraformaldehyde (or trioxan) in a minimum amount of water were refluxed for 4 hr; a few drops of conc. hydrochloric acid were added and the mixture was refluxed for another 4 hr[91].

"Unusual" primary (Table 11, compounds **79**–**82**) and secondary amines (Table 12, compounds **83**–**91**) have been used to synthesize a great number of Mannich bases.

Primary amines **79**, **80**, and **81** react to give secondary Mannich bases of the type



In the case of amines **79**, which possess a very bulky alkyl group, the second H-atom is completely unreactive, and the secondary bases obtained may be hydrolyzed to give primary ketonic bases (see Section 1.3.).

In contrast, the reaction of hydroxylamino derivatives **82** leads to the corresponding tertiary ketonic bases, both of the amino groups having participated in the reaction.

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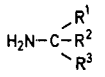
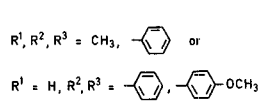
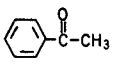
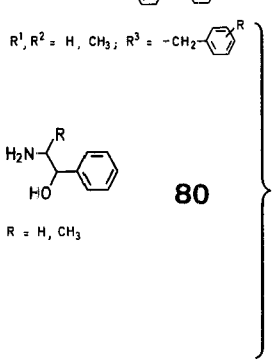
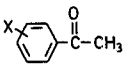
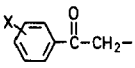
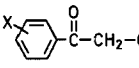
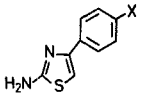
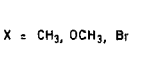
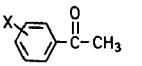
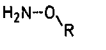
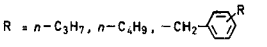
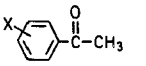
Table 11. Mannich Reactions of Alkyl Aryl Ketones with "Unusual" Primary Amines

Amines	Ketones	Reaction Conditions	Yield (%)	References
 **79** 		[6]	good	27, 28
 **80**	   and di- or trisubstituted analogs	[25]		11, 92
 **81** 		[25]	45–60	93
 **82** 			40–60	94

[25] Ketone, amine hydrochloride, and paraformaldehyde in 95% ethanol in the presence of a few drops of conc. hydrochloric acid were refluxed for 2–3 hr[92,93,98].

The group of secondary amines **83**–**91** (Table 12) includes bicyclic and several cyclic amines having ring systems larger than piperidine.

Some of the amines listed in Table 12 vary in their reactivity depending upon the conditions used; for example, the Mannich reaction with 4-nitroacetophenone and octamethylenimine leads to the simple Mannich base under acidic conditions[99], whereas in alkaline medium the bis-aminomethylated product is obtained[107].

Table 12. Mannich Reactions of Alkyl Aryl Ketones with "Unusual" Secondary Amines

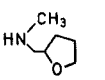
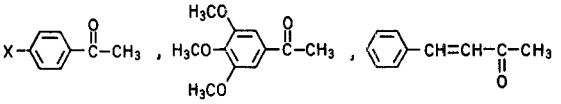
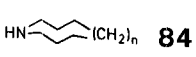
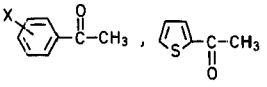
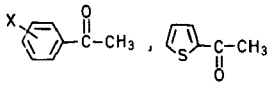
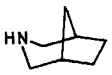
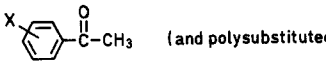
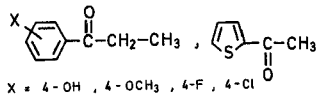
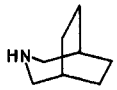
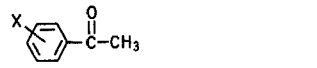
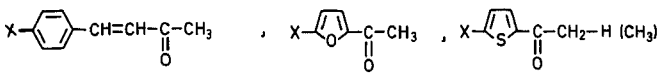
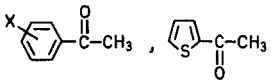
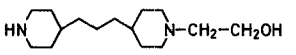
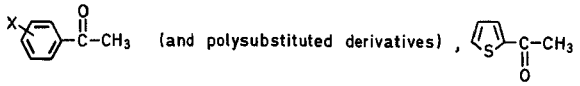
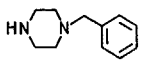
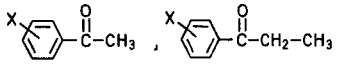
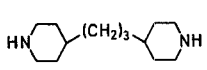
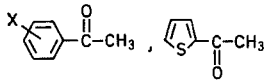
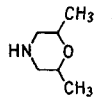
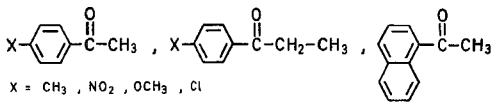
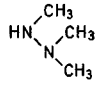
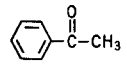
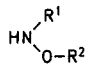
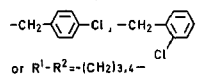
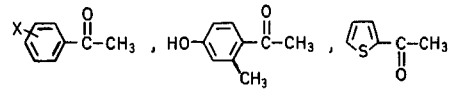
Amines	Ketones	Yield (%)	References
 **83**		32–76	95
 **84**			96
			97

Table 12, continued

Amines	Ketones	Yield (%)	References
 **85**	 (and polysubstituted derivatives) X = H , 2-CF_3 , 2-NO_2 , 2-OH , 3-CH_3 , 3-CF_3 , 3-NO_2 , 3-OH, 3-OCH_3 , 3-Br , 4-CH_3 , 4-CF_3 , 4-NO_2 , 4-OCH_3 , 4-Hal	40–77 (conditions [25])	98
	 X = 4-OH , 4-OCH_3 , 4-F , 4-Cl	21–68	99, 100
	 X = 2-OH , 3-NO_2 , 3-OH , 3-Br , 4-CH_3 , 4-C_2H_5 , 4-C_6H_5 , 4-NH_2 , 4-NO_2 , 4-OAlk , 4-Hal		
	 X = OCH_3 , Cl X = H , NO_2 X = H, Br		
 **86**	 X = 3-NO_2 , 4-NO_2 , 4-F	40–97	101
	 (and polysubstituted derivatives) X = 2-OH , 2-OCH_3 , 3-CH_3 , 3-NO_2 , 3-OH , 3-OCH_3 , 4-CH_3 4-C_6H_5 , 4-CF_3 , 4-NO_2 , 4-OH , 4-OAlk , 4-Hal	30–73	102
 **87**	 X = 4-OCH_3 , 4-Cl		103
 **88**	 X = 2-OH , 3-NO_2 , 4-CH_3 , 4-NO_2 , 4-OH , 4-OAlk , 4-Hal	35–80[a]	104
 **89**	 X = CH_3 , NO_2 , OCH_3 , Cl	40–80	105
 **90**			106
 **91** $R^1 = R^2 = CH_3$, $C_6H_5-CH_2-$  or $R^1-R^2 = -(CH_2)_{3,4}-$	 X = 2-NO_2, 2-OH, 4-NO_2, 4-OCH_3, 4-OH, 4-Br	40–60	94

[a] Only symmetric bases were obtained.

1.4.3. Aminomethylation of Phenols

Variously substituted phenols and naphthols, as well as phenols condensed with cycloalkenes or heterocyclic rings are commonly used in the Mannich reaction. With a few exceptions, aminomethylation always occurs at the position *ortho* to the hydroxy group, even if the *para* position is unoccupied.

Primary amines can react to give various products, as shown by the following scheme.

[120] V. I. Stavrovskaya, S. K. Drusvyatskaya, *Probl. Poluch. Poluprod. Prom. Org. Sin., Akad. Nauk SSSR Otd. Obshch. Tekh. Khim.* **1967**, 164; *C.A.* **68**, 12820 (1968).

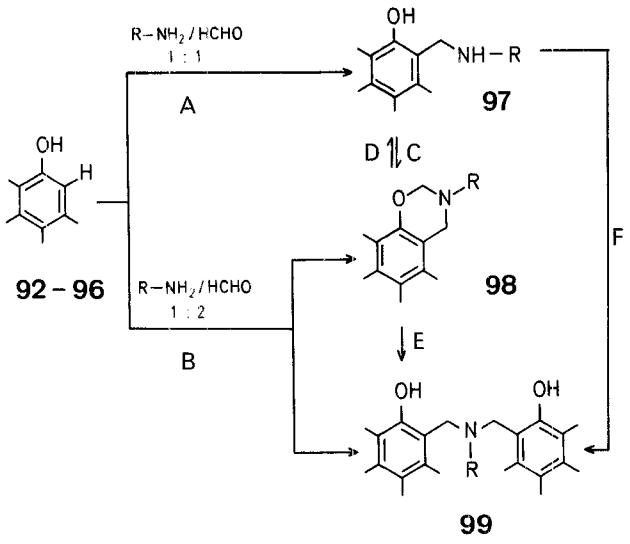
[121] W. L. Bencze, *Belg. Patent* 648916 (1964), CIBA Ltd.; *C.A.* **63**, 13176 (1965).

[122] T. Kametani, M. Ihara, J. *Chem. Soc.* [C] **1967**, 530.

[123] T. Kametani, K. Fukumoto, H. Yagi, H. Iida, T. Kikuchi, *J. Chem. Soc.* [C] **1968**, 1178.

[124] T. Kametani, I. Noguchi, K. Saito, *J. Heterocyclic Chem.* **6**, 869 (1969).

[125] T. Kametani et al., *Yakugaku Zasshi*, **87**, 168, 174, 179 (1967); *C.A.* **67**, 54309, 54310, 54311 (1967).

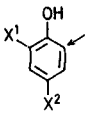
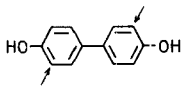
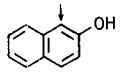
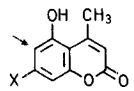
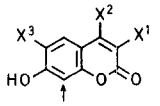


One or both of the amine H-atoms (Pathways A and B, respectively) can be substituted by use of the appropriate reaction conditions. Path A gives secondary bases **97** directly, but the reaction involving acid hydrolysis of dihydrobenzoxazines **98** (Path D) is often preferred. Pathway B usually gives compounds **98** rather than bis-[2-hydroxybenzyl]-amines **99**. For this reason, the latter products are best obtained via Path F (see Table 13).

Product **97** derived from 2,4-dimethylphenol (**92**, $X^1 = X^2 = CH_3$) and threonine have been synthesized in order to study the role played by formaldehyde in a hypothetical Mannich reaction in a biological system[109] (for example aminomethylation of the phenyl group of tyrosine); the relative stability of this compound in acidic medium is very good and decreases with increasing pH in alkaline media.

Pathway F, leading to bis-[2-hydroxybenzyl]-amines (**99**) and using compounds **97** as starting materials, is only practicable if R represents a linear or singly-branched alkyl group (see Table 13). When R is a bulky group (e.g., *t*-butyl or *t*-octyl), the reaction follows Path C and the oxazine derivative **98** is obtained together with considerable amounts of the corresponding *o*,*o*′-dihydroxydiarylmethane (e.g. bis-[2-hydroxy-1-naphthyl]-methane from 2-naphthol, **94**)[111].

Table 13. Mannich Reactions of Phenols with Primary Amines

Phenols	Amines	Reaction Pathway and Conditions	Products	Yield (%)	References
 **92**	H_2N–  , $H_2N-C_6H_{11}$-c	A, [26]	**97**	65	108
		B, [27]	**98**	45	108
		C, [28]	**98**	75	108
$X^1 = X^2 = CH_3$	$H_3C-CH(OH)-CH(NH_2)-COOH$	A, [26]	**87**	67	109
 **93**	H_2N-CH_2–	A; D, [29]	**97**		110
		B	**98**		110
 **94**	$H_2N-C_3H_7$-*i* , $H_2N-C_4H_9$-*t* , $H_2N-C_8H_{17}$-*t* ,	D	**97**	94–100	111
	$H_2N-CH(CH_3)$–	B	**98**	64–90	111
	H_2N-CH_3 , $H_2N-C_3H_7$-*i* , $H_2N-C_4H_9$-*n* ,	F, [30]	**99**	60–83	111
	H_2N-CH_2– , $H_2N-C_6H_{11}$-c				
	$H_2N-CH_2-CH_2-OH$	B	**98**	95–98	112
 **95**					
X = H	H_2N-CH_2–	D, [29]	**97**		113
		B	**98**		113
X = CH_3	H_2N-CH_2–	B, [31]	**98**	70	114
 **96**	H_2N-CH_3 , H_2N-CH_2– , H_2N–	(A), D	**97**	45–70	114
		B, [31] (C)	**98**	60–90	114
X^1 = H ; X^2 = CH_3 ; X^3 = H , C_2H_5 or X^1 = X^2 = CH_3 ; X^3 = Br					

[26] Phenol, amine, and aqueous formaldehyde were refluxed in ethanol for 24 hr. The mixture was then allowed to stand at room temperature for another 24 hr[108]; alternatively, the mixture was allowed to stand without heating for 7 days[109].

[27] Amine and paraformaldehyde were refluxed in dioxan for 2 hr; the phenol was then added and the mixture refluxed for another 12 hr[108].

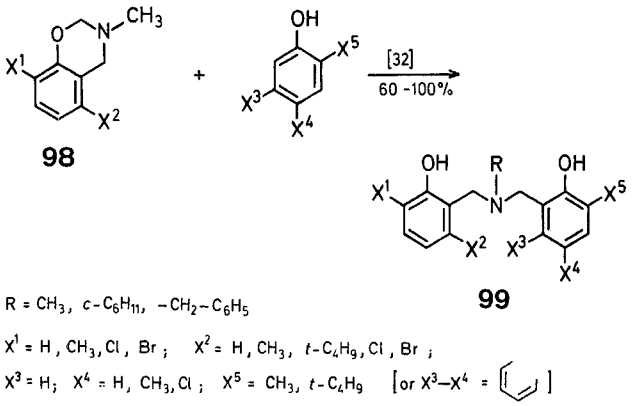
[28] Aminomethylphenol and aqueous formaldehyde were refluxed in isopropanol for 1 hr[108].

[29] Compound **98** was heated in ethanol/conc. hydrochloric acid (2:1)[110], or with half-concentrated hydrochloric acid[113].

[30] The hydrochloride of compound **97** was suspended in water and an ethereal solution of ethanolamine was added with stirring. The free base was isolated and warmed at 60° in 95% ethanol for 5 min. The product crystallized on cooling[111].

[31] A mixture of paraformaldehyde, potassium hydroxide, and absolute ethanol was heated to complete solution. Amine and phenol were added with cooling and the mixture was then heated on a steam bath for 2 hr[114].

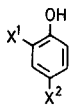
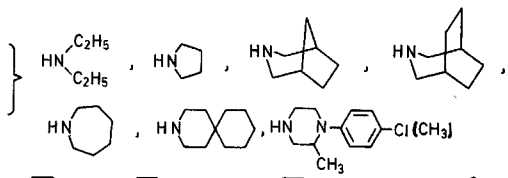
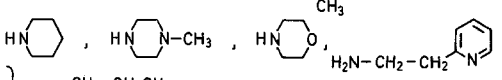
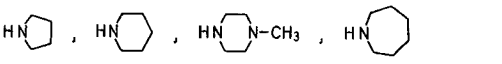
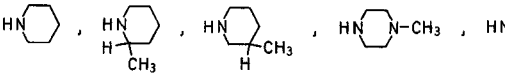
Unsymmetric bis-[2-hydroxybenzyl]-amines **99** have been obtained[115] via Pathway E.



[32] Compound **98** and a suitable phenol were mixed without solvent or with a little ethanol and the mixture was allowed to stand at room temperature for 1–2 days[115].

The preferred position of reaction in this transformation is also *ortho* to the hydroxy group of the phenol residue, and the group R exerts a considerable steric influence; thus, *N*-methyl compounds **98** ($R=CH_3$) are more reactive than the corresponding *N*-benzyl- and *N*-cyclohexyl compounds[115].

Table 14. Mannich Reactions of Phenols with Secondary Amines

Phenols	Amines	Reaction Conditions	Yield (%)	References
 **92**				
X^1 = H,  , $H_2C=CH-CH_2-$	X^2 =  , H		[33]	34–69–101
	H		[33]	good 116
H	t-C_4H_9, *neo*-C_5H_{11}, -O-CO-, Br			60–82 117
H	-NH-CO-CH_3			118, 119
H	-NH-CO--X (X = Cl, NO_2)		[26]	good 108

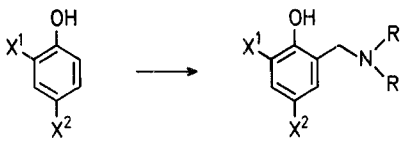
[33] Phenol, amine, and aqueous formaldehyde were heated in alcoholic solvents for various times[101, 116].

The Mannich reaction of several mono- and polynuclear phenols with secondary amines also affords *o*-substituted products. Thus, *o*- and *p*-monosubstituted (**92**, X^1 or $X^2=H$) and disubstituted phenols[101] (**92**, X^1, $X^2 \neq H$) react to give *o*-aminomethylphenols (**100**; see Table 14).

[126] J. E. Fernandez, J. M. Calderazzo, *J. Chem. Eng. Data* **10**, 402 (1965).

[127] R. Andrisano, C. Della Casa, M. Tramontini, *J. Chem. Soc.* [C] **1970**, 1866.

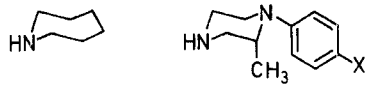
[128] F. Troxler, G. Bormann, F. Seemann, *Helv. Chim. Acta* **51**, 1203 (1968).



92 100

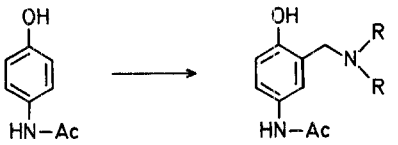
Only 6-allyl-2-methylphenol is aminomethylated in the *p*-position[101].

Several compounds of the type **100** containing "unusual" amino groups (e.g., derived from amines **101**, **102**, and others indicated in Table 12) have been synthesized because of their pharmaceutical interest.

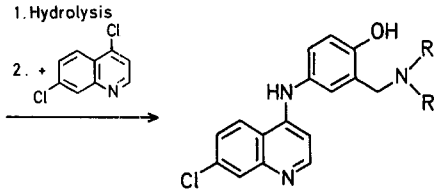


101 102 X = CH_3, Cl

The influence of functional substituents on the orientation of the Mannich reaction in the case of phenols is complex; in addition, the reaction conditions play an important role. Thus, 2-(2-hydroxyphenyl)-benzimidazole (Table 14) is aminomethylated at the phenolic benzene nucleus rather than at the heterocyclic NH group; on the other hand, salicylamides (**92**, X^1 = —CO—NH_2, X^2 = H, Cl; Table 14) first react at the amide group and only subsequently at the position *ortho* to the phenolic hydroxy group[120]. 4-Acetamidophenol (**92**, X^1 = H, X^2 = —NH—Ac) is only aminomethylated at the position *ortho* to the hydroxy group, affording Mannich bases of the type **103** which are starting materials for the synthesis of certain quinoline derivatives (**104**) possessing antimalarial activity[119].



92 (X^1 = H, X^2 = —NH—Ac) 103



104

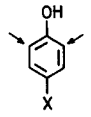
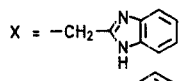
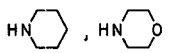
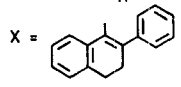
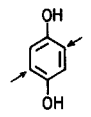
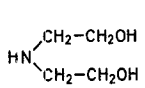
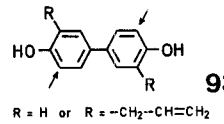
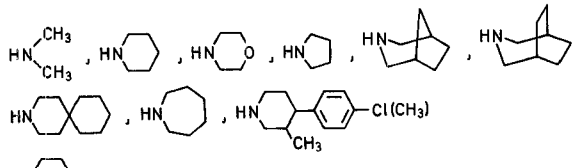
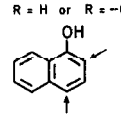
For amine components used, see Table 4.

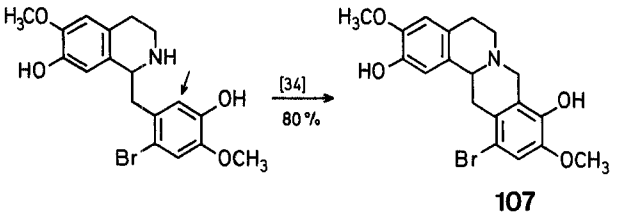
4-Hydroxyacetophenone (**51**, X = OH) undergoes aminomethylation either at the benzene nucleus (in alkaline medium) or at the methyl group (under acidic conditions)[67] (see Section 1.4.2.).

A list of phenols and bis-phenols which undergo bis-aminomethylation in the *o*-positions appears in Table 15.

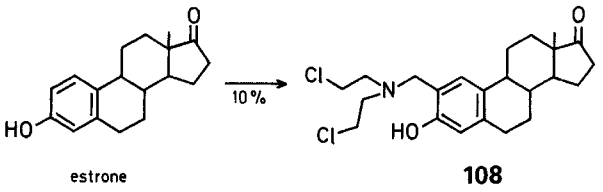
Intramolecular aminomethylation[122] has been used to obtain a series of protoberberine derivatives (e.g. **107**; see also Ref. [123,124,125]).

Table 15. Bis-aminomethylation Reactions of Phenols with Secondary Amines

Phenols	Amines	Reaction Conditions	Yield (%)	References
 92 X = CH_3			90	99
X = 		[33]	good	116
X = 				121
 105				117
 93 R = H or R = —CH_2—CH=CH_2		[33]	38–86	101, 110
 106		[16]		72



107



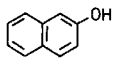
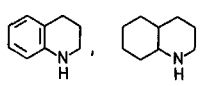
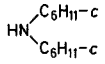
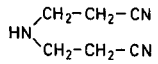
estrone **108**

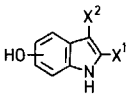
[34] The substrate hydrochloride (1.1 g), aqueous formaldehyde (25 ml), and water (25 ml) were heated on a steam bath for 3 hr[122].

The aminomethylation reaction has also been conducted on polynuclear phenols (including heterocyclic compounds). The reaction of estrone to give **108** is noteworthy[30].

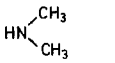
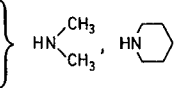
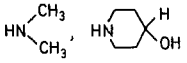
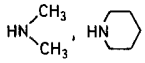
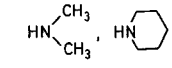
Similarly, aminomethylation reactions on β-naphthol (**94**), and on *O*-and *N*-heterocyclic compounds [hydroxyindoles (**109**), hydroxyquinolines (**110**), hydroxybenzo[*b*]furans (**111**), hydroxycoumarins (**96**), hydroxychromones (**112**)] have been carried out (Table 16).

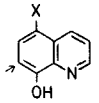
Table 16. Mannich Reactions of Binuclear Phenols with Secondary Amines

Phenols	Position of Reaction	Amines	Yield (%)	References
 **94**	1			126
	3			126
	1		98 (conditions [35])	127



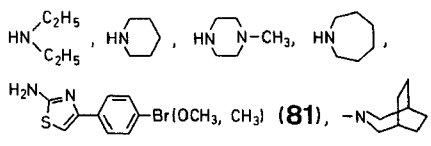
109

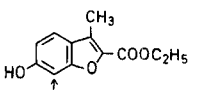
X^1	X^2	Position of OH			
H	H	4	5		80	128
H	H, CH_3	5	4		good	128, 132
CH_3	H, C_2H_5, $-COOC_2H_5$	5	4			
$-(CH_2)_4-$		5	4			
CH_3	$-COOC_2H_5$	5	4		good	133
(as for 5-OH)		6	7			128, 129, 130
H	H	7	6			128, 130
$-(CH_2)_4-$		7	6			



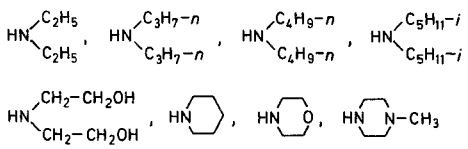
110

X = H, Cl, Br, $-CH_2-OAlk$

7		50–99 (conditions [33])	93, 101, 134

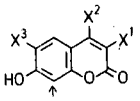
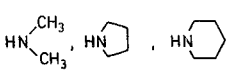
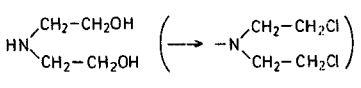
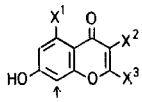
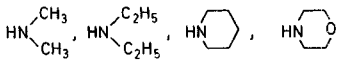


111

7			135

[129] S. A. Monti, W. O. Johnson, *Tetrahedron* **26**, 3685 (1970).
[130] S. A. Monti, W. O. Johnson, D. H. White, *Tetrahedron Lett.* **1966**, 4459.
[131] S. A. Monti, G. D. Castillo, *J. Org. Chem.* **35**, 3764 (1970).
[132] M. Julia, J. Y. Lallemand, *C.R. Acad. Sci.* **267**, 1506 (1969).
[133] M. R. Bell et al., *J. Med. Chem.* **10**, 264 (1967).

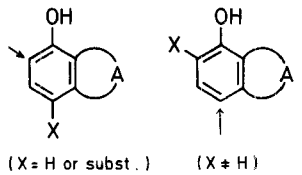
Table 16, continued

Phenols	Position of Reaction	Amines	Yield (%)	References
 **96**				
X^1 = H, X^2 = H, CH_3, n-C_3H_7,  ; X^3 = H, Cl; c-C_6H_{11}	8		50–60	136
X^1 = X^3 = H; X^2 = H, CH_3, C_6H_5	8		30–60	137
 **112**				
X^1 = H OCH_3, X^2 = H, CH_3, C_2H_5; X^3 = CH_3, C_2H_5, C_6H_5	8		35–88	138, 139

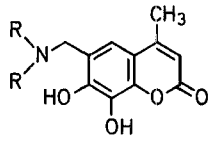
[35] A solution of β-naphthol (0.08 mol) in ethanol (45 ml) was added to the mixture of the amine (0.1 mol) and aqueous formaldehyde (0.08 mol) at 5°. The stirred mixture was gently heated for 1 hr at 30°. The solvent was removed under reduced pressure and the base recrystallized from ethanol[127].

The results obtained in aminomethylation reactions of the above-mentioned phenolic compounds may be summarized as follows:

– In the case of binuclear phenols having the hydroxy group in a position α to ring fusion (**113**), the reaction always proceeds to afford the product of *ortho* attack, even if the *p*-position is free. When the *o*-position (β to ring fusion) is occupied, the product of *p*-substitution is obtained, often in good yield[101,113]. When the *o*-substituent (β to ring fusion) is a hydroxy group, aminomethylation occurs at the position *ortho* to this substituent rather than at the position *para* to the first hydroxy group[113] (cf. **114**).

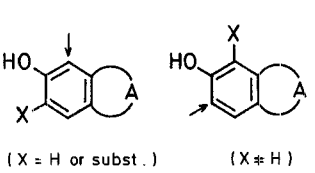


113

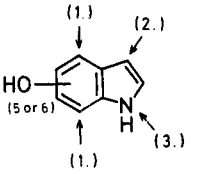


114

– In the case of binuclear phenols having the hydroxy group in a position β to ring fusion (**115**), the reaction always proceeds in the *o*-position α to ring fusion, even if the *o*-β-position is unoccupied; when the *o*-α-position is occupied, the reaction occurs at the free *o*-β-position. However, aminomethylation of β-naphthol (**94**) with bulky amines (e.g. dicyclohexylamine) takes place at the *o*-β-position[126].



115



116

The *o*-β-position of 5- and 6-hydroxyindoles (**116**) has been found inactive in the Mannich reaction[128]. Reaction usually occurs at the *o*-α-position; if this is occupied, attack occurs at position 3 or, when this is also occupied, at the heterocyclic NH group[128,129,130].

In summary, the position *ortho* to the hydroxy group is the preferred position of attack in all phenol derivatives. This fact has led several authors to propose a mechanism (see Formula **12**, Section 1.3.) involving initial formation of a hydrogen bond between the Mannich reagent and the substrate (the reaction does not occur in the absence of the hydroxy group[140]), followed by attack of one of the two *o*-positions whereby the position of attack is dependent on both steric and electronic factors[126,129,134,140,141].

Further examples of the *C*-aminoalkylation of phenols are found in Ref.[427,434].

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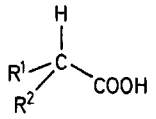
1.4.4. Aminomethylation of Carboxylic Acids and their Derivatives

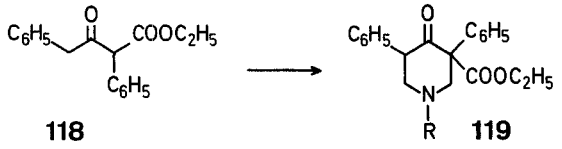
Carboxylic acid derivatives of the type **117** undergo the Mannich reaction when the molecule contains an electron-withdrawing substituent such as a carbonyl- (mainly ketonic), nitrophenyl-, sulfono- ($R—SO_2—$), or cyano group.



117 (or esters, amides, etc.)

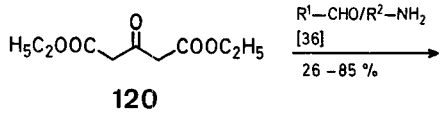
The reaction is often complex with respect to the number of H-atoms substituted, and the stability of the aminomethylated products varies.

Ethyl 2,4-diphenyl-3-oxobutanoate (**118**) and esters (**120**) of acetonedicarboxylic acid possess two reactive positions and react with aldehydes and ammonia or primary amines to afford a piperidone derivative. Using this reaction, several unsymmetric (**119**)[142] and symmetric (**121**) γ-piperidones may by synthesized[143–146].



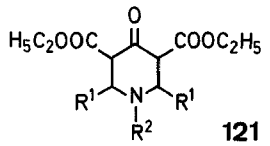
118 **119**

R = CH_3, C_2H_5

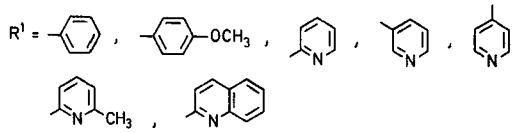


R^1—CHO/R^2—NH_2 [36] 26–85 %

120



121

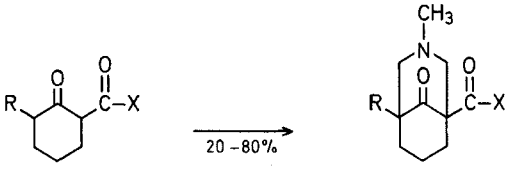


R^2 = H, CH_3, C_2H_5, $-CH_2-CH=CH_2$, $-CH_2-C_6H_5$, $-CH_2-CH_2OH$

[36] Aqueous amine and aqueous formaldehyde were dissolved in ethanol with cooling; the keto-ester was then added with cooling and the mixture allowed to stand at room temperature or at 0° (several min to 24 hr)[143,145].

In several cases, the products partially exist in a considerably stable enol form, which can be isolated[143,144].

The analogous reaction of 2-oxocyclohexanecarboxylic acids and their derivatives (**122**) affords symmetric[39,147,148] and unsymmetric[147] 9-oxo-3-azabicyclo[3.3.1]nonanecarboxylic acid derivatives (**123**).



20–80%

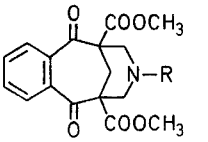
122 **123**

R = H; X = $-NH-n-C_4H_9$, $-NH-C_6H_5$

or

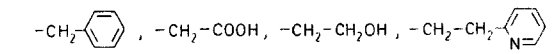
R = $-COOH$, $-COOC_2H_5$, $-CO-NH-C_6H_5$, X = OH, OC_2H_5, $-NH-C_6H_5$

4-Substituted 2,6-dimethoxycarbonyl-1,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-2,6-methano-4-benzazonines (**124**; 20–46%) were obtained by a similar synthesis[149].

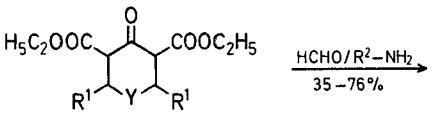


124

R = CH_3, C_2H_5, n-C_3H_7, i-C_3H_7, n-C_4H_9, n-C_5H_{11}, n-C_6H_{13}, c-C_6H_{11}

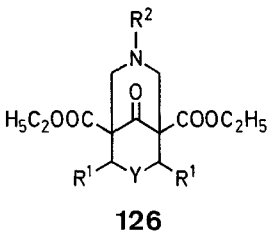


Further, several heterocyclic keto-esters of the type **125** (including piperidones **121**) have been converted into the corresponding Mannich bases (**126**). 6,8-Bis-[2-pyridyl] derivatives of **126** [Y = NH, R^1 = 2-pyridyl] are useful chelating agents for metals such as cobalt and manganese[146].



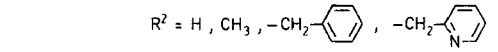
HCHO/R^2—NH_2 35–76%

125



126

Y = NH, N-alkyl; R^1 = alkyl as in **121**;



R^2 = H, CH_3, $-CH_2-C_6H_5$, $-CH_2-C_5H_4N$

Y = O; R^1 = C_6H_5; R^2 = $-CH_2-CH=CH_2$, $-CH_2-C_6H_5$, $-CH_2-C_5H_4N$

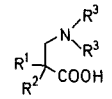
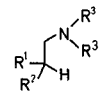
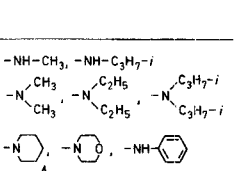
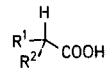
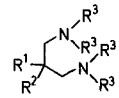
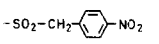
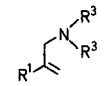
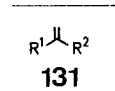
Y = S; R^1 =  ; R^2 = $-CH_2-C_5H_4N$

The Mannich reaction with secondary amines has mainly been studied with carboxylic acid derivatives **117**[150–152]. The reaction has been shown to be quite complex as the product undergoes further aminomethylation, decarboxylation, or deamination reactions (see Table 17).

[142] G. Settimj, R. Landi Vittory, F. Gatta, N. Sarti, S. Chiavarelli, *Gazz. Chim. Ital.* **96**, 604 (1966).

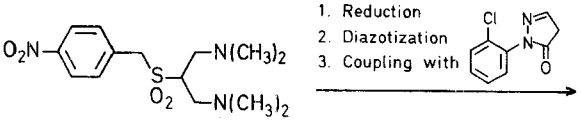
[143] K. W. Merz, E. Müller, R. Haller, *Chem. Ber.* **98**, 2317 (1965).

Table 17. Mannich Reactions of Substituted Acetic Acids (**117**) with Formaldehyde and Secondary (or Primary) Amines

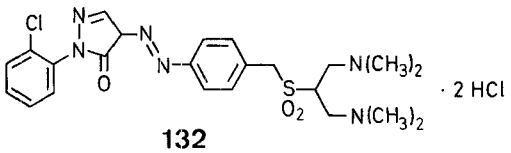
Products	R^1	R^2	$-N(R^3)_2$	Yield (%) [Conditions]	References
 **127**		H	 **(89)**	60–90[a]	105, 150
	–CN			93 [37]	151
 **128**	–CO–CH_3	CH_3, C_2H_5, i-C_3H_7,	–NH–CH_3, –NH–C_3H_7-i, 	various[b]	152
	–CO–CH_3	C_2H_5		50	51
		H		14[c]	150
  **129**		H			90
		H		66[c]	150
 **130**		H		29[a]	150
 **131**	see **128**		first entry	[b]	152

[a] Compound **127** was obtained in mixture with **130**.
[b] Compound **128** was obtained in mixture with **131**.
[c] Compound **128** was obtained in mixture with **129**.

[37] Acid (0.1 mol) and piperidine (0.1 mol) were mixed with cooling; aqueous formaldehyde was then added at room temperature to the salt (dissolved in the minimum amount of ethanol) and the mixture was allowed to stand for 20 min. The solid obtained by precipitation with methanol was isolated by filtration; yield: 93%; m. p. 104–105° [151].



129a



132

Aminomethylation of 4-nitrophenylacetic acid and cyanoacetic acid derivatives affords the normal Mannich bases in good yields. In addition, reaction of the former compounds also affords vinylamines **130**, whereas aminomethylation of acetoacetic compounds yields decarboxylated bases **128** and vinyl ketones **131** (R^1 = —CO—CH_3). Mannich reaction of dinitrophenylacetic acid and sulfonoacetic acid derivatives mainly yields decarboxylated bis-bases **129**.

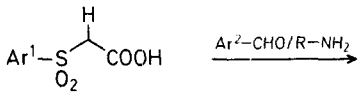
4-Nitrobenzylsulfono Mannich base **129a** is an intermediate in the synthesis of cationic azo dyes[90] such as **132** (cf. Section 1.4.2.).

The complexity of the reaction with carboxylic acids is related to the reactivity of the product β-amino-acids[150,151,152] (cf. Section 2.2.).

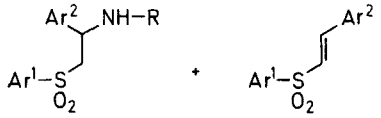
Arylsulfonoacetic acids of the type **117a** can be aminomethylated using aromatic aldehydes and primary amines or ammonia. The products[153,154] are β-amino-sulfones (**133**) and vinyl sulfones (**134**); these products correspond structurally to derivatives **128** and **131** (Table 17).

[144] S. Chiavarelli, L. Gramiccioni, F. Töffler, G. P. Valsecchi, *Gazz. Chim. Ital.* **97**, 1231 (1967).

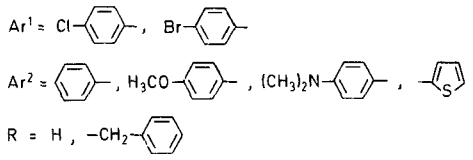
[145] K. W. Merz, R. Haller, *Pharm. Acta Helv.* **38**, 442 (1963).
[146] R. Haller, *Arzneimittelforschung* **15**, 1327 (1965); **13**, 1117 (1963).
[147] S. Rossi, W. Buttá, *Ann. Chim. (Roma)* **52**, 381 (1962).
[148] W. Schneider, H. Götz, *Arch. Pharm.* **294**, 506 (1961).



117a

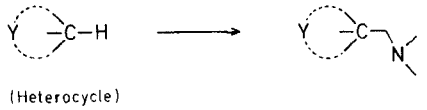


133 134

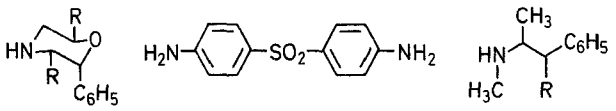


1.4.5. Aminomethylation of Heterocyclic Compounds

Several five- and six-membered heterocyclic compounds have been *C*-aminomethylated using primary and secondary amines (cf. Tables 18 and 19).



In some cases, "unusual" amines (e.g. **135**, **136**, **137**) have been used in order to obtain pharmacologically active products.



135 136 137

R = CH_3, C_2H_5, *n*-C_3H_7, *n*-C_4H_9, *n*-C_5H_{11} R = H, OH

Diamine **136** reacts at one or both of the amino groups.

Table 18. Mannich Reactions of Five-membered Heterocyclic Compounds and Ring-fused Analogs with Primary and Secondary Amines

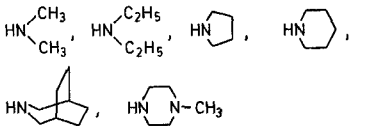
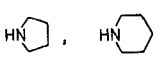
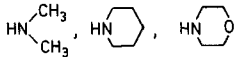
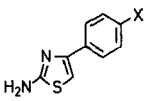
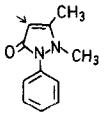
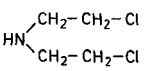
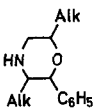
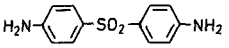
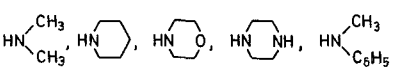
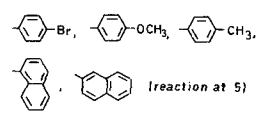
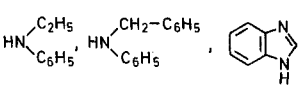
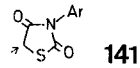
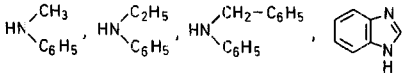
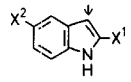
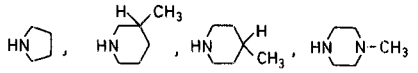
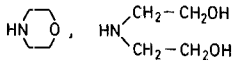
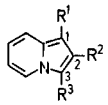
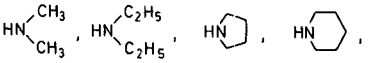
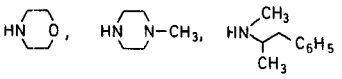
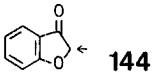
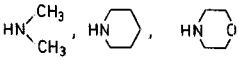
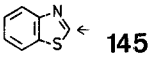
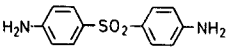
Heterocyclic Substrates	Amines	Reaction Conditions	Yield (%)	References
 **138** Y = N-CH_3, R = C_6H_5, 2,5-dioxo		[38]	16–79	155
Y = O, R = H, 2,4-dioxo, 5-H or 5-C_6H_5			good	156
Y = S, R = H, 4-oxo, 5-H or 5-$COOC_2H_5$		[39]	35–72	157
 **139** Y = N-C_6H_5, R = CH_3	 X = Br, OCH_3, CH_3	[15]	45–60	93
Y = O, R = CH_3, C_6H_5			good	160
			60–65	55, 158
 **140**		[40]	good	159
R^1 = R^2 = H (reaction at 2)				161
R^1 = -NH-Ac, R^2 =			good	162
 (reaction at 5)				

Table 18, continued

Heterocyclic Substrates	Amines	Reaction Conditions	Yield (%)	References
 **141**				
Ar = 		[15]	60–73	93
 **142**				
$X^1 = X^2 = H$			21–41	163
$X^1 = C_6H_5$, $X^2 = H$, NO_2	H_2N-CH_3, $H_2N-C_2H_5$, $H_2N-C_3H_7-i$, $H_2N-CH_2-C_6H_5$, 		25–55	164
$X^1 = COOC_2H_5$, $X^2 = -O-CH_2-C_6H_5$				132
 **143**				
$R^1 = H$; $R^2 = C_6H_5$; $R^3 = CH_3$, C_2H_5 (reaction at 1)		[41]	75–90	165–168
$R^1 = C_6H_5$, $-CH_2-CH_2OH$; $R^2 = C_6H_5$; $R^3 = H$ (reaction at 3)				
 **144**		[39]	47–66	157
 **145**				161

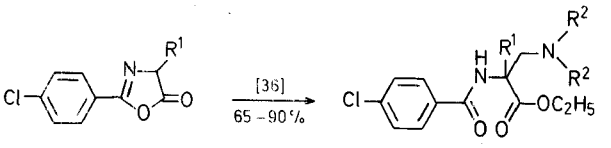
[38] Substrate, aqueous amine (40%), and aqueous formaldehyde were heated in acetic acid on a steam bath for 1–2 hr. In some cases, substrate, amine, and aqueous formaldehyde (or paraformaldehyde) were refluxed in toluene or cyclohexanol for 20–24 hr[155].

[39] The substrate was added to a stirred mixture of amine (0.1 mol), conc. hydrochloric acid (0.12 mol), and aqueous formaldehyde (0.1 mol); the mixture was then heated with stirring at 60° for 15 hr[157].

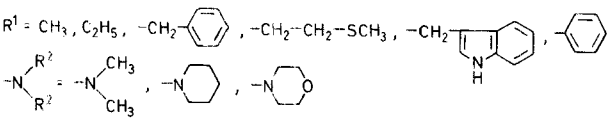
[40] A solution of the substrate in water was added to a solution of the amine and aqueous formaldehyde in methanol; the pH was adjusted to 2–3 with hydrochloric acid and the mixture was stirred for 2–3 hr at 25°[159].

[41] Substrate, amine, and aqueous formaldehyde in dioxan/water were allowed to stand for various times[165].

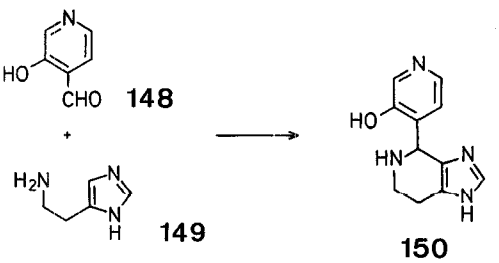
3-Monosubstituted 2-(4-chlorophenyl)-5-oxo-Δ^2-1,3-oxazolines (**146**) undergo aminomethylation with simultaneous cleavage of the heterocyclic ring to give, in good yield, amino-amido-esters (**147**) of pharmacological interest[169].



146 **147**



The Mannich condensation of histamine (**149**) with 3-hydroxypyridine-4-aldehyde (**148**) proceeds with cyclization to give a pyrido[3,4-*b*]imidazole derivative (**150**); the reaction is biologically interesting[170].



148 **149** **150**

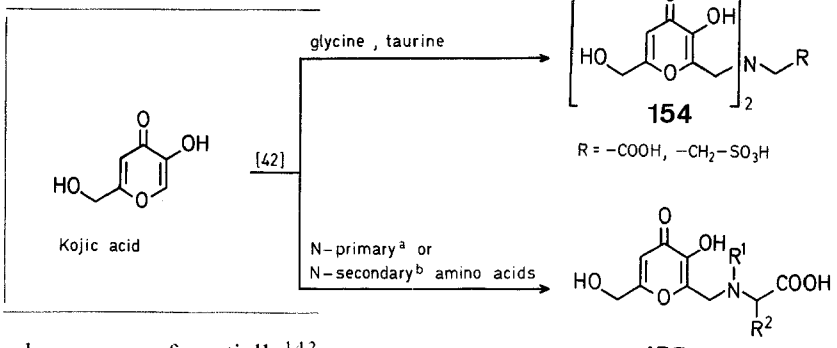
[149] W. E. Hahn, C. Korzeniewski, *Roczniki Chemii* **40**, 37 (1966), *C.A.* **65**, 3829 (1966).

[150] J. H. Schauble, E. Hertz, *J. Org. Chem.* **35**, 2529 (1970).

[151] M. Tramontini, unpublished data.

From the reported examples, it is quite difficult to state a general rule for the orientation of the Mannich reaction in the case of such heterocyclic systems; however, some general remarks may be made:

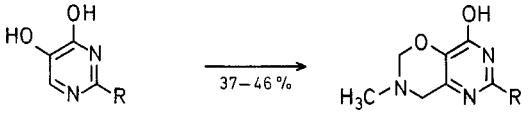
- When a carbonyl group (or the corresponding enol form) is present in the substrate, the preferred position of attack is α to this group;

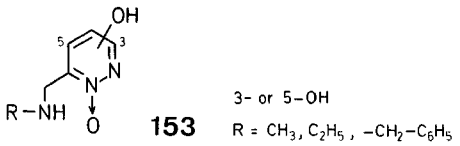


[a] Valine, leucine, isoleucine, methionine.
[b] Sarcosine, proline.

- In the indole ring, attack occurs preferentially[142] at position 3, whereas in the case of the indolizine ring, positions 1 and 3 undergo reaction[165–168].
- In the imidazole ring, all positions (1, 2, 4, and 5) can undergo reaction; in acidic medium, only *N*-substituted derivatives are obtained (see Section 1.5.1.), whereas in alkaline medium all positions are reactive (1>4,5>2) and aminomethylation at the N-atom is reversible[171];
- The 1,2-oxazoline ring (**139**, Y = O) reacts at position 4; when this position is occupied, reaction occurs at the N-atom or at any amino groups present in the molecule[160].

The reactivity of six-membered heterocyclic compounds is in some regards comparable to that of phenols; for example, reaction of 4,5-dihydroxypyrimidines (**151**) with formaldehyde and primary amines (in a ratio of 2:1) affords 8-hydroxy-3-methyl-2,3-dihydro-4*H*-pyrimido[4,5-*e*]-1,3-oxazines (**152**), and reaction of 2,4,5-trihydroxypyrimidine (**151**, R = OH) with formaldehyde and piperidine yields the corresponding 6-piperidinomethyl derivative (57%)[172].





In contrast, aminomethylation of 3- or 5-hydroxypyridazine-1-oxide always affords[173] the 6-aminomethyl derivative (**153**).

Kojic acid has been aminomethylated with several primary and secondary amino-acids in a biologically interesting reaction[174]. Tertiary bases **154** have only been obtained with two primary amino-acids; use of other primary amino-acids and of several secondary ones instead affords derivatives **155**.

[42] Glycine and aqueous formaldehyde were heated in ethanol for 10 min and then kojic acid was added; the mixture was allowed to stand at −20° for 2–3 hr; yield: 62%. Proline reacted at room temperature in 3 hr; yield: 70%. Other amino-acids reacted with heating for 15 min–12 hr; yields: 40–80%[174].

This different behaviour and the lack of reactivity of six other amino-acids has been attributed to steric and solubility factors[174].

Other examples of Mannich reactions with secondary amines and six-membered mono- or polynuclear heterocyclic compounds (**156–159**) are summarized in Table 19.

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[153] W. L. Nobles, B. B. Thompson, *J. Pharm. Sci.* **54**, 576 (1965).
[154] W. L. Nobles, B. B. Thompson, *J. Pharm. Sci.* **54**, 709 (1965).
[155] H. C. Clemson, E. O. Magarian, G. C. Fuller, R. O. Langner, *J. Pharm. Sci.* **57**, 384 (1968).
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[157] M. Mühlstädt, A. Zschunke, *Chem. Ber.* **101**, 1052 (1968).
[158] W. J. Serfontein, H. H. E. Schroeder, *J. S. African Chem. Inst.* **19**, 38 (1966); *C.A.* **65**, 13700 (1966).
[159] H. C. Stärk, H. Siemer, A. Doppstadt; *Brit. Patent* 852727 (1960), Ravensberg GmbH, Chemische Fabrik; *C.A.* **55**, 11443 (1961).
[160] W. Barbieri et al., *Tetrahedron* **23**, 4409 (1967).
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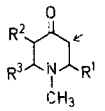
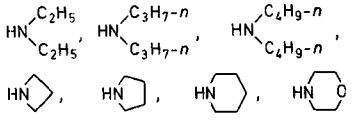
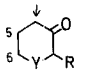
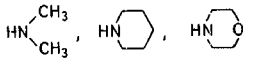
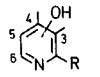
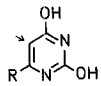
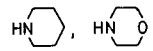
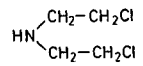
[162] P. N. Bhargava, S. C. Sharma, *Bull. Chem. Soc. Japan* **38**, 909 (1965).

Table 19. Mannich Reactions of Six-membered Heterocyclic Compounds and Their Ring-fused Analogs with Secondary Amines

Heterocyclic Substrates	Position of Reaction	Amines	Reaction Conditions	Yield [%]	References
 **156**					
$R^1 = R^2 = CH_3$; $R^3 = H$	3		[43]	38–68	175
R^1–R^3 = $-CH_2-CH_2-$; $R^2 = H$	3 and 5			28	39
 **157**	4		[39]	35–72	157
Y = O; R = H; 5,6-benzo or Y = S; R = H, $COOC_2H_5$					
 **158**					
R = OH; 3-OH	6 or 4 and 6		[44]	90–95	176, 177
R = CH_3; 4-OH; 5,6-benzo	3				
 **159**					
R = H	5		[44]	65–80	178
R = H, CH_3	5			45–58	179

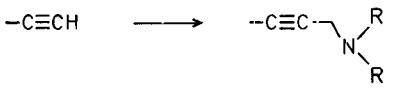
[43] A mixture of aqueous formaldehyde (0.15 mol) and amine hydrochloride (0.11 mol) was added dropwise, with stirring and cooling below 10°, to the piperidone (0.1 mol). The mixture was stirred at room temperature for 2 hr[175].

[44] Substrate, amine hydrochloride, and paraformaldehyde in ethanol were refluxed for 5–15 hr; alternatively, substrate, amine, and aqueous formaldehyde in water (or ethanol) were allowed to stand for 2–10 days[177,178].

Further examples of *C*-aminomethylation reactions of heterocyclic compounds are found in Ref.[435,436,437].

1.4.6. Aminomethylation of Alkynes

The Mannich reaction has been successfully carried out with acetylenic substrates (**160**, **161**; Table 20), including propargyl alcohols, to give the corresponding 1-amino-2-alkynes (**162**).



160, 161 **162**

[163] R. E. Orth, J. W. Bennet, On-Hou Ma, L. Joung, *J. Pharm. Sci.* **57**, 1814 (1968).

[164] R. P. Rao, *Labdev* [A] **7**, 99 (1969); *C.A.* **71**, 91198 (1969).

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[167] W. B. Harrell, *J. Pharm. Sci.* **59**, 275 (1970).

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[177] I. Nabih, M. Nast, *Can. J. Chem.* **44**, 1863 (1966).

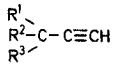
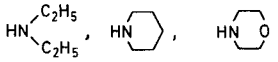
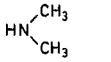
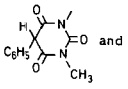
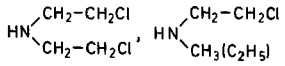
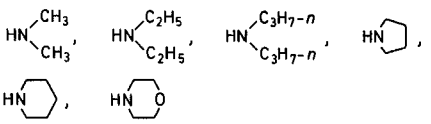
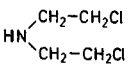
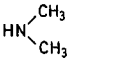
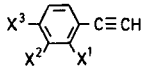
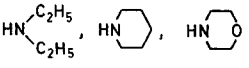
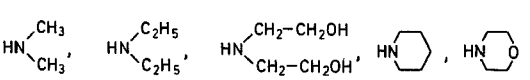
[178] J. H. Burckhalter, R. J. Seiwald, H. C. Scarborough, *J. Amer. Chem. Soc.* **82**, 991 (1960).

[179] R. C. Elderfield, J. R. Wood, *J. Org. Chem.* **26**, 3042 (1961).

[180] K. Schulze, U. Pfüller, H. B. Tichek, M. Mühlstädt, *Tetrahedron Lett.* **1968**, 2999.
5642 (1965).

[181] B. Danielsson, *Acta Pharm. Suecica* **2**, 149 (1965); *C. A.* **63**, 5642 (1965).

Table 20. Mannich Reactions of 1-Alkynes with Secondary Amines

Alkynes	Amines	Reaction Conditions	Yield (%)	References[a]
 **160**				
$R^1 = R^2 = H$; $R^3 = H_3C-(CH_2)_{0-6}-$			60–95	180
$R^1 = R^2 = H$; $R^3 = C_6H_5-\overset{O}{\overset{\|}{C}}-(CH_2)_{2,3,8}-$		[22]	41–63	80
$R^1 = R^2 = H$; $R^3 =$  and similar derivates; 3-unsubstituted hydantoins				181
$R^1 = R^2 = H$; $R^3 = OH$		[45]	80–92	182
$R^1 = OH$; $R^2 = CH_3$; $R^3 = CH_3$, C_2H_5		[46]	62–85	183
$R^1 = OH$; $R^2-R^3 = -(CH_2)_5-$ or				
$R^1, R^2, R^3 =$ 				184
 **161**				
$X^1 = H$; $X^2 = H, OCH_3$; $X^3 = OH$			35–60	185
$X^1 = CH_3$; $X^2 = H$; $X^3 = OH$				
$X^1 = X^2 = H$; $X^3 = -C\equiv C-\overset{CH_3}{\overset{\|}{C}}-OH$, CH_3			40–85	186, 187
$-C\equiv C-\overset{C_6H_5}{\overset{\|}{C}}-OH$, $-C\equiv C-(CH_2)_5-OH$, C_6H_5				

[a] see also Ref.[4,38].

[45] The pH of a solution of the amine (1.2 mol) in water (80 ml) was adjusted to 9 with sulfuric acid. Substrate (1 mol), aqueous formaldehyde (1.16 mol), and aqueous copper(II) sulfate were then added, and the pH adjusted to 8.4 by the addition of amine. The mixture was refluxed for 1 hr, then cooled, and extracted with ether for 9 hr in a continuous extractor[182].

[46] The acetylenic substrate and an equimolar amount of copper(II) chloride were refluxed in ethanol for 30 min (or in *t*-butanol for 60 min). Aqueous formaldehyde and amine were added and the mixture was refluxed for 1 hr[183].

Copper salts are often used in the reaction, since they have been found to increase the nucleophilicity of the acetylenic substrates towards the Mannich reactants.

Variation of the pH also appears to affect the reaction, as indicated by the following data on propargyl alcohol (**160**, $R^1 = R^2 = H$, $R^3 = OH$; Table 20; amine used: diethylamine)[182].

pH	Reaction Time	Yield (%) of Mannich Base
9	55 min	92
8.4	55 min	80
6	5.5 hr	80
3.8	5.5 hr	65
3	5.5 hr	–

Mechanistic studies indicate[182] that the reaction proceeds via attack of the methylolamine (or a derivative) on the acetylenic substrate rather than by attack of the amine on the hydroxymethyl derivative of the substrate.

The reactions of acetylenic Grignard reagents as substrates with aminomethyl butyl ethers as amine component[18], and the orientation of the Mannich reaction in the case of acetylenic ketones are discussed in Sections 1.2. and 1.4.2., respectively.

Aminomethylation of 17α-ethynyl-17β-hydroxysteroids (**163**) requires protection of the hydroxy group via acetal formation (with dihydro-4*H*-pyran), and affords Mannich bases of the type **164**. Androstane and estrone derivatives have successfully been aminomethylated using this procedure[188].

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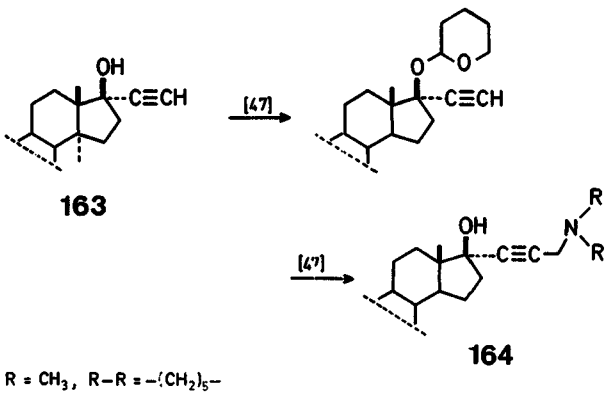
[183] G. R. Pettit, B. J. Danley, *Can. J. Chem.* **46**, 792 (1968).



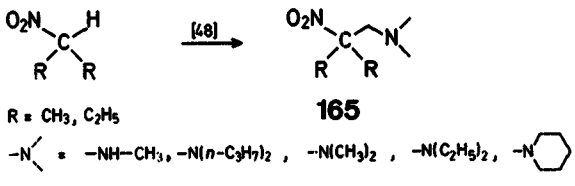
R = CH_3, R–R = $-(CH_2)_5-$

[47] *Protection of the Hydroxy Group:* Ethynyl-steroid, dihydro-4*H*-pyran, and phosphorus oxychloride were stirred in anhydrous benzene for 2 hr at room temperature.
Mannich Reaction: A solution of the substrate in dioxan is heated at 100° for 2-6 days; portions of aqueous amine and aqueous formaldehyde were daily added. The product was then submitted to acid hydrolysis; yields: ~100%[188].

1.4.7. Aminomethylation of Nitroalkanes

The Mannich reaction using nitroalkanes as substrates has been studied for several reaction media and various reagents. The aminomethylating power of methylene-bis-amines (**8**) is an increasing function of their base strength and of the dielectric constant of the reaction solvent[189,190]. When water is present in the reaction medium, the more reactive hydroxymethylamines (methylolamines, **7**) are formed, and the substrate can undergo bis-aminomethylation[190,191]. The aci-nitro form of the substrate appears to be involved in a cyclic or linear transition state, the former being favored in solvents having a low dielectric constant.

Successful synthesis of Mannich bases **165**, derived from α-branched mononitroalkanes, has been reported[192].

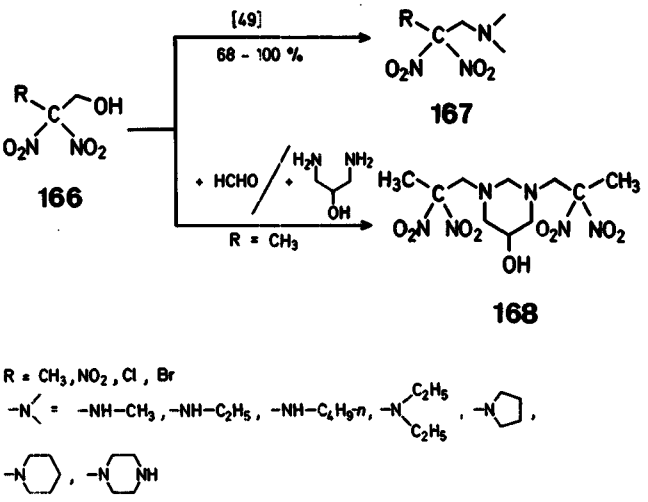


R = CH_3, C_2H_5

$-N\langle$ = $-NH-CH_3$, $-N(n\text{-}C_3H_7)_2$, $-N(CH_3)_2$, $-N(C_2H_5)_2$, $-N\bigcirc$

[48] To a stirred and cooled aqueous solution of the amine was added paraformaldehyde. The mixture was stirred at room temperature for 2 hr and then added to the nitroalkane in 0.13 *M* potassium hydroxide solution. Carbon dioxide was bubbled into the mixture, which was then extracted with ether[192].

Di- and trinitroethylamines (**167**) have been synthesized by condensation of nitroalkanols **166** with primary and secondary amines[193]. Hexahydropyrimidine derivative **168** has been obtained in a reaction using formaldehyde, and 1,3-diamino-2-hydroxypropane as the amine component.



R = CH_3, NO_2, Cl, Br

$-N\langle$ = $-NH-CH_3$, $-NH-C_2H_5$, $-NH-C_4H_9\text{-}n$, $-N(C_2H_5)_2$, $-N\bigcirc$, $-N\bigcirc$, $-N\bigcirc NH$

[49] A concentrated solution of β,β-dinitroethanol (**166**) and amine in water was stirred for 30 min and then extracted with ether. Some modifications were required for the reaction with arylamines[193].

A recent review on the chemistry of aliphatic polynitro compounds[194] devotes an entire chapter to the Mannich bases derived from the compounds.

The Mannich reaction of aci-3,5-dinitrocyclohexene salts, obtained from the corresponding *m*-dinitrobenzene derivatives (**169**) by reduction with complex hydrides or organometallic reagents, is of synthetic relevance.

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185 M. I. Bardamova, R. M. Myasnikova, I. L. Kotlyarevskii, *Izv. Akad. Nauk SSSR, Ser. Khim.* **1967**, 443; *C.A.* **67**, 21541 (1967).
186 I. L. Kotlyarevskii, L. B. Fisher, E. K. Andrievskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.* **1967**, 397; *C. A.* **67**, 21525 (1967).
187 L. B. Fisher, I. L. Kotlyarevskii, E. K. Andrievskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.* **1964**, 1543; *C.A.* **64**, 14116 (1966).
188 D. Burn, V. Petrov, *Tetrahedron* **20**, 2295 (1964).
189 J. E. Fernandez, J. S. Fowler, *J. Org. Chem.* **29**, 402 (1964).
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194 P. Noble, F. G. Borgardt, W. L. Reed, *Chem. Rev.* **64**, 19 (1964).
195 T. Severin, R. Schmitz, M. Adam, *Chem. Ber.* **96**, 3076 (1963).
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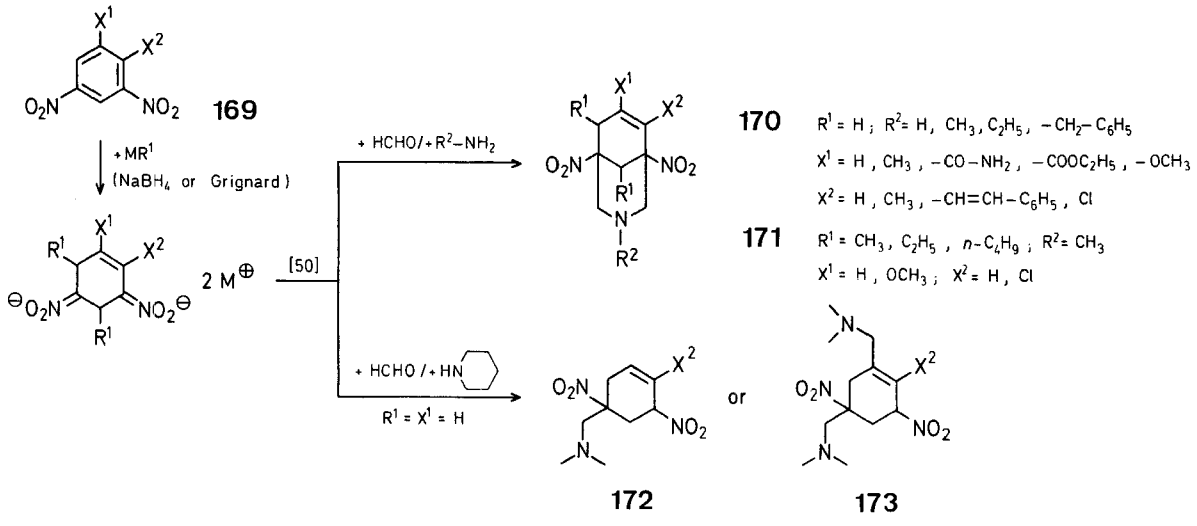
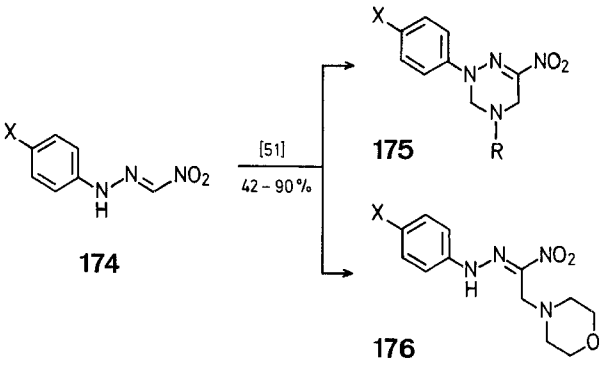
200 M. I. Farberov, G. S. Mironov, *Dokl. Akad. Nauk SSSR* **148**, 1095 (1963); *C.A.* **59**, 5062 (1963).



[50] Reduction of **169** was carried out in tetrahydrofuran, dimethylformamide or methanol/dimethylformamide with sodium borohydride at 5–18°. The Grignard reactions were performed under the usual conditions. Amine, aqueous formaldehyde, and acetic acid were then added with cooling to the above reaction mixtures diluted with water; yield: **170**, 44–94%; **171**, 12–37%; **172**, 45–68%; **173**, 23 to 42%[195,196,197].

1,5-Dinitro-3-azabicyclo[3.3.1]non-6-enes **170** and **171** have been obtained by aminomethylation of aci-3,5-dinitrocyclohexene salts with primary amines[195,196,197], whereas mono- or bis-Mannich bases **172** or **173** have been obtained in the reaction with secondary amines[195,196].

Similarly, 6-nitro-2,3,4,5-tetrahydro-1,2,4-triazines (**175**) have been obtained by Mannich reaction of nitroformaldehyde arylhydrazones (**174**) and primary amines, whereas the reaction with morpholine affords[198] acyclic bases **176**; the use of other secondary amines only affords 1,3-dihydrazono-1,3-dinitropropanes.



X = H, –NO₂, –OC₂H₅, Cl
R = CH₃, C₂H₅, n-C₃H₇, i-C₃H₇, n-C₄H₉, –CH₂–CH=CH₂, –CH₂–C₆H₅, c-C₆H₁₁, C₆H₅

[51] Substrate, amine, and aqueous formaldehyde are heated in ethanol or dioxan on a steam bath for 10–20 min; the mixture is allowed to stand for 1–2 days; yields: 42–90%[198].

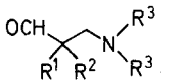
[201] G. S. Mironov, M. I. Farberov, M. A. Korshunov, *Uch. Zap. Yaroslavsk. Tekhn. Inst.* **1962**, 33; *C.A.* **61**, 568 (1964).

[202] G. S. Mironov, M. I. Farberov, I. I. Bespalova, *Zh. Obshch. Khim.* **34**, 1642 (1964); *C.A.* **61**, 5505 (1964).

1.4.8. Aminomethylation of Miscellaneous Compounds

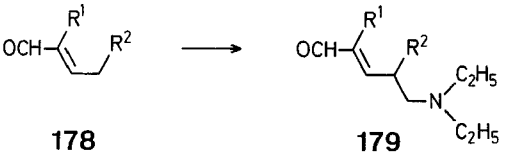
This Section deals with the aminomethylation of aliphatic aldehydes, α,β-unsaturated ketones, hydroxynaphthoquinones, tropolones, methylheteroarenes, arylamines, ferrocenes, and hydrogen cyanide.

Several α-branched aliphatic *aldehydes* and phenylacetaldehydes undergo Mannich reaction[199,200,201] to give β-amino-aldehydes (**177**).



R¹ = H, CH₃, C₂H₅
R² = CH₃, C₂H₅, n-C₃H₇, i-C₃H₇, n-C₄H₉, C₆H₅
R³ = CH₃, C₂H₅

α,β-Unsaturated aldehydes (**178**) are in contrast aminomethylated at the γ-position[202] to give 5-aminopent-2-enals (**179**); the activation by the carbonyl group in these compounds is thus transmitted through the double bond.

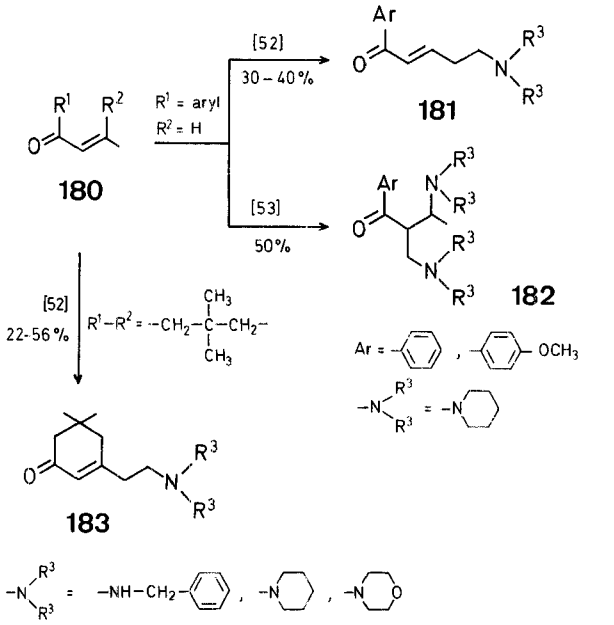


R¹= R²= CH₃; or R¹= C₂H₅, R²= CH₃, C₂H₅

A similar phenomenon has been observed in the case of *propenyl aryl ketones* (**180**, R¹ = aryl, R² = H), which, in acidic medium, react to give vinylogous Mannich bases **181** (see also Ref.[161]). In alkaline medium, however, diamine **182** is the product; this is probably formed by addition of the amine to the double bond, followed by aminomethylation of the position α to the carbonyl group[203].

Vinylogous Mannich base **183** is the product of the reaction with 3-oxo-1,5,5-trimethylcyclohexene (iso-

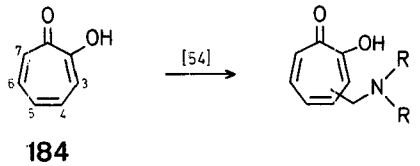
phorone); only by use of two equivalents of Mannich reactants per equivalent of substrate can a second aminomethyl group be introduced α to the carbonyl group[204] (the normally expected position).



[52] Substrate, amine, paraformaldehyde, and a few drops of a strong acid were heated in acetic acid at 80° for 4 days (yields: 30–40%)[203], or were refluxed in propanol for 40 min (yields: 22–56%)[204].

[53] Substrate, amine, and aqueous formaldehyde were allowed to react at room temperature for 24 hr[203].

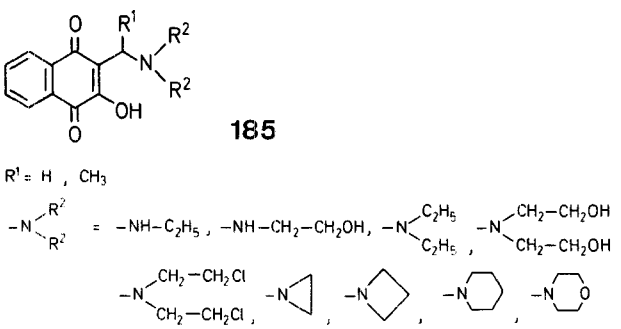
Tropolone (**184**) and its 6-substituted derivatives are aminomethylated in alkaline medium[205] at position 3, whereas the reaction of 3-substituted tropolones in acidic medium affords the 5,7-bis-[aminomethyl]derivatives[206]. The lack of reactivity of 4- and 3,4,7-substituted tropolones has been attributed to steric hindrance.



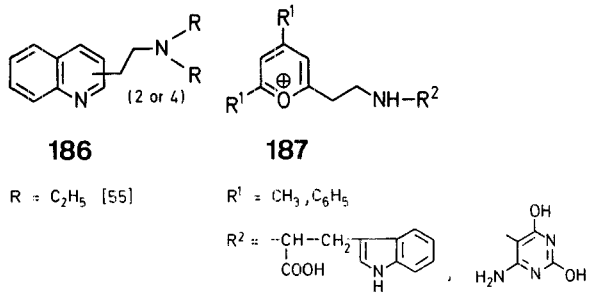
Substituents	Site of Aminomethylation
none or 6-CH_3	3
4-CH_3, or 3,7-di-Br-4-CH_3	no reaction
3-*i*-C_3H_7	5 and 7

[54] Substrate and methylene-bis-amine were refluxed in ethanol for 6 hr; yield: 55–92%[205]. Alternatively, substrate, amine, and aqueous formaldehyde were heated in acetic acid with stirring for 1 hr at 60°; yield: 60–70%[206].

The pharmacologically interesting 3-(1-aminoalkyl)-2-hydroxynaphthoquinones **185** have been obtained from the reaction of *2-hydroxy-1,4-naphthoquinone* ("lawsone") with formaldehyde, and with acetaldehyde (one of the few examples of aminoalkylation with the latter reagent). The reaction conditions are, however, critical, since the products are easily transformed into 3,3′-methylene-bis-[2-hydroxy-1,4-naphthoquinone][207].



In the case of a few six-membered *heteroaromatic rings*, the 2- or 4-methyl group undergoes the aminomethylation reaction. Thus, direct synthesis of 2- or 4-aminoethylquinolines[208] (**186**), as well as 2-aminoethylpyrylium salts[209] (**187**) is possible; see also Ref[437].

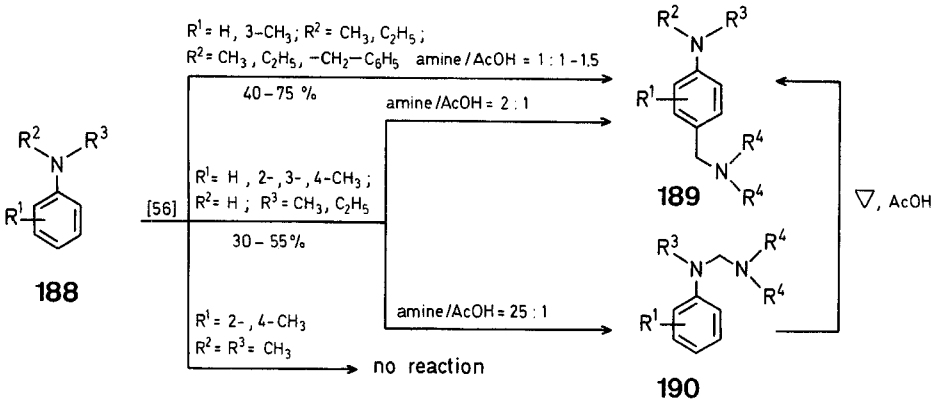


[55] Substrate, amine hydrochloride, and aqueous formaldehyde were dissolved in ethanol; the pH was adjusted to 7.5–8.0 with triethylamine, and the mixture heated for 2 hr at 60°; yield: 70%[208].

Arylamines (**188**) having an alkyl group at nitrogen and/or in the *o*- or *m*-position are aminomethylated *para* to the amino group to afford products **189**; under particular conditions and in some cases, attack at nitrogen occurs to yield **190**.

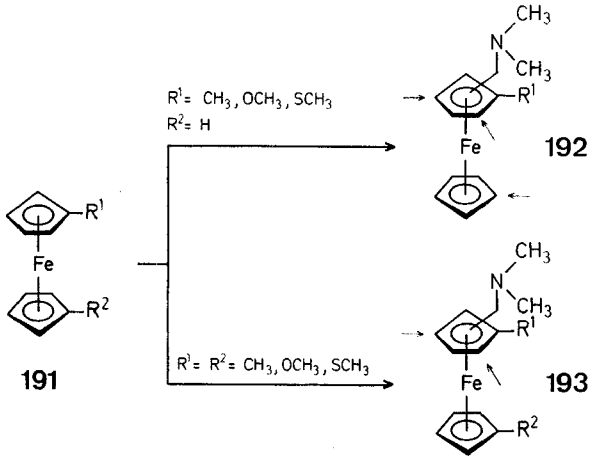
Specifically, *N,N*-dialkylanilines only react *para* to the amino group; under similar conditions, *N*-monoalkylanilines (but not *N*,4-dialkylanilines) also react in the *p*-position, but aminomethylation at nitrogen has been observed when the concentration of acetic acid is reduced. Steric and electronic factors seem to inhibit ring aminomethylation of *N,N*,3- and *N,N*,4-trimethylanilines[210]. The reversibility of the aminomethylation of arylamines is strongly affected by the reaction pH.

[203] K. Bodendorf, P. Kloss, *Liebigs Ann. Chem.* **677**, 95 (1964).
[204] H. J. Roth, G. Langer, *Arch. Pharm.* **301**, 695 (1968).
[205] P. L. Pauson, P. B. Kelly, R. J. Porter, *J. Chem. Soc.* [C] **1970**, 1323.
[206] K. Ogura, *Bull. Chem. Soc. Japan* **34**, 838 (1961).



[56] Arylamine **188** and acetic acid were added to a mixture of alkylamine and aqueous formaldehyde and the mixture was heated on a steam bath for 30 hr. Compounds **190** were obtained by heating the mixture for 1 hr[210].

Reaction of *ferrocene* with 2 mol of 1,1-diaminoalkanes in acetic acid/phosphoric acid affords aminoalkylation at both the ferrocene rings[211]. The Mannich reaction of monomethyl-, monomethoxy-, and monomethylthioferrocenes (**191**, $R^2 = H$) always affords ternary mixtures of monoaminomethylated products (**192**). The reaction of disubstituted ferrocenes (**191**) affords binary mixtures (**193**)[212]. The yields of aminomethylation products are good and the products can be separated by chromatography.

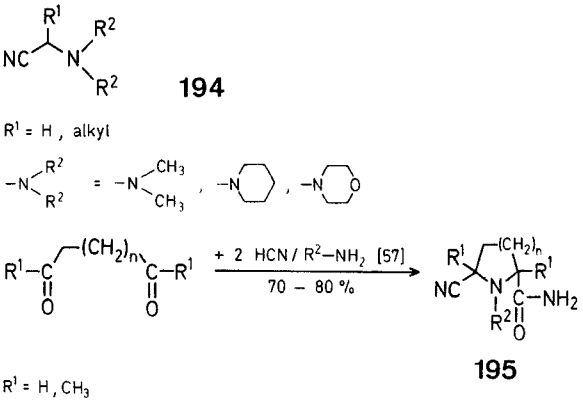


Positions 3, 2, and 1′ are the most reactive (in decreasing order) in monomethylferrocenes. In the case of monomethoxy- and monomethylthio derivatives, the order of reactivity is position 2 > 3 > 1′. Substitution increases the reactivity of the rings, whereby decreasing activity is shown in the substitution series $OCH_3 > SCH_3 > CH_3$.

For aminomethylations of metallocenes, see also Ref.[439,440,441].

Hydrogen cyanide has been aminomethylated using amines such as primary and secondary ethylenediamines and melamine to give α-aminonitriles **194** ($R^1 = H$)[8].

Compounds **194** (R^1 = Alkyl) have been obtained in yields of 60–80% by reaction of various aldehydes, amine hydrochlorides, and potassium cyanide in water at room temperature[213] (see also Ref.[442,443]).



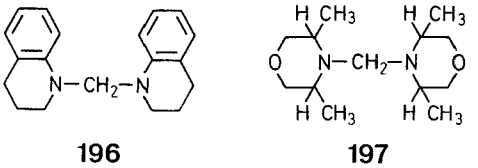
[57] Sodium cyanide, amine, and aldehyde are stirred in aqueous methanol/6 *N* hydrochloric acid for 1 hr at 0 °; the mixture is then allowed to stand at the same temperature for 12 hr[214].

Cyclic amines of the type **195** may be obtained by a synthesis involving reaction of hydrogen cyanide with γ- or δ-dicarbonyl compounds (glutardialdehyde, hexane-2,5-dione) and primary amines[214].

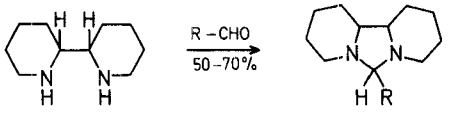
1.5. *N*-, *S*-, *Se*-, and *P*-Aminomethylation Reactions

1.5.1. *N*-Aminomethylation of Amines, Acyclic Carboxamides, and NH-Heterocyclic Compounds

Aminomethylation of *amines* affords methylene-bisamines, which have been widely used as reagents in mechanistic studies on the Mannich reaction. To this end, several new compounds (e.g. **196**, **197**) have been prepared from sterically hindered alkylamines[126].

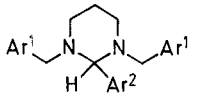


The reaction of *β*- or *γ-diamines* (e.g. **197**) with various aldehydes may be used to synthesize *N*-heterocyclic compounds having the structure of cyclic aminals (e.g. **198**)[215]. Thus, pharmacologically interesting hexahydropyrimidine derivatives (**199**) have been obtained from 1,3-bis-[benzylamino]-propanes and substituted benzaldehydes[216,217] see also Ref.[444,445].

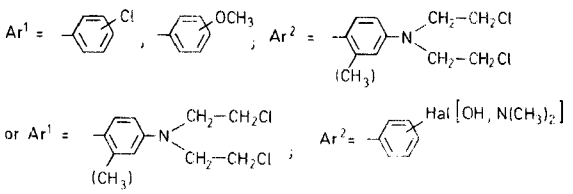


197 **198**

R = H, CH_3, C_6H_5



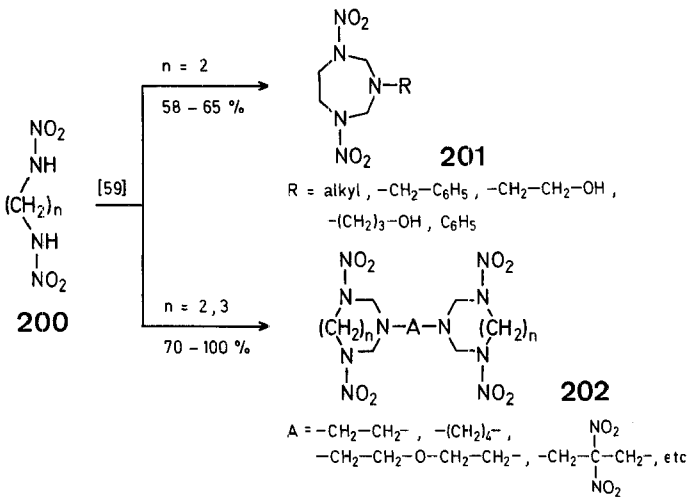
199 [58]



[58] The amine was added to a hot solution of the aldehyde in ethanol. The mixture was refluxed for 15 min and then part of the solvent was distilled off. The product crystallized upon cooling of the solution[216]. Alternatively, a solution of amine and aldehyde in methanol was shaken vigorously for 4 hr at room temperature. The product precipitated out; yields: 40–90%[217].

The *N*-aminomethylation of *aniline* derivatives, which competes with the aminomethylation reaction at the aromatic ring, and also that of amino-1,2-oxazoles (cf. Sections 1.4.8 and 1.4.5) should also be noted here.

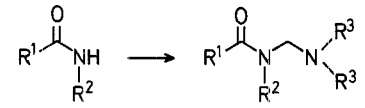
1,2- and *1,3-Bis[nitramino]-alkanes* **200** may be cyclized by Mannich reaction using primary amines to give 1,5-dinitrohexahydro-1,3,5-triazepine- (**201**, **202**, for n=2) or 1,5-dinitrooctahydro-1,3,5-triazocine derivatives (**202**, for n=3), respectively[218].



200 **201** **202**

[59] Substrate, amine, and aqueous formaldehyde in water (pH 5.4–5.9) were warmed at 70° for 10 min[218].

The *N*-aminomethylation of acyclic *carboxamides* has been carried out with primary and secondary amines (see also Ref.[446,447]). The reactions of acyclic carboxamides (**203**) with formaldehyde and secondary amines to give Mannich bases (**204**) are summarized in Table 21.

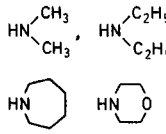
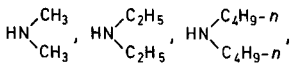
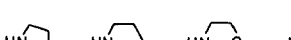
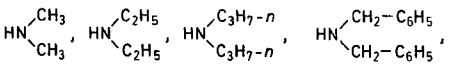
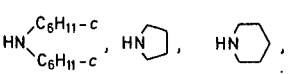
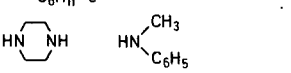


203 **204**

A study concerning the aminomethylation reaction with several benzamides and chloroacetamides established that the reaction only takes place with sufficiently basic amines, or with amides derived from sufficiently strong carboxylic acids (pK_a = 1.25–2.85)[221].

[207] W. R. Vaughan et al., *J. Org. Chem.* **26**, 2392 (1961).
[208] E. S. Kagan, B. I. Ardashev, *Khim. Geterotcikl Soed.* **1967**, 701; *C.A.* **68**, 114408 (1968).
[209] A. N. Narkevich, G. N. Dorofeenko, Y. A. Zhdanov, *Zh. Org. Khim.* **1**, 975 (1965); *C.A.* **63**, 7007 (1965).
[210] M. Miocque, J. M. Vierfond, *Bull. Soc. Chim. France* **1970**, 1896, 1901, 1907.
[211] P. L. Pauson, M. A. Sandhu, W. E. Watts, *J. Chem. Soc.* [C] **1966**, 251.
[212] G. R. Knox et al., *J. Chem. Soc.* [C] **1967**, 1842, 1847, 1851, 1853.
[213] M. Götz, K. Zeile, *Tetrahedron* **26**, 3185 (1970).
[214] O. Dold, *Chem. Ber.* **96**, 2052 (1963).
[215] T. P. Abbiss, A. H. Soloway, V. H. Mark, *J. Med. Chem.* **7**, 644 (1964).
[216] J. H. Billman, J. L. Meisenheimer, *J. Med. Chem.* **7**, 115 (1964).
[217] J. H. Billman, M. S. Khan, *J. Pharm. Sci.* **57**, 1817 (1968).
[218] S. S. Novikov, A. A. Dudinskaya, N. V. Makarov, N. I. Khmelnitskii, *Izv. Akad. Nauk SSSR, Ser. Khim.* **1967**, 1833, 1837, 1839; *C.A.* **68**, 29687, 29688, 29689 (1968).
[219] H. Möhrle, P. Spillmann, *Tetrahedron* **25**, 5595 (1969).
[220] H. Möhrle, P. Spillmann, *Tetrahedron* **26**, 4895 (1970).
[221] V. I. Stavrovskaya, S. K. Drusvyatskaya, M. O. Kolosova, *Zh. Org. Khim.* **4**, 488 (1968); *C.A.* **68**, 104640 (1968).
[222] V. I. Stavrovskaya, S. K. Drusvyatskaya, *Zh. Org. Khim.* **5**, 388 (1969); Engl. Edit., p. 375.
[223] J. Strating, A. M. Van Leusen, *Rec. Trav. Chim.* **81**, 966 (1962).
[224] G. B. Singh, S. P. Agrawal, *J. Indian Chem. Soc.* **40**, 777 (1963); *C.A.* **60**, 450 (1964).
[225] G. B. Singh, A. S. Chawla, V. K. Vijjan, *Indian J. Pharm.* **30**, 231 (1968); *C.A.* **70**, 28790 (1969).
[226] W. J. Gottstein, W. F. Minor, L. C. Cheney, *J. Amer. Chem. Soc.* **81**, 1198 (1959).
[227] M. A. Kaplan, W. T. Bradner, F. H. Buckwalter, M. H. Pindell, *Nature* **205**, 399 (1965); *C.A.* **62**, 11030 (1965).
[228] I. de Carneri, G. Coppi, F. Lauria, W. Logemann, *Il Farmaco, Ed. Prat.* **16**, 65 (1961).

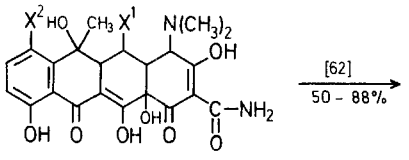
Table 21. Mannich Reactions of Acyclic Carboxamides with Secondary Amines

Carboxamides	Amines	Reaction Conditions	Yield (%)	References
 **203**				
R^1 = H; R^2 = CH_3, C_2H_5, $-CH_2-C_6H_5$, C_6H_5		[60]	~ 100	219, 220
				118
$ClCH_2-$, Cl_2CH-	 $R = CH_3, C_2H_5, t\text{-}C_4H_9$		25–56	221, 222
C_2H_5O-			80	223
 X = H, 2-OH, 4-NO_2, 2-OH-5-Cl	 		good	29, 118, 120, 224
	  	[61]	40–91	225

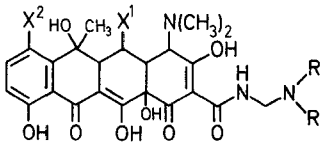
[60] Substrate, amine, and aqueous formaldehyde were allowed to stand at room temperature for 30 min[219,220].

[61] Pyridine-3-carboxamide (0.05 mol) and amine (0.05 mol) in methanol were treated at 0–5° with aqueous formaldehyde (0.05 mol) (or in ethanol with 0.075 mol of paraformaldehyde). The mixture was allowed to stand at 5° for 15 hr and was then refluxed for 2–3 hr[225].

The amide moiety of tetracycline and several of its derivatives may be aminomethylated in good yields to give new pharmaceutically interesting derivatives (**205**)[226,227].

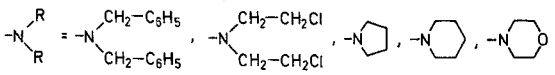


Tetracycline (or derivative)



205

$X^1 = OH$; $X^2 = H$ or $X^1 = H$; $X^2 = Cl$



[62] A solution of tetracycline, amine, and aqueous formaldehyde in *t*-butanol was allowed to stand at room temperature for 30 min and was then refluxed for 15 min[226,227].

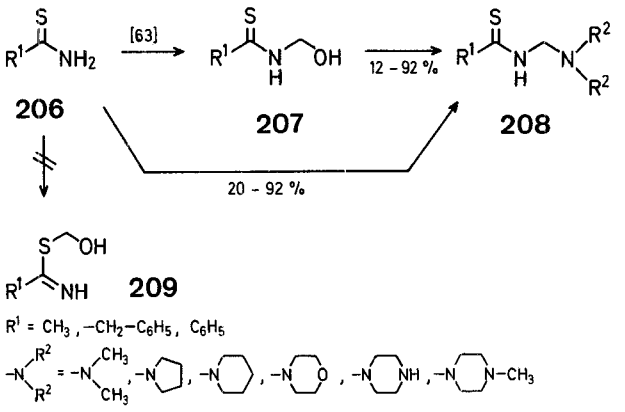
It has been shown[226] that aminomethylation occurs at the amide N-atom, not at the phenolic ring D, as previously supposed; this fact is in accordance with the greater reactivity of the amide N—H group compared to that of the position (9) *ortho* to the phenolic hydroxy group (cf. Section 1.4.3. and Ref.[120]). Other investigations in this field relate to the synthesis of *N*-lysinomethyltetracycline, which is extremely soluble in water[228], and to dissociation constants of several *N*-aminomethyltetracyclines[229].

The aminomethylation of *thiourea* (**206**, $R^1 = NH_2$)[230] and *thiocarboxamides*, (**206**, R^1 = C-residue) to give Mannich bases of the type **208** proceeds either directly or by condensation of the *N*-hydroxymethyl derivative **207** with alkylamine; neither *S*-aminomethylation nor *S*-hydroxymethylation (**209**) have ever been observed in these cases[231].

[229] R. Hüttenrauch, I. Keiner, *Arch. Pharm.* **301**, 97 (1968).

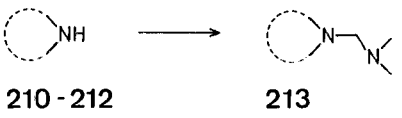
[230] V. Mozolis, S. Jokubaityte, *Liet. TSR Mokslu Akad. Darb. Ser. B* **1970**, 129; *C.A.* **73**, 77152 (1970).

[231] H. Böhme, H. H. Hotzel, *Arch. Pharm.* **300**, 241 (1967).

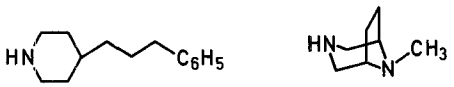


[63] Aqueous formaldehyde was added dropwise, with stirring, to a solution of **206** in hot water; the mixture was then heated on a steam bath for 15 min, so obtaining **207** in good yields. Amine was added to a solution of **207** in methanol, and the mixture was heated on a steam bath for 10 min. The reaction can also be carried out with **206**, paraformaldehyde, and amine in methanol[231].

Examples of *N*-aminomethylation of *heterocyclic* compounds are numerous; reactions of four- and five-membered NH-heterocyclic compounds and their condensed ring derivatives (**210**) are summarized in Table 22, those of five-membered NH,N-, NH,O- and NH, S-heterocyclic compounds as well as condensed-ring derivatives, (**211**) in Table 23, and those of six-membered NH- and NH,N-heterocyclic compounds and condensed-ring derivatives (**212**) in Table 24 (see also Ref. [448,449,450]).

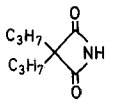
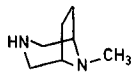
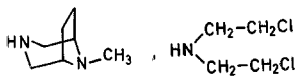
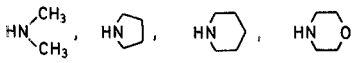
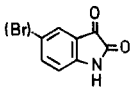
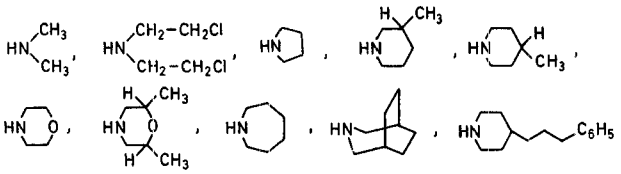
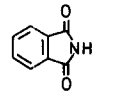
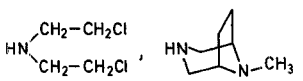
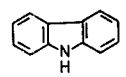
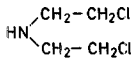


Various derivatives **213**, often of pharmacological interest, were thus synthesized; in some cases, more "unusual" amines were used, e.g. **214**, **215**, and others noted in previous Sections.



In addition to the five-membered NH-heterocyclic compounds mentioned in Table 22, several hydroxyindole derivatives (see Section 1.4.3.) have been aminomethylated; reaction at the N-atom has only been observed when the more reactive positions (position *β* to the N-atom, or *ortho* to a hydroxy group) were occupied[129,130]. It has proved possible to aminomethylate position 1 (N) of non-substituted indoles (see Table 22) ,but the products were easily rearranged to the more stable 3-aminomethylindoles[234].

Table 22. *N*-Aminomethylation Reactions of Four- and Five-Membered NH-Heterocyclic Compounds and Condensed-Ring Derivatives with Secondary Amines

Heterocyclic Compounds **210**	Amines	Reaction Conditions	Yield of **213** (%)	References
		[64]	90	232
		[64]	70–84	30, 232, 233
			12–79	234
		[64]	37–86	233, 235, 236
		[64]	good	232, 233, 236
		[64]	42	233

[64] Substrate, amine, and aqueous formaldehyde were refluxed in ethanol for 10–90 min[232,235], or in benzene for 25 min[233].

[232] G. Cignarella, E. Occelli, G. Maffii, E. Testa, *J. Med. Chem.* **6**, 29 (1963).

[233] R. C. Elderfield, J. R. Wood, *J. Org. Chem.* **27**, 2463 (1962)

Table 23. *N*-Aminomethylation Reactions of Five-Membered NH,Y-Heterocyclic Compounds and Condensed-Ring Derivatives with Secondary Amines

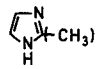
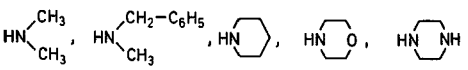
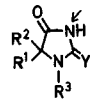
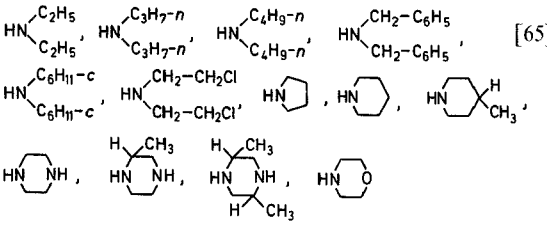
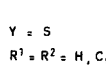
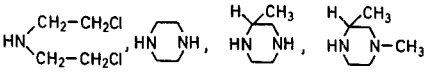
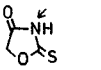
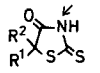
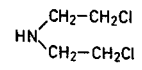
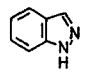
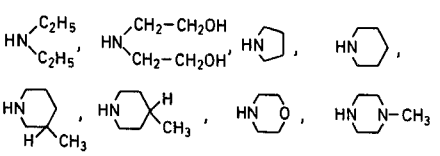
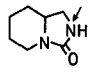
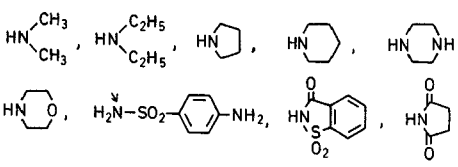
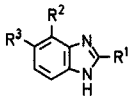
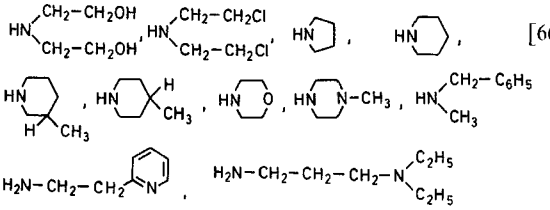
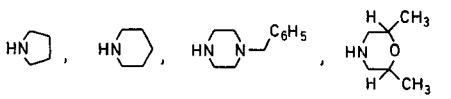
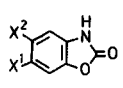
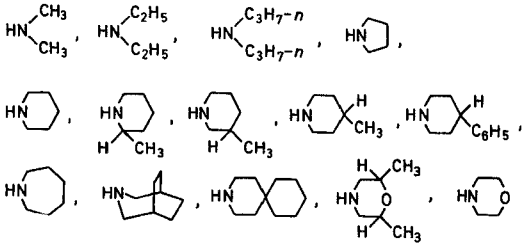
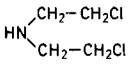
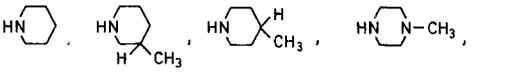
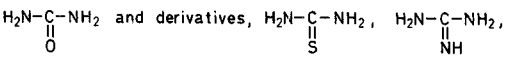
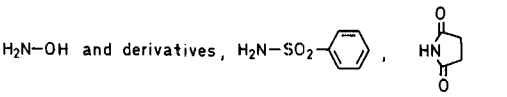
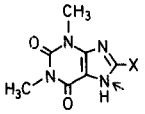
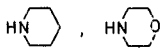
Heterocyclic Compounds **211**	Amines	Reaction Conditions	Yield of **213** (%)	References
			70–90	171
 Y = O; R^1 = H, CH_3, C_6H_5; R^2 = H, CH_3, C_2H_5, i-C_3H_7, $-CH{=}CH-C_6H_5$, C_6H_5; or R^1,R^2 = $-(CH_2)_{4,5}-$, $=CH-C_6H_4-N(C_2H_5)_2$; R^3 = H, CH_3, $-CO-CH_3$		[65]	60–90	237–240
 Y = S; R^1 = R^2 = H, C_6H_5; or R^1,R^2 = $=CH-C_6H_4-N(C_2H_5)_2$; R^3 = H			60–80	238, 240
  R^1,R^2 = H, H; $=CH-C_6H_4-N(C_2H_5)_2$			56–82	238
		[66]	50–80	163, 241
		[65]	good	242
 R^1 = H, CH_3, $-CH_2-C_6H_5$, C_6H_5; R^2 = H, CH_3, Cl, Br; R^3 = H, OCH_3 or R^2–R^3 =		[66]	60–70	116, 163, 243, 244
		[66]	good	116
 X^1 = H, Cl; X^2 = H Cl, Br			50–95	245, 246

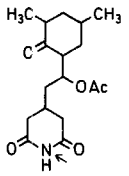
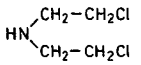
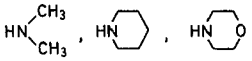
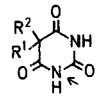
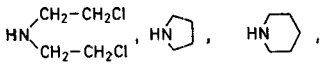
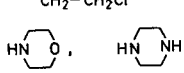
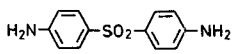
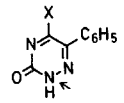
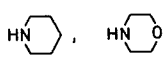
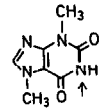
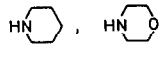
Table 23, continued

Heterocyclic Compounds **211**	Amines	Reaction Conditions	Yield of **213** (%)	References
			89	236
	  		80–95	163, 230
 X = H, Br			80–90	243, 247
 R = H, *n*-C_3H_7			73–87	248

[65] Substrate, amine, and aqueous formaldehyde were allowed to react in alcoholic solvents at room temperature[237,248,251], or with cooling for one to several hours[239,242].

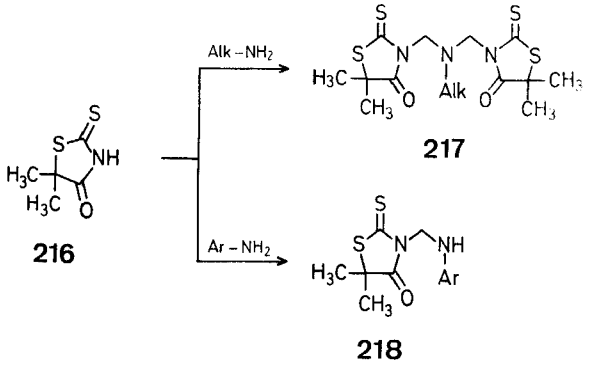
[66] *N*-Hydroxymethylindazole (prepared by reaction of indazole with aqueous formaldehyde in aqueous hydrochloric acid at room temperature for 1 hr) was heated with the amine for 1–3 hr[241].

Table 24. *N*-Aminomethylation Reactions of Six-Membered NH- and NH,Y-Heterocyclic Compounds and Condensed-Ring Derivatives with Secondary Amines

Heterocyclic Compounds **212**	Amines	Yield of **213** (%)	References
		84	30
 3-OH; 3-OH-4,5-benzo; 3-CH_3, 5-CN		good	249
 R^1 = C_2H_5, $-CH_2-CH=CH_2$; R^2 = C_2H_5, *n*-C_3H_7, C_5H_{11}, $-CH_2-CH=CH_2$,  , C_6H_5	 	45–90 (conditions [65])	29, 238, 250, 251
R^1,R^2 = O			161
 X = OH, C_6H_5		70–80	252
		90	247

In addition to the five-membered heterocyclic compounds mentioned in Table 22, several 1,2-oxazole derivatives (e.g. **146**, Section 1.4.5.) could be *N*-aminomethylated at the ring N-atom or at an amino group (when present in the molecule) when position 4 was occupied[160].

The Mannich reaction of 4-oxo-2-thiono-1,3-thiazolidines (type **216**, "thiohydantoins", "rhodanines") with primary aliphatic amines affords tertiary Mannich bases (**217**), whereas that with primary arylamines yields secondary bases[253] (**218**).



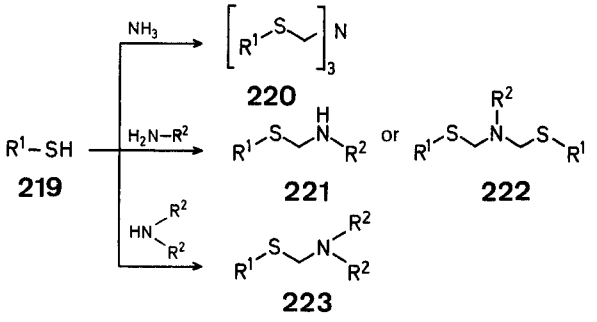
Hydantoins (2,4-dioxoimidazolidines, Table 23) react at the N-atom in position 1, which displays lower acidity[237] than the N-atom in position 3.

1.5.2. Aminomethylation of Thiols and Sulfinic Acids

S-Aminomethylation reactions have succeeded using thiols, sulfinic acids, and sodium-hydrogen sulfite as substrates.

The Mannich reaction of *thiols* (**219**) with ammonia affords tertiary bases (**220**)[254], whereas both secondary (**221**) and tertiary bases (**222**) are obtained with primary amines (see Table 25).

The reaction of thiophenols does not afford dihydrobenzo-1,3-thiazines, as could have been expected in analogy to the reaction of phenols affording dihydrobenzo-1,3-oxazines under similar conditions (Section 1.4.3.).



S-Aminomethyl derivatives **223** have been obtained by reaction with secondary amines; when an aromatic amine is used, the products are not stable and easily undergo rearrangement (see Section 2.3.2.).

Thiouracil may also be subjected to *S*-aminomethylation; for example with bis-[2-chloroethyl]-amine in an acetic acid medium, product **224**, derived from the thiol form, is obtained[158].

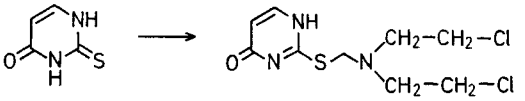
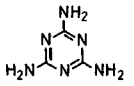
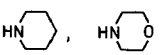
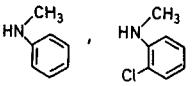
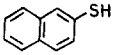
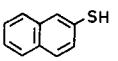
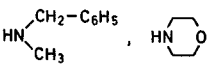


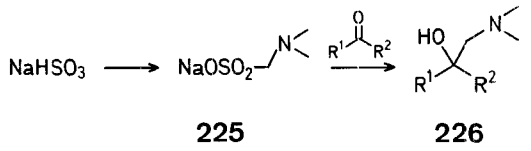
Table 25. Mannich Reactions of Thiols with Primary or Secondary Amines

Thiols	Amines	Products	Yield (%)	References
C_2H_5–SH	 , $H_2N-CH_2-CH_2-NH_2$	**221**		8
C_2H_5–SH		**223**		8
		**223**	good (conditions [67])	255, 256
		**223**	42–63	257
	H_2N-CH_3, $H_2N-C_3H_7-i$, $H_2N-C_4H_9-t$, $H_2N-C_8H_{17}-t$, $H_2N-CH_2-C_6H_5$	**222**	55–59 (conditions [67])	258
		**223**		

[67] Aqueous formaldehyde was added to a mixture of thiol (or selenophenol) and amine with stirring at 65°; the mixture was then refluxed for 30 min[256]. In other cases, the mixture of the components in ethyl acetate was allowed to stand at room temperature for 2 days[258].

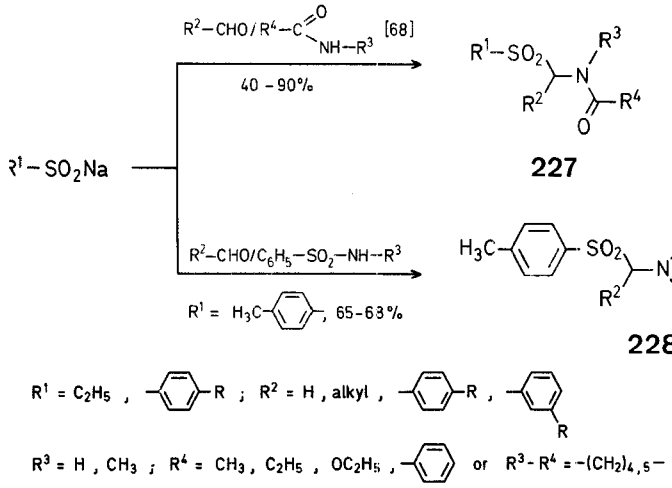
[234] S. Swaminathan, K. Narasimhan, *Chem. Ber.* **99**, 889 (1966).
[235] R. S. Warma, W. L. Nobles, *J. Med. Chem.* **10**, 510 (1967).

Sodium-hydrogen sulfite reacts with formaldehyde and melamine or 1,2-diaminoethane[8] to give aminomethanesulfonic acid derivatives (**225**); further reaction of compounds **225** with ketones yields β-amino-alcohols (**226**)[259].



225 **226**

The reaction of the sodium salts of *sulfinic acids* with formaldehyde or other aliphatic or aromatic aldehydes and ethyl carbamates, carboxamides, or sulfonamides as amine component affords β-ethoxycarbonylamino- (**227**, $R^4 = OC_2H_5$), β-amido- (**227**, R^4 = alkyl, aryl), or β-sulfonamido-sulfones (**228**) in good yields[260,261,262].

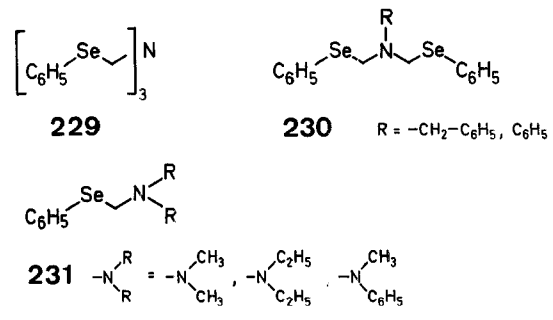


227 **228**

[68] The amine was added to a solution of sulfinate and aldehyde in water or methanol, and the pH was adjusted to 3–4 with acetic or formic acid. The mixture was allowed to stand at room temperature for various times (up to several days)[260,261].

1.5.3. Aminomethylation of Selenophenol

Selenophenol behaves similarly to thiophenols towards aminomethylating agents. Thus, *Se*-aminomethyl derivatives **229**, **230**, **231** are obtained in yields of 45–85% by the reaction with formaldehyde and ammonia or primary or secondary amines[263].

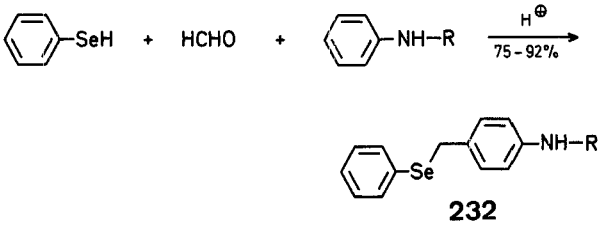


229 **230** R = $-CH_2-C_6H_5$, C_6H_5

231

Conditions [68]

The reaction takes a different course when aniline or *N*-methylaniline is used as the amine component in acidic medium; in this case, the corresponding 4-aminobenzyl phenyl selenides (**232**) are obtained[263]. With *N*,*N*-dimethylaniline, 4-dimethylaminobenzyl phenyl selenide is only obtained in very low yield.

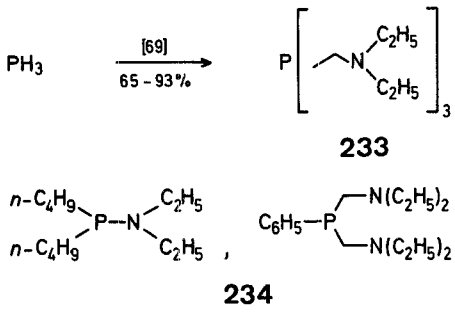


232

R = H, CH_3

1.5.4. Aminomethylation of Phosphines and Phosphorus Acids

Phosphine and some of its organic derivatives react with formaldehyde and secondary amines to give aminomethylphosphines[264] of the types **233** and **234**.



233

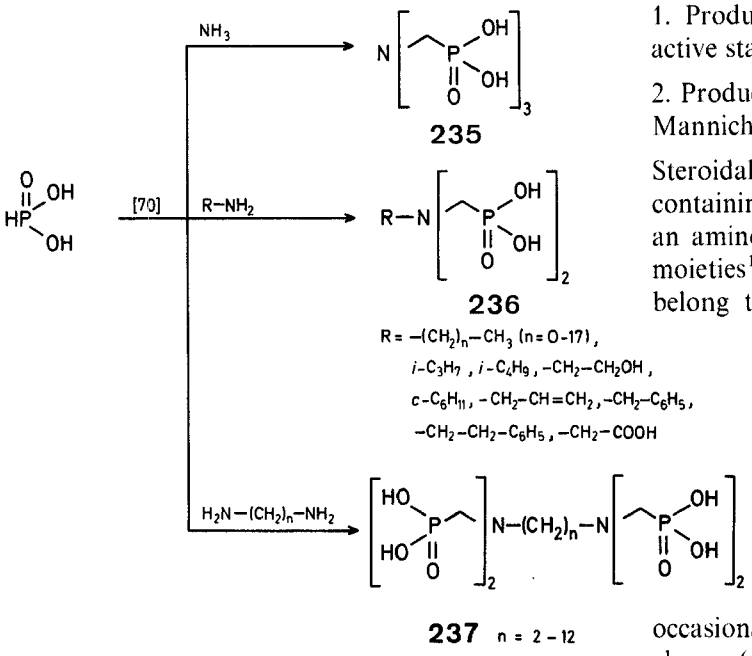
234

[69] The phosphine was bubbled into a stirred mixture of amine and aqueous formaldehyde at 20° under a nitrogen atmosphere for 10 hr[264].

Diethyl phosphite has also been *P*-aminoalkylated[451].

Aminomethanephosphonic acids of the types **235**, **236**, and **237** are obtained in good yields by aminomethylation of *orthophosphorous acid*[265]. The products display interesting metal-chelating properties.

[236] G. R. Pettit, J. A. Settepani, *J. Org. Chem.* **27**, 1714 (1962).
[237] O. O. Orazi, R. A. Corral, *Tetrahedron* **15**, 93 (1961).
[238] W. Werner, *Arch. Pharm.* **299**, 513 (1966).
[239] A. Zejc, *Diss. Pharm. Pharmacol.* **19**, 173 (1967); *C.A.* **67**, 43727 (1967).
[240] B. Lucka-Sobstel, A. Zejc, *Diss. Pharm. Pharmacol.* **22**, 13 (1970); *C.A.* **72**, 111418 (1970).
[241] F. T. Pozharskii, M. A. Kazanbieva, B. A. Tertov, *Zh. Obshch. Khim.* **34**, 3367 (1964); *C.A.* **62**, 4021 (1965).
[242] K. Winterfeld, G. B. Singh, *Arch. Pharm.* **294**, 404 (1961).
[243] T. Okuda, *Yakugaku Zasshi* **80**, 205 (1960); *C.A.* **54**, 13141 (1960).
[244] G. R. Revankar, S. Siddappa, *Monatsh. Chem.* **98**, 169 (1967).
[245] S. Toyoshima, N. Morishita, *Yakugaku Zasshi* **87**, 1546 (1967); *C.A.* **69**, 27303 (1968).
[246] R. S. Varma, W. L. Nobles, *J. Pharm. Sci.* **57**, 39 (1968).



[70] Orthophosphorous acid, amine, and aqueous formaldehyde were allowed to react at low pH (adjusted with hydrochloric acid)[265].

1.6. Optically Active Mannich Bases

Optically active Mannich bases may be divided into two main groups:

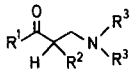
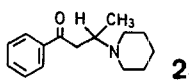
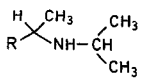
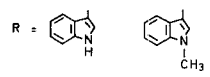
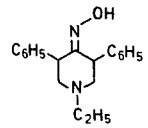
1. Products of Mannich syntheses using optically active starting materials (substrates or amines).

2. Products obtained from the resolution of racemic Mannich bases.

Steroidal derivatives and several β-amino-ketones containing optically active alcoholic groups (from an amino-alcohol component)[11,266] or amino-acid moieties[174,267] (from an amino acid component) belong to the first group; such derivatives were occasionally also obtained via amino-group exchange (see Section 2.3.3.).

The second group includes several β-amino-ketones bearing the asymmetric center in the α- or β-positions (**238** and **239**, respectively), aminoalkylindoles (**240**), and cyclic β-aminoketoximes (**241**); the absolute configuration of a few of these compounds is known (Table 26).

Table 26. Optically Active Mannich Bases obtained by Resolution of Racemic Mannich Bases

Mannich Base	References for the Optical Resolution	for the Absolute Configuration
 **238**		
R^1 = CH_3, R^2 = CH_3, $-N(CH_3)_2$	268	268
R^1 = C6H5, R^2 = CH_3, $-N(CH_3)_2$	82, 269, 270	270 (cf. 271)
R^1 = C6H5, R^2 = CH_3, –N(CH2)4	270	270
R^1 = C6H5, R^2 = CH_3, –N(CH2)2O(CH2)2	270	270
R^1 = C6H5, R^2 = $-CH_2-C_6H_5$, –N(CH2)4	82	
 **239**	82	272
 **240**	273	
R = 		
 **241**	274	

Optically active derivatives, e.g. the methiodide[275] and oxime[276] of **238** ($R^1=R^2=R^3=CH_3$), the oxime[276] of **239**, and amino-alcohols have been prepared. The latter are obtained by reduction of the carbonyl group (see Section 2.4.) in derivatives **238** ($R^1=R^1=R^3=CH_3$; and $R^1=C_6H_5$, $R^2=R^3=CH_3$)[268].

The best method of resolution for these bases involves reaction with *O,O*-dibenzoyltartaric acid (0.5 mol per 0.5 mol of amine in 4000 ml solvent) in acetone or occasionally in ethanol at room temperature[269]. After a few hours reaction time, amino-ketones yield ~50% of the corresponding salt; the additional salt which crystallizes after a longer period always contains the same optical isomer as first obtained. The reason for this is that the amine racemizes in solution and reacts to form the original, less soluble salt. It is thus possible to totally transform the amino-ketone into a single optical isomer[269]. However, the free bases are not optically pure (see Ref.[268]); thus, either the salt obtained is not homogeneous or the alkaline treatment necessary to obtain the free base catalyzes the racemization of the unstable product. Recrystallization of the salt often does not increase the optical purity of the base and sometimes leads to decomposition of the amino-ketone. It is probable that carboxylic acids in weakly dissociating media (see also Section 2.2.) favor the decomposition of the β-amino-ketones.

2. Reactions of Mannich Bases

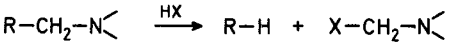
The main types of reactions of Mannich bases are as follows:

- Deaminomethylation (Section 2.1.), involving cleavage of the R—CH_2 bond.
- Deamination (Section 2.2.) involving cleavage of the CH_2—N bond.
- Substitution of the Amino Group (Sections 2.3.1. to 2.3.6.), involving cleavage of the CH_2—N bond and formation of a new bond, e.g. CH_2—C or CH_2—S.
- Reduction (Section 2.4.), affecting only the group derived from the original substrate, the amino group being probably involved in the reaction.
- Reactions with organometallic compounds (Section 2.5.).
- Cyclization (Section 2.6.), which deals with ring closure to the aminomethyl group, either at the C-atom (with elimination of the amine residue), at the N-atom, or at a substituent of the amino group.
- Miscellaneous Reactions (Section 2.7.).

[247] H. J. Roth, R. Brandes, *Arch. Pharm.* **298**, 765 (1965).
[248] C. P. Bryant, R. E. Harmon, *J. Med. Chem.* **10**, 104 (1967).

2.1. Deaminomethylation of Mannich Bases

Deaminomethylation may be considered a reverse Mannich reaction, which therefore represents an equilibrium.



This cleavage reaction has to be regarded as a possible side reaction in all Mannich syntheses.

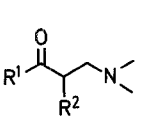
The formation of methylene-bis-derivatives R—CH_2—R from Mannich bases (cf. Ref. [277,278]), and the transaminomethylation reaction (cf. Ref.[41]) involve with certainty the deaminomethylation reaction. The interesting cytostatic activity of some Mannich bases derived from succinimide, benzamide, and benzenesulfonamide[279] and of some other Mannich bases[8], has been studied with respect to their ability to undergo transaminomethylation.

The deaminomethylation reaction has been studied using bases derived from, e.g., ketones, phenols, nitroalkanes, and heterocyclic compounds.

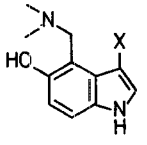
An extensive study[280] on the deaminomethylation of β-amino-ketones (**242**) further confirmed the reversibility of the Mannich reaction; substituent and reaction medium effects were considered, and mono- and bimolecular mechanisms discussed. It was particularly observed that the deaminoalkylation reaction, which is often accompanied by deamination (see Section 2.2., cf. Ref.[281]), is easily undergone by α-substituted β-aminoalkyl phenyl ketones (**242**, $R^1=C_6H_5$, especially when $R^2=C_6H_5$), and does not occur in the case of alkyl β-aminoalkyl ketones (**242**, R^1 = alkyl). The nature of the amino group affects the reaction rate, the highest rate being observed for aniline derivatives in acidic medium and for piperidine derivatives in basic medium.

Cyclic β-amino-ketones such as 3,7-diethyl-1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonane (**23**, $R=C_2H_5$ $Ar^1=Ar^2=C_6H_5$; a "bispidone") undergo the deaminomethylation reaction during oximation[274] or attempted exchange reactions in strongly alkaline medium[282].

Deaminomethylation, sometimes accompanied by transaminomethylation, has also been observed during investigations of the reactivity of Mannich bases derived from naphthols[278] or benzimidazoles[283].



242

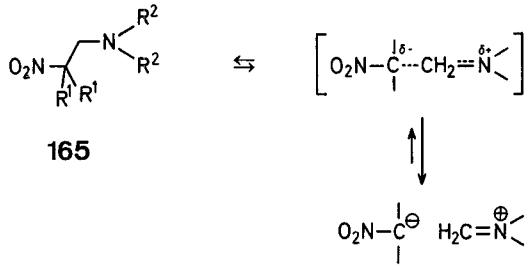


243

A systematic study of the chemistry of 4-aminomethyl-5-hydroxyindoles (**243**) showed that reaction

with alkylamines affords either the products of amine exchange or of deaminomethylation[131]. The latter reaction is favored by the presence of primary amines in the reaction mixture, and probably proceeds via substitution of the original amino group; steric and electronic characteristics of the substituent in position 3 (when $X = -COOC_2H_5$, the reaction is more facile than when $X = C_2H_5$) affect the ease of reaction, whereas substitution at positions 1 or 2 does not exert an influence.

Mechanistic studies of the deaminomethylation reaction have been carried out with α,α-disubstituted nitro-Mannich bases of the type **165**; in these cases, deamination, which often occurs as an undesired side reaction, is avoided[192,284,285].



165

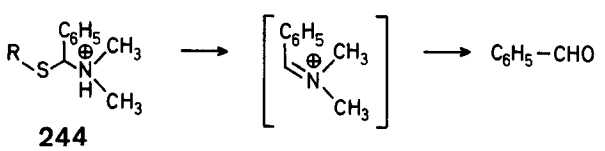
$R^1 = CH_3, C_2H_5$

$-NR^2R^2 = -NH-CH_3, -N(CH_3)_2, -N(C_2H_5)_2, -N(C_3H_{7(n,i)})_2$

The proposed mechanism is presumed to be valid either in acidic or in alkaline medium, and involves dissociation of the substrate with subsequent formation of carbanion and imonium ions.

Steric factors play a significant role in the deaminomethylation reaction; the presence of bulky substituents in the substrate strongly favors the cleavage reaction[192,285]. This fact is not surprising, since the influence of steric factors in substrate and amine on the Mannich synthesis is well known (see Section 1.3.).

The deaminomethylation reaction of β-amino-sulfides (**244**) in aqueous medium, initially considered a solvolysis, is now regarded as the first example of an S_N1 reaction on the *S*-alkyl bond of a sulfide[286].

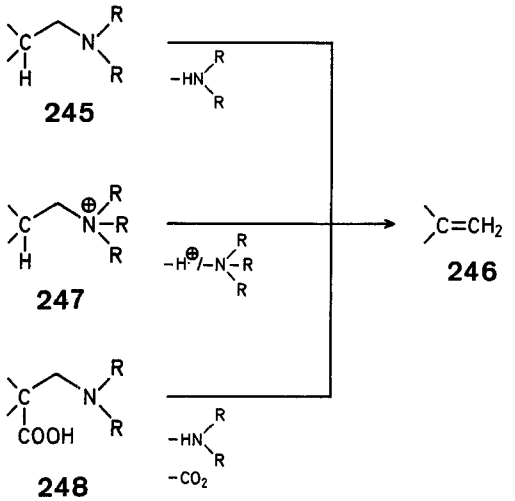


244

$R = C_2H_5, t\text{-}C_4H_9$

2.2. Deamination of Mannich Bases

The deamination reaction involves elimination of a primary or secondary amine from a Mannich base (**245**), or of a tertiary amine from the methiodide (**247**) of a Mannich base; in both cases, the products are vinyl derivatives (**246**) of the orginial substrate.

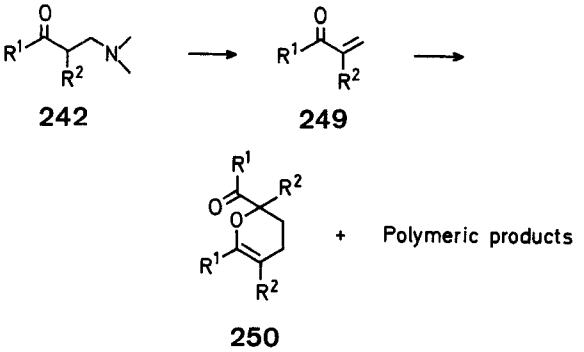


245 **247** **248** **246**

In this Section, the deamination-decarboxylation of Mannich bases having the structure of amino-acids (**248**) will also be discussed.

The deamination reaction has been observed and studied in the case of practically all *C*-Mannich bases; it possesses both theoretical and practical interest. For example, during many exchange reactions of the alkylamino group, the deamination is almost certainly the first step, followed by nucleophilic addition of the reactant to the C=C double bond of **246** (see, e.g., Ref.[82,127,287,288] and other References in Section 2.3.). Deamination is also postulated to occur during several other exchange- and cyclization reactions.

From the practical point of view, the reaction allows facile synthesis of several vinyl compounds, e.g., α,β-unsaturated aldehydes and ketones, vinylacetylenes, etc. When, however, the reaction is carried out with some α-substituted ketonic (and phenolic) Mannich bases (**242**; whereby the phenolic bases can be considered the ketonic forms of *o*-aminomethylphenols), the corresponding vinyl ketones cannot be isolated, since they undergo dimerization to yield dihydro-4*H*-pyrans (**250**) or oligomerize or polymerize to afford still more complex derivatives[61,157,278,289]. The data reported below clearly show that the structural features of the individual α-aminomethyl-cycloketone strongly affect the dimerization reaction[289].

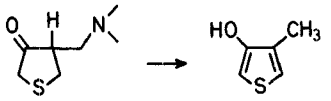


242 **249** **250** + Polymeric products

Mannich base **242**, $R^1-R^2=-(CH_2)_n-$ heated with sodium acetate in acetic anhydride for 40 min

n	Yield (%)		
	249	**250**	higher-molecular products
3	50	–	~ 50
4	–	98	–
5	35	41	24

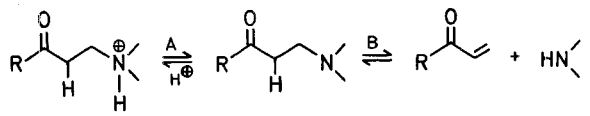
Mannich bases derived from 3-oxotetrahydrofurans and 3-oxotetrahydrothiophenes (**251**) undergo the deamination reaction with isomerization of the primary cleavage product to the stable heteroarene[157].



251

Several studies on the mechanism of the deamination reaction, mainly concerning β-amino-ketones, have been published. This reaction has been investigated using either the free bases[82,287,290–294] or the corresponding tetraalkylaminium derivatives[287,290]. In some cases, the reaction has been studied as a step in the substitution of the amino group[82,287].

The deamination of β-amino-ketones involves a pre-equilibrium A, which is dependent on the pH of the reaction medium; elimination of the amino group together with the H-atom α to the carbonyl group then occurs (equilibrium B). In this connection, it is worth noting that α,α-disubstituted β-amino-ketones only undergo deaminomethylation.



Stage B has not been completely interpreted; several cyclic transition states with and without participation of a hydroxy group or of the enolic form of the β-amino-ketone have been postulated. Several studies involving enolization of the β-amino-ketone[295] and the addition of arylamines to vinyl ketones[296], whereby the latter represents the reverse of the deamination reaction, are noteworthy in this context. The postulated mechanism[296] of the addition involves participation of a molecule of catalyst (acetic acid, phosphoric acid) in the transition state; this appears to agree with available data concerning the deamination reaction in non-aqueous solvents in the presence of carboxylic acids (Table 27). In these results, in fact, only the carboxylic acid could act as a suitable catalyst for an intramolecular proton transfer in the transition state.

[249] H. Hellmann, *German Patent (DBP.)* 1028127 (1960), Farbenfabriken Bayer; *C.A.* **54**, 18564 (1960).

Table 27. Deamination Reactions of 1-Oxo-2-piperidinomethyl-1-phenylpropane (**242**, $R^1=C_6H_5$, $R^2=CH_3$) in Ethanol[a] (concentration: 0.08 *M*) in the Presence of Hydrochloric Acid or *O,O*-Dibenzoyltartaric Acid (DBT) at 60°[151]

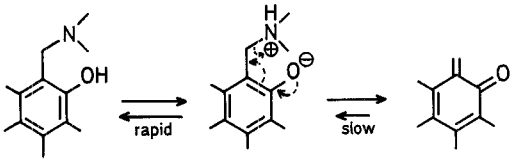
Acid	Molar Ratio Base:Acid	Reaction Time (hr)	Yield (%) of Deamination Product
none	–	23	10
DBT	1:0.25	5	50
DBT	1:1	10	50
DBT	1:2	24	50
HCl	1:1	>20	10

[a] The reactions in dioxan (concentration: 0.04 *M*) were slower, but gave analogous results.

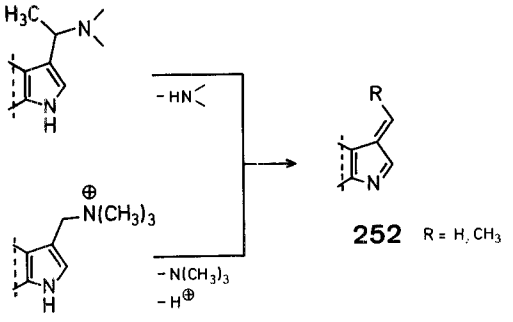
Nucleophilic attack of the anion derived from the acid on the carbonyl C-atom has been postulated to be the rate-determining step[297,298] in the reaction between β-amino-ketones and triethyl phosphite in dimethylformamide (see Section 2.3.6.).

For the base-catalyzed deamination of methiodides of Mannich bases[287,290], an E2 mechanism involving partial carbanionic character of the intermediate has been proposed.

The deamination of phenolic Mannich bases has been studied as the rate-determining step in some substitution reactions[127,299]. A pre-equilibrium similar to the case with β-amino-ketones is followed by elimination of the amino group via an E1cB-type mechanism[127].



Deamination of indolic Mannich bases[273] and the corresponding tetraalklylaminium salts[288] affords azomethine derivatives (**252**), which in turn are readily attacked by the nucleophilic reagent. In the case of the free bases, slow elimination of the amino group simultaneously or subsequently to that of the NH proton has been proposed[273].



252 R = H, CH_3

[250] M. Eckstein, A. Zejc, J. Sulko, *Diss. Pharm. Pharmacol.* **18** 131 (1966); *C.A.* **65**, 7175 (1966).

[251] L. Rylski, L. Senczuk, K. Falandysz, L. Konopka, D. Zimna *Acta Pol. Pharm.* **24**, 369 (1967); *C.A.* **68**, 105144 (1968).

Deamination of the methiodides has been postulated to involve rapid elimination of a proton from N—H, followed by rate-determining elimination of trialkylamine[288].

A number of synthetically interesting vinyl derivatives corresponding to the Mannich bases derived from aldehydes, α,β-unsaturated aldehydes, ketones, acetylenes, oximes, and 2-methylquinolines have been produced via the deamination reaction.

The synthesis of butenone (**249**, $R^1=CH_3$, $R^2=H$) via Mannich reaction and deamination, together with a synopsis of the synthetic applications (including some steroidal syntheses) of this reactant, which is often generated *in situ*, has been reported[300].

Acrolein derivatives (**249**, $R^1=H$) have been obtained from aminomethylation of aliphatic aldehydes (**253**, $R^1=H$) followed by deamination, often without isolation of the intermediate bases **242** ($R^1=H$)[200,201] (see Table 28).

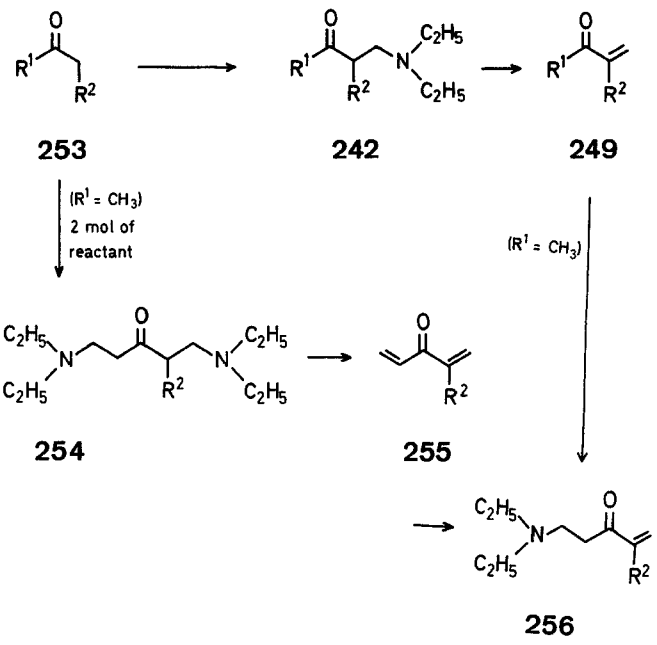


Table 28. Synthesis of α,β-Unsaturated Aldehydes and Vinyl Ketones by Deamination of Mannich Bases

Reaction Products Structure	R^1	R^2	Reaction Conditions	Yield (%)	References
 **249**	H	CH_3, C_2H_5, i-C_3H_7	[71]	90–99	200, 201
	CH_3	H	[72]	92	200, 300, 301
	CH_3	H, CH_3, i-C_3H_7			200
	CH_3	C_2H_5, i-C_3H_7, $-CH_2-C_6H_5$	[73]	50–71	302
		H, CH_3		31–62	200, 301, 303
	 X = H, CH_3, C_6H_5, NO_2, OCH_3, Cl	H	[74]	70–86	281
		H		30	76
 **255**	–	H, CH_3, i-C_3H_7		55–83	52, 200, 303

[71] Aldehyde **253** ($R^1=H$; 1.1 mol), aqueous formaldehyde (1 mol), and diethylamine hydrochloride (1 mol) were dissolved in water (380 ml), and the pH of the solution was adjusted to 7 with sodium carbonate. The mixture was heated at 45° for 20 min and then distilled azeotropically[200,201].

[72] The β-amino-ketone in diethyleneglycol was treated with gaseous hydrogen chloride at 220°[301].

[73] The *N*-methyl methyl-sulfate of **242** was shaken with aqueous sodium hydroxide at room temperature for 1 hr[302].

[74] The Mannich base hydrochloride was heated in benzene with potassium hydroxide[281].

Analogously, the mono- (**242**, **256**) and bis-bases (**254**) derived from dialkyl ketones (**253**, $R^1=$alkyl) are deaminated to afford, often in high yield, monovinyl- (**249**) or divinyl ketones (**255**); 2-aminoalkyl aryl ketones (**242**, $R^1=$aryl) react under various conditions to give aryl vinyl ketones (**249**, $R^1=$aryl) (see Table 28).

[252] A. Mustafa, A. K. Mansour, H. A. Zaher, *Liebigs Ann. Chem.* **733**, 177 (1970); *C.A.* **72**, 132681 (1970).

[253] M. A. Borisova, A. I. Ginak, E. G. Sochilin, *Zh. Org. Khim.* **6**, 1738 (1970); *C.A.* **73**, 109732 (1970).

[254] I. E. Pollak, G. F. Grillot, *J. Org. Chem.* **32**, 2891 (1967).

[255] B. D. Vineyard, *J. Chem. Eng. Data* **11**, 620 (1966); *C.A.* **66**, 10294 (1967).

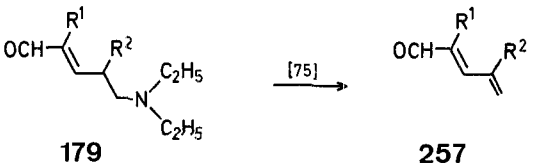
[256] I. E. Pollak, A. D. Trifunac, G. F. Grillot, *J. Org. Chem.* **32**, 272 (1967).

[257] G. F. Grillot, P. T. S. Lau, *J. Org. Chem.* **30**, 28 (1965).

[258] C. Weatherbee, R. T. Sleeter, P. Zung-Jih Han, *Tetrahedron Lett.* **1965**, 4069.
C. Weatherbee, *Carib. J. Sci. Math.* **1**, 43 (1968); *C.A.* **73**, 14533 (1970).

Deamination of steroidal Mannich bases may also be carried out with Florisil®[60,63] or alumina[61]; in the latter case, the reaction yields a dimeric product of the type **250** derived from the cycloaddition of two molecules of vinyl ketone.

Mannich bases of the type **179**, obtained from the aminomethylation of α,β-unsaturated aldehydes at the allylic C-atom (see Section 1.4.8.) are deaminated to give conjugated pentadienals (**257**)[202].



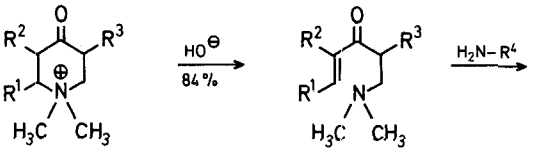
179 **257**

$R^1, R^2 = CH_3, C_2H_5$

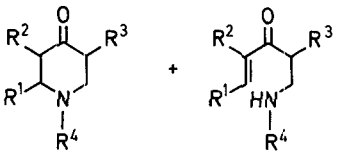
[75] Compounds **179** were heated under reduced pressure at 150–210° in the presence of hydroquinone[202].

Analogously, base **183** (Section 1.4.8.) is deaminated to give a synthetically useful conjugated dienone[204] (see Section 2.6.).

2-Aminoalkyl vinyl ketones (**259**) are obtained by intramolecular deamination of *N*-methyl-γ-piperidone methiodides (**258**)[184] (see also Ref.[304]).



258 **259**



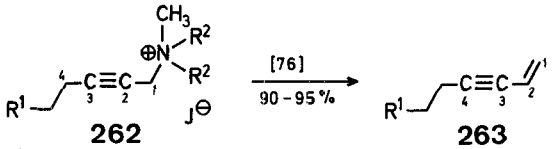
260 **261**

$R^1 = R^3 = CH_3, R^2 = H$; or $R^1 = R^2 = CH_3, R^3 = H$; or $R^1–R^2 = -(CH_2)_4-, R^3 = H$

$R^4 = CH_3, t\text{-}C_4H_9$

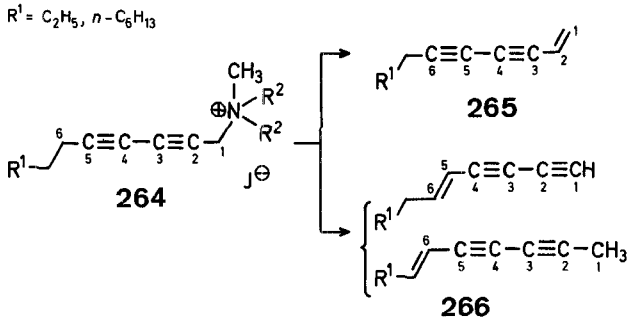
Treatment of compounds **259** with methyl iodide and subsequently with a primary amine affords *N*-substituted γ-piperidones (**260**), *N*-monosubstituted 2-aminoalkyl vinyl ketones (**261**), or a mixture of the two products. Steric factors play an important role in the reaction (see also Section 2.3.3.).

The deamination of Mannich bases (**262**, **264**) derived from 1-alkynes and 1,3-alkadiynes represents a method for the synthesis of conjugated alkenynes (**263**) and alkenediynes (**265**, **266**), respectively.



262

$R^1 = C_2H_5, n\text{-}C_6H_{13}$



264 **265** **266**

[76] The methiodide **262** was heated in 20% aqueous potassium hydroxide for several hours, or was steam-distilled at 70–80° under reduced pressure in the presence of 30% potassium hydroxide[180].

Deamination of ***264****:*

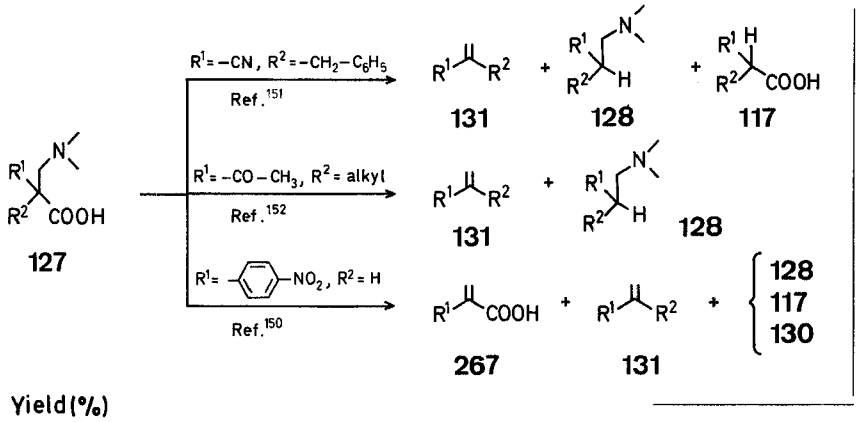
R^1	Yield (%)	
	265	**266**
CH_3	100	–
C_2H_5	83	16
$n\text{-}C_3H_7$	~50	~50

In the case of **262**, the reaction proceeds with migration of the triple bond to give alk-1-en-3-ynes (**263**). Deamination of compounds **264** proceeds mainly with migration of both triple bonds to give alk-1-ene-3,5-diynes (**265**)[180]; the reaction is complicated by the formation of isomers (**266**), the yield of which increases with the number of C-atoms in the group R^1.

The Mannich bases **186**, derived from 2- and 4-methylquinolines[208], and Mannich bases derived from ketoximes[305,306] may be deaminated to give the corresponding vinyl derivatives, which possess considerable synthetic interest, in 60–90% yields.

β-Aminocarboxylic acids **127** (see Section 1.4.4.) undergo deamination and decarboxylation under suitable conditions to give vinyl derivatives (**131**) as main reaction products[150,151,152]. (In an investigation of this reaction, amino acids **127** were not isolated, but used directly as obtained by Mannich synthesis[152]).

[250] H. E. Zaugg, R. J. Michaels, *J. Org. Chem.* **33**, 2167 (1968).
[260] J. B. F. N. Engberts, J. Strating, *Rec. Trav. Chim.* **83**, 733 (1964).
[261] J. B. F. N. Engberts, J. Strating, *Rec. Trav. Chim.* **84**, 942 (1965).
[262] T. Olijnama, J. B. F. N. Engberts, J. Strating, *Rec. Trav. Chim.* **86**, 463 (1967).
[263] I. E. Pollak, G. F. Grillot, *J. Org. Chem.* **31**, 3514 (1966).
[264] H. Coates, P. A. T. Hoye, *Brit. Patent* 854182 (1960), Albright & Wilson Ltd.; *C.A.* **56**, 1482 (1962).
[265] K. Moedritzer, R. R. Irani, *J. Org. Chem.* **31**, 1603 (1966).
[266] K. Thiele, V. W. Bebenburg, *French Patent* 1477040 (1967), Degussa; *C.A.* **68**, 12708 (1968).



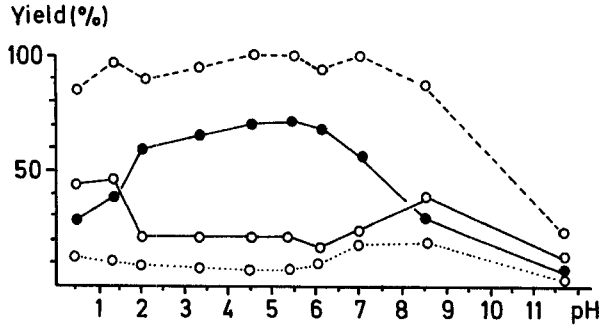
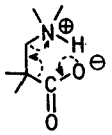


Figure. Decomposition of piperidine Mannich base **127** (R^1=—CN, R^2=—CH_2—C_6H_5) as a function of the pH. Reaction conditions: Mannich base (0.01 mol), water (80 ml), and a suitable buffer (50 ml) were refluxed for 1 hr. Yields (%) of **131** (●—), **117** (○—), **128** (○·····), **131**+**117**+**128** (○---)[151].

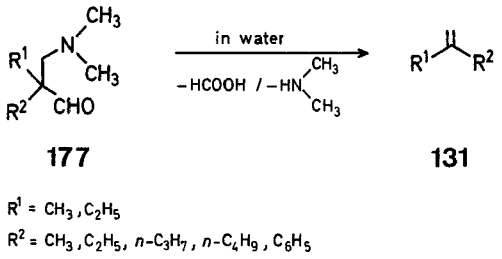
The reaction also affords by-products **128** and **117** via decarboxylation and deaminomethylation reactions, respectively. In the case of **127**, R^1=H, the deamination product **267** was also obtained[150].

Investigation of the influence of the pH on the reaction[151] showed that in the case of **127** (R^1=—CN, R^2=—CH_2—C_6H_5) (Figure) the maximum yield of vinyl derivative **131** was obtained at pH 5. The data obtained are in good agreement with those reported for the reactions of other amino-acids[150,152] and correspond well with the proposed mechanism[152], which involves fragmentation of zwitterion **268**, which is favored by pH values near the isoelectric point of the amino-acid.

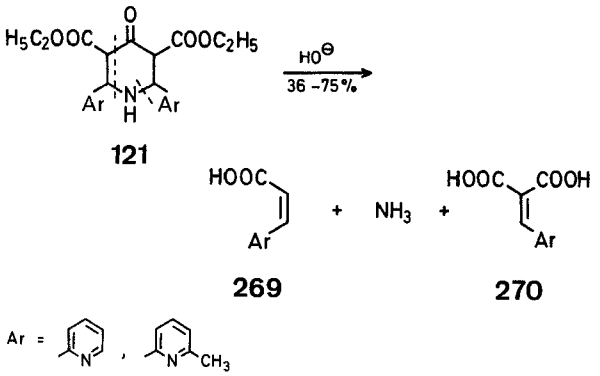


268

α,α-Disubstituted β-amino-aldehydes (**177**, R^1 and R^2 ≠H) can be induced to eliminate amine and formic acid to afford[199] the corresponding vinyl derivatives **131**.

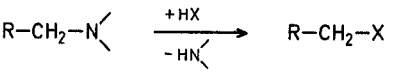


γ-Piperidones of the type **121** undergo deamination with fragmentation to give α,β-unsaturated carboxylic acids (**269** and **270**)[145].



2.3 Substitution of other Groups for the Amino Function

One of the most interesting properties of Mannich bases is their ability to undergo substitution of the amino group by a group X.



This substitution reaction (with elimination of the amino group) can be (when designated as an *X*-alkylation) an

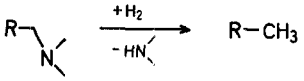
- *H*-Alkylation (Section 2.3.1.);
- *C*-Alkylation (Section 2.3.2.) on a CH-acidic group, on activated aromatic rings, or on heterocyclic compounds;
- *N*-Alkylation (Section 2.3.3.) on alkyl- or arylamines, amides, or NH-heterocyclic compounds;
- *O*-Alkylation (Section 2.3.4.);
- *S*-Alkylation (Section 2.3.5.);
- *P*-Alkylation (Section 2.3.6.).

[267] J. C. Graig, S. R. Johns, M. Moyle, *J. Org. Chem.* **28**, 2779 (1963).
[268] L. Angiolini, P. Costa Bizzarri, M. Tramontini, *Tetrahedron* **25**, 4211 (1969).
[269] A. Pohland, L. R. Peters, H. R. Sullivan, *J. Org. Chem.* **28**, 2483 (1963).

In the majority of cases, the *X*-alkylation by Mannich bases is experimentally simple and therefore has significant synthetic interest.

2.3.1. *H*-Alkylation

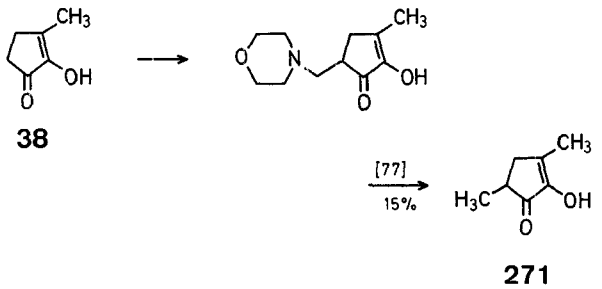
The substitution of an H-atom for an amino group has been obtained either by hydrogenolysis of the free Mannich bases (dimethylamino, piperidino, and morpholino derivatives) or of the corresponding methiodides.



The best yields are obtained by catalytic hydrogenation in ethanol at a pressure of 2–3 atm, and using palladium on charcoal as a catalyst. An example is the hydrogenolytic cleavage of Mannich bases **33** and **34** (Section 1.4.1.) to give 2-methylcyclohexanones[50]. Further preparative useful examples are the catalytic hydrogenolysis of phenolic (as methiodides)[307], hydroxyindole-[128], hydroxycoumarin-[136,139], *N*-heterocyclic (3-aminomethyl-4-hydroxyquinolines[177], 5-aminomethyluracils[178]), and steroidal[60] Mannich bases to give the corresponding methyl derivatives.

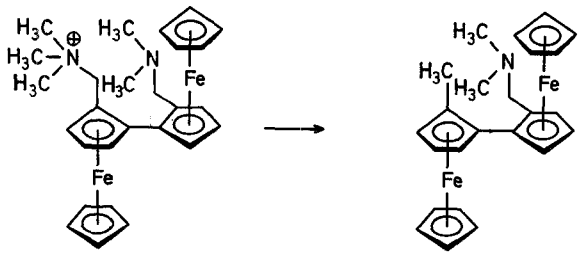
It is noteworthy that 6-dimethylamino-7-hydroxyindole, in contrast to other isomers, does not undergo reductive deamination[128]. Several *o*-phenolic Mannich bases may by hydrogenated in the form of their hydrochlorides; the intramolecular hydrogen bond between O and N, responsible for the usual lack of reactivity of *o*-phenolic Mannich bases[308], is not present in the case of the hydrochlorides.

The flavoring agent 1,4-dimethyl-2-hydroxy-3-oxocyclopentene (**271**) may be obtained from the morpholine Mannich base of 2-hydroxy-1-methyl-3-oxocyclopentene (**38**: Table 4) by reduction with zinc and acid[56].



[77] The Mannich base hydrochloride was heated with zinc and acetic acid (plus a trace of hydrochloric acid) for 6 hr at 75°[56].

Hydrogenation of the ferrocene Mannich base **272**, containing both a dimethylamino- and a trimethylaminio group, yields 2-dimethylaminomethyl-1-(2-methylferrocen-1-yl)-ferrocene (**273**), thus displaying the higher reactivity of the trimethylaminio group[309].

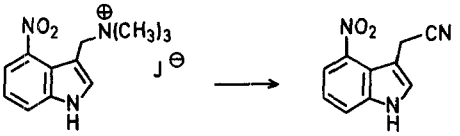


272 **273**

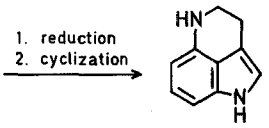
2.3.2. *C*-Alkylation

The following compounds have been found to undergo *C*-alkylation with Mannich bases: hydrogen cyanide, alkylboranes, alkyl ketones, aliphatic carboxylic acid derivatives, enamines, aromatic and heterocyclic substrates, and nitroalkanes. This Section will not deal with *C*-alkylations affording cyclic products; these reactions are discussed in Section 2.6.

The alkylation of *hydrogen cyanide* may be achieved by heating a mixture of the methiodide of a Mannich base with alkaline cyanide in water at 80–100° for a few hours. Using this method, various types of Mannich bases can be converted into the corresponding cyanomethyl derivatives (e.g. **274**) in good yield.



274



275

The following compounds have been thus prepared: 2-cyanoethyl ketones[49,76], 2- and 4-cyanomethylphenols[307,310], 3-cyanomethyl-4-nitroindole (**274**) (which could be cyclized to afford the biologically interesting 1,3,4,5-tetrahydropyrrolo[4,3,2-*dc*]-quinoline, **275**, after reduction of the cyano- and nitro groups[311]), and cyanomethylferrocenes[309,312,313].

The reaction between Mannich bases and suitable *dialkylboranes* allows C-chain elongation. Using this procedure[314], 2-propylcyclopentanone (**276**), 2-oxo-3-propylbicyclo[2.2.1]heptane (**277**), and several other alkyl ketones have been prepared.

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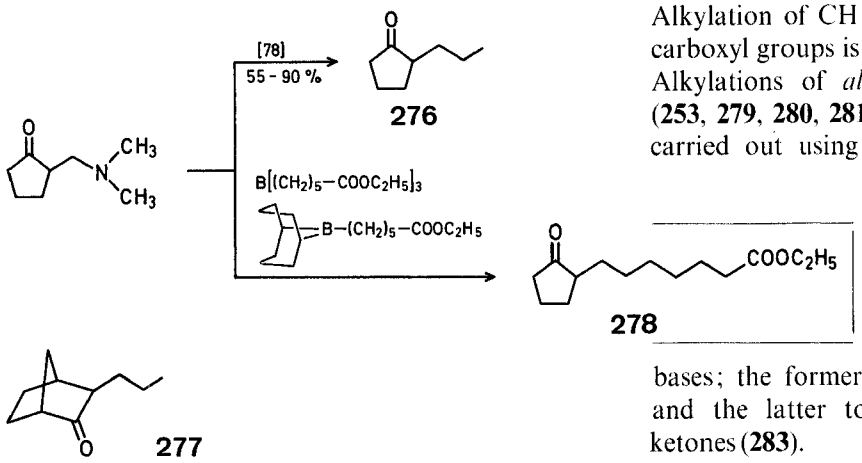
[270] A. S. Angeloni, G. Gottarelli, M. Tramontini, *Tetrahedron* **25**, 4147 (1969).

[271] H. R. Sullivan, J. H. Beck, A. Pohland, *J. Org. Chem.* **28**, 2381 (1963).

[272] V. Cannata, B. Samori, M. Tramontini, *Tetrahedron* **27**, 5247 (1971).

[273] J. D. Albright, H. R. Snyder, *J. Amer. Chem. Soc.* **81**, 2239 (1959).



[78] An aqueous solution of the Mannich base hydrochloride (0.1 mol) was added to the alkylborane (0.2 mol) in tetrahydrofuran. Methyl iodide and then potassium carbonate were added, and the mixture was stirred at room temperature for 24 hr[314].

This reaction has also been applied to more complex alkylboranes to synthesize keto-esters of the type **278** and thus represents a synthetic approach to prostaglandine analogs[315].

Alkylation of CH groups activated by carbonyl or carboxyl groups is of considerable practical interest. Alkylations of *alkyl ketones* and *cycloalkanones* (**253**, **279**, **280**, **281**; cf. Table 29) have mainly been carried out using ketonic and phenolic Mannich bases; the former react to give δ-diketones (**282**), and the latter to give 2-(2-hydroxyphenyl)-alkyl ketones (**283**).

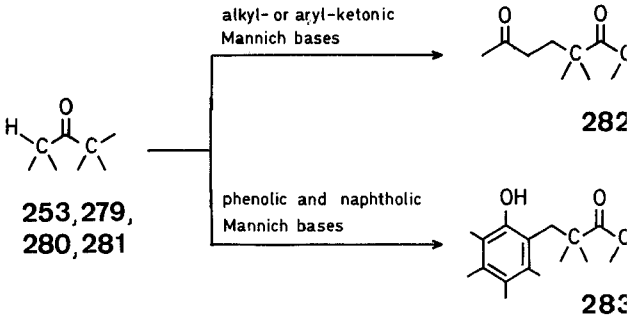
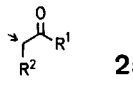
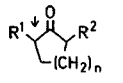
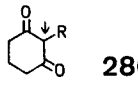
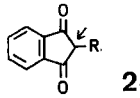


Table 29. *C*-Alkylation of Alkyl Ketones and Cycloalkanones with Mannich Bases

Ketones	Mannich Bases derived from	Products	Conditions	Yield (%)	References
 **253**					
$R^1 = H$; $R^2 = n\text{-}C_4H_9$ or $R^1 = n\text{-}C_5H_{11}$; $R^2 = H$	Aryl ketones	**282**	[79]	48–77	316
$R^1 = C_6H_5$; $R^2 = H$	Phenols	**283**			317
$R^1 = R^2 = C_6H_5$	Naphthols	**283**		97	318
 **279**					
$n = 1$; $R^1 = H, CH_3, C_2H_5$; $R^2 = H$	Alkyl and aryl ketones	**282**		40–47	316, 319, 320
$n = 2$; $R^1 = CH_3$; $R^2 = H$	Alkyl ketones	**282**		15	46
$n = 2$; $R^1 = H, CH_3$; $R^2 = CH_3$ $n = 4$; $R^1 = R^2 = H$	Aryl ketones	**282**		13–70	316
 **280** $R = CH_3, -NH-CO-CH_3$	Naphthols	**283**	[80]	66–86	321
 **281** $R = -CO-C_6H_5, -CO-CH_2-C_6H_5$	Naphthols	**283**	[80]	66–86	321

[79] Mannich base (1 mol) and ketone (3 mol) were heated at 160–180° for 30–60 min[316].

[80] Mannich base, ketone, and magnesium ethoxide were refluxed in chlorobenzene for 1 hr[321,324,325].

[274] R. Andrisano, A. S. Angeloni, G. Gottarelli, *Gazz. Chim. Ital.* **97**, 1726 (1967).

[275] A. F. Casy, J. L. Myers, *J. Chem. Soc.* **1964**, 4639.

[276] R. J. McConaill, F. L. Scott, *Tetrahedron Lett.* **1970**, 2993.

[277] K. Ogura, *Bull. Chem. Soc. Japan* **35**, 420 (1962).

[278] R. Andrisano, C. Della Casa, M. Tramontini, *Ann. Chim. (Roma)* **57**, 1073 (1967).

[279] G. Weitzel, F. Schneider, K. Seynsche, H. Finger, *Z. Physiol. Chem.* **336**, 107 (1964); *C.A.* **61**, 2864 (1964).

[280] H. Rivière, *Ann. Chim. (Paris)* **5**, 1273 (1960); *C.A.* **55**, 27050 (1961).

Analogous reactions of β-oxocarboxylic acid derivatives (mainly esters, **284**; cf. Table 30) afford dioxo-esters of the type **285**, dialkyl 2-hydroxybenzylmalonates (**286**), or heterocyclic substituted dialkyl acetamidomalonates (**287**).

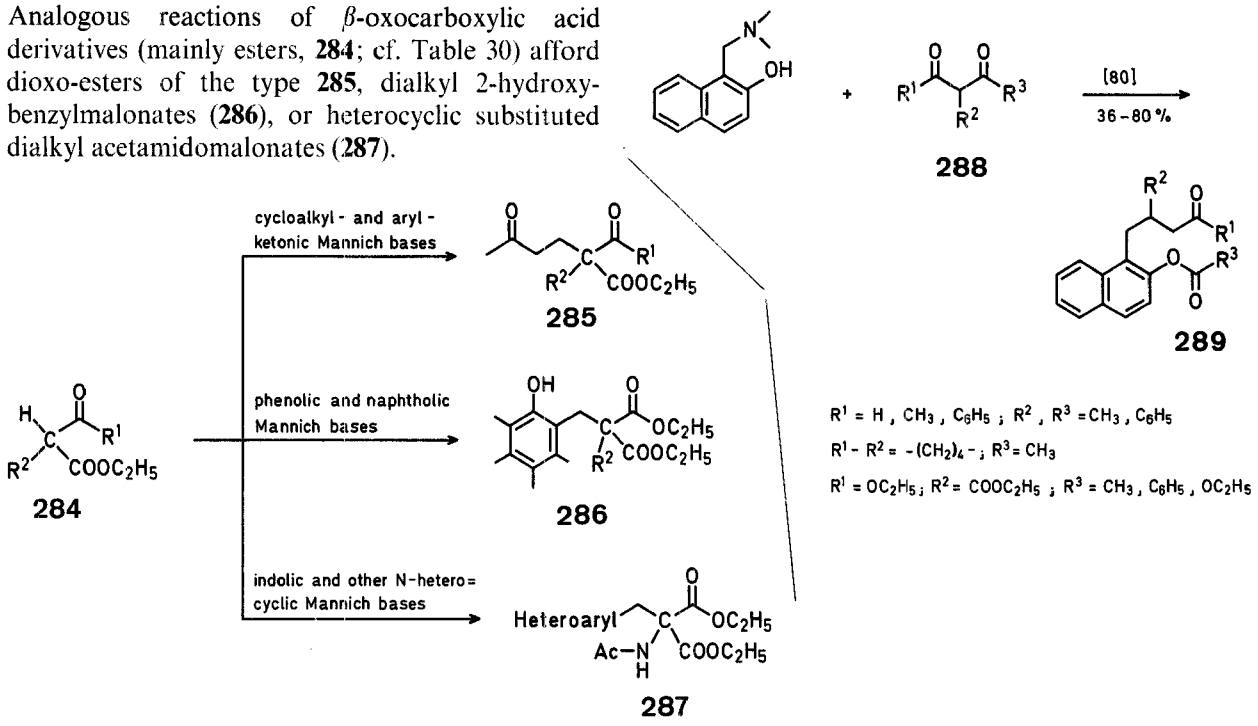


Table 30. *C*-Alkylation of β-Oxo-esters with Mannich Bases

β-Oxo-esters	**284**	Mannich Bases derived from	Products	Yield (%) [Conditions]	References
R^1	R^2				
CH_3	H	Aryl ketones	**285**	52–68 [79]	316
—$(CH_2)_3$—					
OC_2H_5	H	Cycloalkanones	**285**	60–80	58
		Aryl ketones	**285**	42 [79]	316
		Phenols	**286**		307, 317
OC_2H_5	—NH—CHO	Phenols	**286**		310
OC_2H_5	—NH—Ac	*N*-Heterocyclic compounds	**287**	50–65	273, 283

In the case of unsymmetric dialkyl ketones, the reaction takes place at the less substituted C_α-atom, in contrast to the orientation observed in the Michael addition using vinyl ketones in the presence of potassium hydroxide[322]. The mechanism of alkylation using ketonic Mannich bases appears to involve initial deamination of the β-amino-ketone to afford the vinyl ketone, followed by reaction of the ketonic substrate with the eliminated amine to give a vinylamine, and reaction of the vinyl ketone with the vinylamine[323].

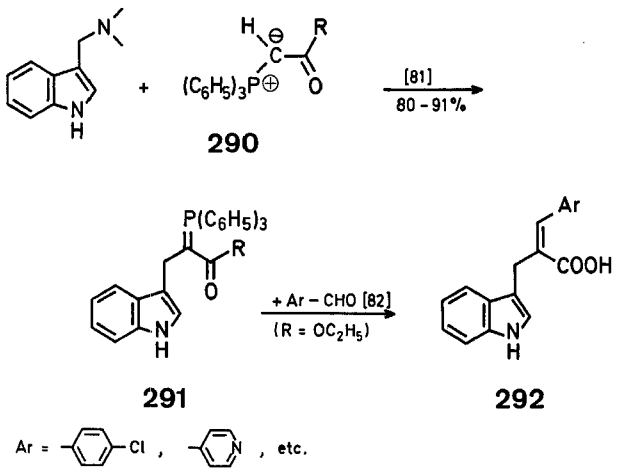
It is also worthwhile noting the possibility of transaminomethylation involving the Mannich base and the substrate, as was observed in several cases with cyclopentanone[41,322].

The reaction of naphtholic Mannich bases with open-chain β-diketones, β-oxo-esters, or α-oxoalkylmalonic acid esters (**288**) affords *O*-acylated products **289** via migration of an acyl group to the phenolic hydroxy group[324,325].

The reaction with cyclic β-diketones **280** and **281** (Table 29) does not lead to this rearrangement, but, via slight modification of the reaction conditions, affords heterocyclic products (see Section 2.6.).

The reaction of *phosphoranes* of the type **290** (R = C_6H_5, OC_2H_5) with some indolic and *p*-phenolic Mannich bases also affords *C*-alkylated products (e.g. **291**) in good yield; however, the reaction with *o*-phenolic Mannich bases gives instead cyclized products[326] (see Section 2.6.). Esters **291** (R = OC_2H_5) have been transformed into α-substituted β-arylacrylic acids (**292**).

[281] G. Dienys, J. Steponavicius, *Zh. Org. Khim.* **4**, 1391 (1968); *C.A.* **69**, 86551 (1968).
[282] G. Gottarelli, *Tetrahedron Lett.* **1965**, 2813.
[283] T. Okuda, *Yakugaku Zasshi* **80**, 208 (1960); *C.A.* **54**, 13141 (1960).
[284] V. M. Belikov, Y. N. Belokon, M. M. Dolgaya, N. S. Martinkova, *Izv. Akad. Nauk SSSR, Ser. Khim.* **1967**, 471, 1721, 2234; *C.A.* **67**, 32226 (1967); **68**, 12228, 86632 (1968).

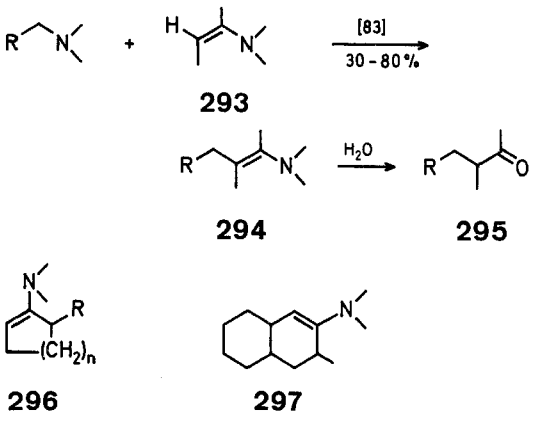


[81] The Mannich base and phosphorane **290** were refluxed in toluene under a nitrogen atmosphere for 6–7 hr[326].

[82] Compound **291** and the aromatic aldehyde were refluxed in dioxan for 18–24 hr[326]; yields: 24–60%.

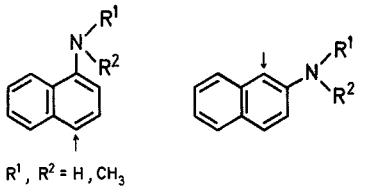
Carboxylic acid derivatives such as acetamide, acetonitrile, and levulinic acid have been alkylated using indolic or alkyl-ketonic Mannich bases[327,328], whereby up to three alkyl groups were introduced at the same activated methyl group. It is worth noting that 2-aminomethyl-3-methylindole does not display an alkylating effect in this reaction.

Enamines (**293**) have also been *C*-alkylated by Mannich bases (analogous reaction using vinyl ketones, see Ref.[329]). Often, the resultant amines (**294**) were not directly isolated, but hydrolyzed to the corresponding ketones (**295**) in the reaction medium[330,331]. Examples of vinylamines which undergo reaction with ketonic, phenolic, and indolic Mannich bases are compounds of the types **296** and **297**.

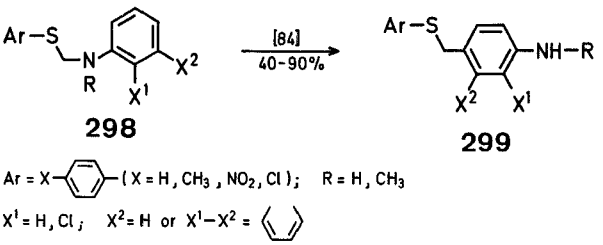


[83] Equimolar amounts of Mannich base and enamine were refluxed in dioxan or benzene for 24 hr. In several cases, the reactants were heated without solvent under a nitrogen atmosphere at 100–110°[330,331].

Ketonic, phenolic, and indolic Mannich bases have also been used to alkylate aromatic compounds such as phenols and arylamines; very good results were obtained in the cases of *N,N*-dimethylaniline, 1-aminonaphthalenes (alkylation at position 4), 2-aminonaphthalenes, and *β*-naphthol (position 1)[332]. It is interesting to observe that aminonaphthalenes, unlike anilines, preferentially undergo *C*-alkylation, even if they possess amine H-atoms.

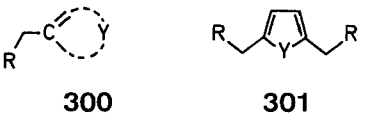


S-Aminomethylation products of the type **298** having a free *p*-position, as well as analogous Se- and NAr derivatives, undergo *C*-alkylation via rearrangement to give 4-(arylthiomethyl)-anilines (**299**) or the Se- and NAr analogs, respectively. When the *p*-position is occupied, only deamination is observed[333]. A suggested mechanism[257] involving the group Ar—S—$CH_2^{\oplus}$ as thiomethylating agent is not probable, since the arylthiomethyl cation is unlikely to be sufficiently stable (the same applies to the arylselenomethyl and arylsulfonomethyl cations). Instead, the reaction can be regarded to proceed by a much more complicated mechanism involving C—S and C—N cleavage steps, intermolecular transaminomethylation at the *p*-position of the anilino group, followed by deamination of the 4-aminobenzyl intermediate, and, finally, reaction of an arenethiolate anion with the 4-aminobenzyl cation formed by deamination[334].



[84] Compound **298** (1 mol) and conc. hydrochloric acid (1 mol) were refluxed in ethanol for 90 min[333].

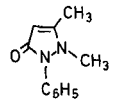
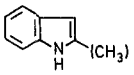
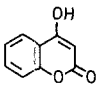
Several *heterocyclic compounds* (cf. Table 31) have been *C*-alkylated with ketonic and phenolic Mannich bases. In such reactions, monosubstituted products (**300**) were normally obtained, but disubstituted (2,5) products (**301**) were obtained directly in the case of five-membered heterocyclic compounds.



[285] M. M. Dolgaya, Y. N. Belokon, V. M. Belikov, *Izv. Akad. Nauk SSSR, Ser. Khim.* **1969**, 74; *C.A.* **70**, 114397 (1969).

[286] W. M. Shubert, Y. Motoyama, *J. Amer. Chem. Soc.* **87**, 5507 (1965).

Table 31. *C*-Alkylation of Heterocyclic Compounds with Mannich Bases

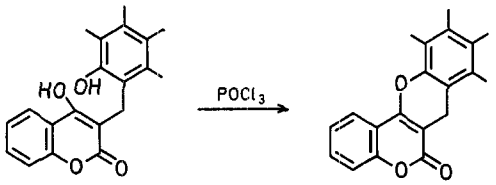
Heterocyclic Compound	Position of Reaction	Mannich Bases derived from	Reaction Conditions	Products	Yield (%)	References
	2 and 5	Alkyl-, aryl-, and styryl ketones	[85]	**301**	50–80	328, 332
	2 and 5	Aryl ketones	[86]	**301**	76	335
	4	Naphthols		**300**	41	318
	3	Aryl ketones	[85]	**300**	24–31	332
		Alkyl- and styryl ketones	[86]	**300**	72–85	328, 335
		Phenols, naphthols		**300**	30–45	336
	3	Phenols, naphthols	[87]	**302**	30–80	337

[85] The Mannich base hydrochloride and pyrrole (indole) were refluxed for 3 hr in ethanol/water; alternatively, the free base and pyrrole were refluxed in *p*-xylene for 4–5 hr[332].

[86] The morpholine Mannich base hydrochloride and furan were refluxed in water for 6–8 hr[335].

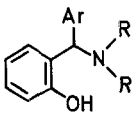
[87] The diethylamine Mannich base and hydroxycoumarin were heated without solvent at 180° for 15 min to 3 hr[337].

Condensed pyran derivatives of the type **303** may be obtained by heating the benzylation products **302** (obtained from 4-hydroxycoumarin and *o*-phenolic Mannich bases) with phosphorus oxychloride for a few minutes[337].

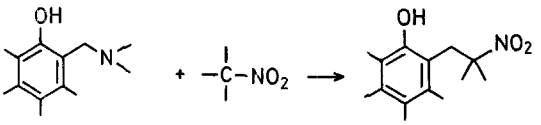


302 **303**

Such cyclizations often occur directly and in good yield during the alkylation reaction, especially in the case of phenolic bases of the type:



Alkylation of *nitroalkanes* with Mannich bases affords products which are mono- or polysubstituted α to the nitro group. Phenolic bases react with nitromethane, nitroethane, 2-nitropropane, and nitrocyclohexane to give monobenzylation products (**304**)[310,318], whereas the reaction of bases derived from ketones or indoles with nitromethane affords mono- and polysubstituted products[327,328,335].



304

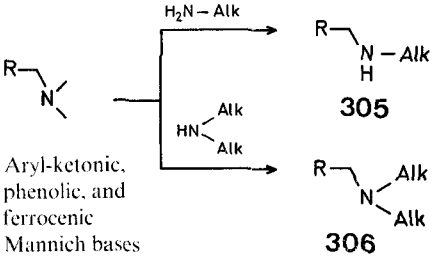
Further examples of *C*-alkylations using Mannich bases are found in Ref.[436,452].

2.3.3. *N*-Alkylation

N-Alkylation using Mannich bases is successful in the case of most compounds containing an NH group, e.g., ammonia, primary and secondary amines, amides, and NH-heterocyclic compounds.

The reaction of *ammonia* (in the form of ammonium carbonate) with Mannich bases derived from indole[327] yields bis- and tris-[3-indolylmethyl]-amines.

The reaction of aryl-ketonic, phenolic, and ferrocene Mannich bases with *primary amines* is of particular practical interest, since the resultant secondary amines (**305**) in general are not easily available by other methods of synthesis. The reaction has been carried out with a variety of amines, including amino-alcohols[266] and amino-acids[267]. The analogous reaction with dialkylamines affords tertiary amines of the type **306** (Table 32).



Aryl-ketonic, phenolic, and ferrocenic Mannich bases

305 **306**

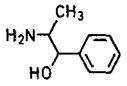
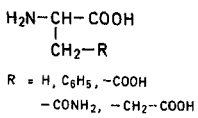
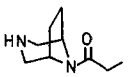
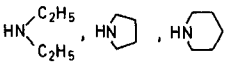
[287] A. S. Angeloni, L. Angiolini, P. De Maria, A. Fini, *J. Chem. Soc.* [C], **1968**, 2295.

[288] E. Baciocchi, A. Schiroli, *J. Chem. Soc.* [B] **1968**, 401.

[289] H. J. Roth, C. Schwenke, G. Dvorak, *Arch. Pharm.* **298**, 326 (1965).

[290] V. Horák, J. Michl, P. Zuman, *Tetrahedron Lett.* **1961**, 744.

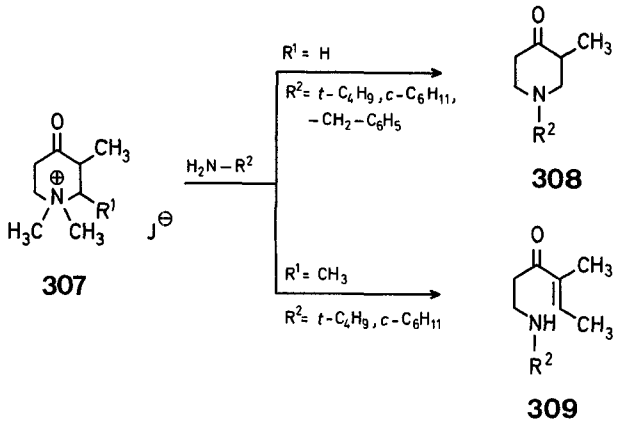
Table 32. *N*-Alkylation of Primary and Secondary Aliphatic Amines with Mannich Bases (Amine-Exchange Reactions)

Amines	Mannich Bases derived from	Products	Yield (%) [Conditions]	References
$H_2N-C_4H_9-n$, $H_2N-C_6H_{11}-c$	Aryl ketones	**305**	good	267
$H_2N-C_3H_7-i$, $H_2N-C_6H_{11}-c$	Phenols	**305**		131
 **80**	Aryl ketones	**305**		266
 R = H, C_6H_5, $-COOH$, $-CONH_2$, $-CH_2-COOH$	Aryl ketones	**305**	good [88]	267
	Phenols	**306**		131
	Aryl ketones	**306**	65	338
	Ferrocenes	**306**	40–90 [89]	309, 339, 340
	Phenols	**306**		317

[88] An aqueous solution of Mannich base hydrochloride and amino-acid (equimolar amounts) was heated for 2 hr[267].

[89] The amine and the ferrocene Mannich base methiodide were refluxed in water for 1–3 days[339,340].

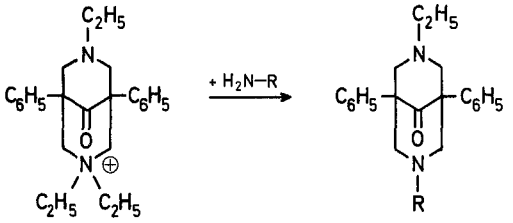
Interesting examples are provided by the exchange reaction in aqueous medium between alkylamines and *N*-methyl-γ-piperidone methiodides (**307**).



307 **308** **309**

γ-Piperidones (**308**) are the products when the 2-position of **307** is unsubstituted, whereas acyclic α,β-unsaturated β′-amino-ketones (**309**) are obtained when this position is occupied[341]. Steric factors are certainly relevant, as shown by the reaction between methiodide **307** ($R^1=CH_3$) and benzylamine (the benzyl substituent is less bulky than cyclohexyl or *t*-butyl groups), which affords a cyclic amino-ketone analogous to **308** (cf. also **260** and **261**, Section 2.2. and Ref.[453]).

An analogous exchange reaction between the quaternary salts of "bispidinones" (e.g. 1,5-diphenyl-9-oxo-3,3,7-triethyl-7-aza-3-azoniabicyclo[3.3.1]-nonane salts, **310**) and primary amines represents a facile synthesis[282] of unsymmetric 9-oxo-3,7-diazabicyclo[3.3.1]nonanes (e.g. **311**), which previously could only be obtained[342] as a mixture together with the symmetric derivative via direct synthesis from the corresponding ketone and two molecules of amine.

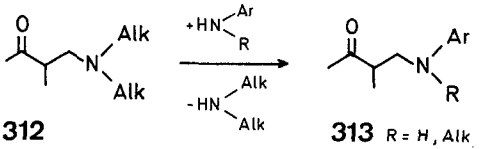


310 **311**

R = alkyl

Amine exchange between optically active 2-dimethylaminomethyl-1-oxo-1-phenylpropane methiodide and pyrrolidine affords a completely racemic product; an elimination-addition mechanism is therefore suggested for the reaction[275].

β-Arylamino-ketones (**313**), which represent starting materials for the synthesis of quinolines (see Section 2.6.), may be prepared by the amine-exchange reaction between β-dialkylamino-ketones (**312**; readily obtained by Mannich synthesis) and arylamines (Table 33).



312 **313** R = H, Alk

Good yields were obtained using the Mannich base hydrochlorides (or the free bases and arylamine

hydrochlorides) in alcohol or alcohol/water and refluxing for one hour. Some examples of the amine-exchange reaction using phenolic Mannich bases have also been reported[317].

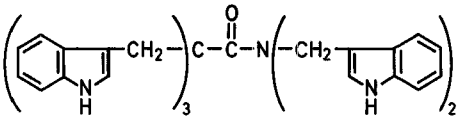
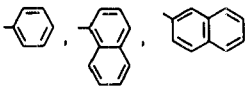
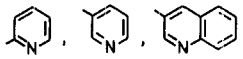
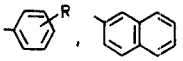
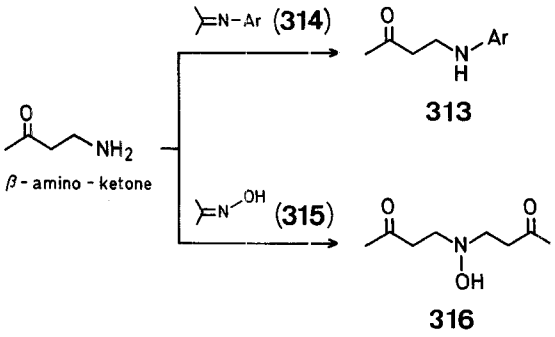


Table 33. *N*-Alkylation of Primary and Secondary Aromatic Amines with Mannich Bases (Amine-Exchange Reactions)

Arylamines		Mannich Bases derived from	References
R	Ar		
H	 and substitution products	Alkyl ketones, cycloalkanones Aryl ketones Styryl ketones	343, 344, 345 75, 118, 344, 346–350 118, 348, 351
H		Aryl ketones	347
CH_3		Aryl ketones Styryl ketones	347, 348 348, 352

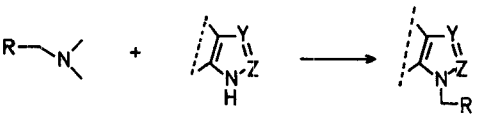
The results obtained in a mechanistic study of the amine-exchange reaction using 4-dimethylamino-butanone and *N*-deuterated arylamines[347] suggest that the reaction involves both direct substitution (S_N1 or S_N2) and elimination-addition mechanisms, the nature of the arylamine used determining which mechanism predominates. In this connection, a mechanistic study of the addition of arylamines to vinyl ketones[296] deserves mention.

N-Arylimines (**314**) are also capable of introducing an arylamino group into ketonic Mannich bases via an exchange reaction. The analogous reaction using *oximes* (**315**) affords[118] *N,N*-bis-[3-oxoalkyl]-hydroxylamines (**316**), whereas direct reaction of *hydroxylamine* with ketonic Mannich bases usually gives the corresponding ketoximes, which in some cases cyclize to afford 1,2-oxazolines (see Section 2.6.).



Carboxamides have been alkylated by both ketonic (including styryl-ketonic)[328] and indolic[327] Mannich bases. With phthalimide and cyanoacetamide, the ketonic bases give only *N*-alkylation products; the reaction of indolic Mannich bases with acetamide, however, yields both *N*- and *C*-alkylated products. An example of the latter products type (cf. Section 2.3.2.) is:

NH-Heterocyclic compounds such as pyrazole, imidazole, indazole, benzimidazole, and benzotriazole react with Mannich bases derived from ketones, phenols, and indoles. The best yields of products **317** have in some cases been obtained by use of the hydrochlorides in ethanol/water (reflux: 1–2 hr), and in others by using the free bases in aprotic medium (xylene, reflux: 2–5 hr)[332] (cf. Ref.[283]).



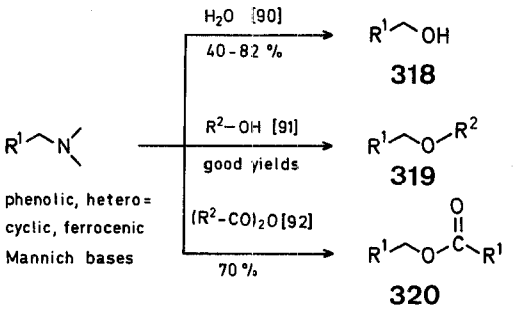
aryl-ketonic, naphtholic, 3-indolic Mannich bases

Y, Z = CH, N

317

2.3.4. *O*-Alkylation

The *O*-alkylation reactions with Mannich bases are summarized in the following scheme:

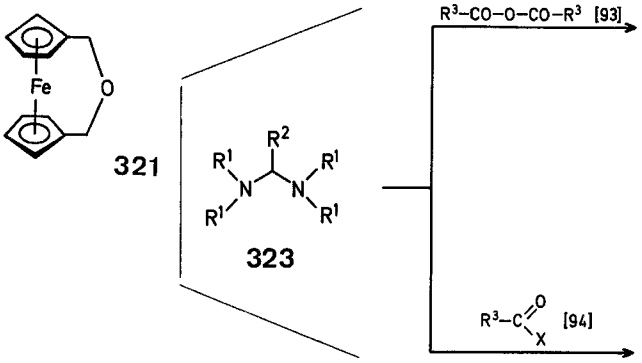


[90] The methiodide of the Mannich base was refluxed in aqueous sodium hydroxide for 24 hr[309,340].

[91] The methiodide of the Mannich base was refluxed with sodium ethoxide in ethanol for 50–60 hr[339].

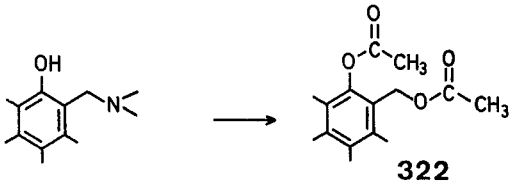
[92] The Mannich base was refluxed with sodium acetate in acetic anhydride for 2 hr[138].

Substitution of an alkylamino group by a hydroxy group (by treatment with *aqueous* sodium hydroxide) according to the above reaction scheme has been carried out with several aminomethylferrocene methiodides as substrates[211,309,312,340]. The products are hydroxymethylferrocenes (**318**, R^1 = ferrocenyl). When both of the rings of ferrocene contain aminomethyl groups, it is possible to obtain a bridged product[211], e.g. **321.**



Use of *alcohols* and *phenols* as reagents allows the synthesis of ethers (**319**) from Mannich bases. This reaction has been successfully carried out on phenolic Mannich bases[307] and aminomethylferrocene methiodides[211,309,339,340] using sodium alkoxide, sometimes alcoholic sodium hydroxide solutions, or aqueous alkali metal phenoxide solutions.

Esters (**320**) can be synthesized from various Mannich bases using *acetic anhydride* in the presence of sodium acetate. In the case of *o*-phenolic substrates, the hydroxy group also undergoes reaction[110,136,138] to give diacetoxy compounds (**322**).



Mannich bases derived from tropolones (see Section 1.4.8) may similarly be converted into the corresponding acetoxymethyl derivatives, which quantitatively undergo substitution of the acetoxy group by bromine[277] to give bromomethyltropolones.

Some bases derived from purines are converted into the acetoxymethyl derivatives by treatment with acetic acid; however, under such experimental conditions, the bases sometimes undergo deaminomethylation[247].

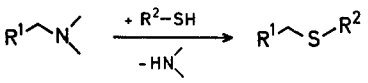
The course of the reaction of some standard acylating agents with 1,1-diaminoalkanes (**323**) is dependent upon the reagent used; whereas reaction with *anhydrides*[353] affords 1-aminoalkyl carboxylates (**324**), *acyl halides* react to give 1-amino-1-haloalkanes (**325**) in good yield[354].

[93] Compound **323** was allowed to react with acetic anhydride at room temperature with exclusion of moisture[353].

[94] Compound **323** and the acyl halide were allowed to react in anhydrous ether at room temperature for 30 min[354].

2.3.5. *S*-Alkylation

The substitution of the amino group in Mannich bases by an —S—R group to give thioethers (**326**) is carried out by refluxing the Mannich base hydrochlorides with *thiols* in an aqueous or aqueous-alcoholic medium for a short time. The yields, often high, are affected by the pH of the medium which, in the absence of buffers, is governed by both the acidity of the thiol and the basicity of the Mannich base. The reaction has been carried out using bases derived from ketones, phenols, and indoles (Table 34: see also Ref.[454,455]).

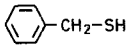
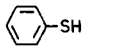
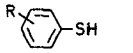


326

aryl-ketonic, naphtholic, and indolic Mannich bases

[291] P. Čársky, P. Zuman, V. Horák, *Collect. Czech. Chem. Commun.* **29**, 3044 (1964).
[292] K. T. Koshy, H. Mitchner, *J. Pharm. Sci.* **53**, 1381 (1964).
[293] A. S. Angeloni, M. Tramontini, *Ann. Chim. (Roma)* **54**, 745 (1964).
[294] J. A. Mollica, J. B. Smith, I. M. Nunes, H. G. Govan, *J. Pharm. Sci.* **59**, 1770 (1970).
[295] J. K. Koward, T. C. Bruice, *J. Amer. Chem. Soc.* **91**, 5339 (1969).
[296] Y. Ogata, A. Kawasaki, I. Kishi, *J. Chem. Soc.* [B] **1968**, 703.
[297] B. E. Ivanov, V. F. Zheltukhin, *Izv. Akad. Nauk SSSR, Ser. Khim.* **1969**, 1016; *C. A.* **71**, 48940 (1969).
[298] B. E. Ivanov, V. F. Zheltukhin, *Izv. Akad. Nauk SSSR, Ser. Khim.* **1969**, 1022; *C.A.* **71**, 48941 (1969).
[299] K. Higashi, T. Kitamura, Y. Fukusaki, E. Imoto, *Kôgyô Kagaku Zasshi* **61**, 1035 (1958); *C.A.* **55**, 22210 (1961).

Table 34. *S*-Alkylation of Alkylmercaptans and Arenethiols with Mannich Bases

Thiols	Mannich Bases derived from	Reaction Conditions	Yield (%)	References
	Aryl ketones	[95]		355
	Aryl ketones	[95]	good	82, 287, 355
	Naphthols	[95]	30–98	127
	Aryl ketones	[95]	good	82, 287, 355
	Naphthols	[95]	30–98	127
	Indoles	[96]	75–100	288

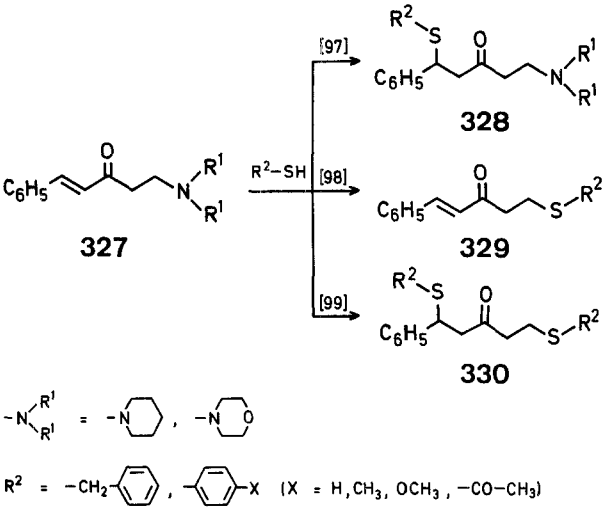
[95] A 0.1 *M* solution of Mannich base hydrochloride (sometimes the free base) and an equimolar amount of the thiol in ethanol/water (1:1) were refluxed for 1 hr; the product precipitated upon cooling, or was extracted with ether after dilution of the reaction mixture with water[355].

[96] A solution of the Mannich base methiodide, sodium methoxide, and the thiol in methanol was allowed to stand at room temperature for 3–4 hr. In the case of the *N*-methylindole derivative, the mixture was refluxed[288].

The reaction mechanism, as investigated for the *S*-alkylation with ketonic[82,287], naphtholic[127], and indolic Mannich bases[288] (including the corresponding quaternary salts), consists of the elimination of the amino group, followed by fast addition of the thiol to the vinyl intermediate (vinyl ketone, quinone methide, or azomethine). The elimination step is discussed in Section 2.2.

Styryl-ketonic Mannich bases (**327**) show a different behaviour; the reaction with thiols may give rise to three types of products; products of substitution of the amino group (**329**), of the addition to the styryl double bond (**328**), and of both substitution and addition(**330**)[355,356].

The yield and type of products are controlled by the nature of the amino group and thiol, by the solvent, and by the reaction time. Addition products (**328**), which predominate at short reaction times, disappear in favor of substitution products (**329** and **330**) after longer reaction periods. The best yields of 2-aminoethyl 2-phenyl-2-thioethyl ketones (**328**) are obtained by carrying out the reaction without solvent, of styryl 2-thioethyl ketones (**329**) in aprotic solvents, and of 2-phenyl-2-thioethyl 2-thioethyl ketones (**330**) in aqueous alcoholic medium.



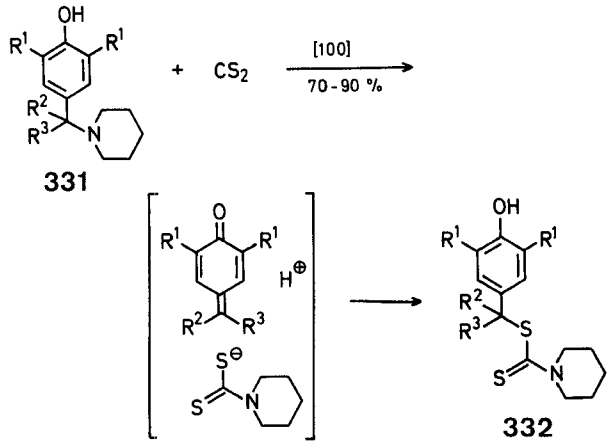
[97] Compound **327** (used as the free base), thiol, and a few drops of a suitable amine (piperidine or morpholine) were mixed with cooling. The mixture was allowed to stand at room temperature or 0° for 2–4 hr. The product was isolated and purified as the hydrochloride[355,356].

[98] A suspension of the Mannich base hydrochloride in a solution of the thiol in xylene was refluxed for 1 hr; the product was purified from the bis-sulfide **330** by fractional crystallization from ethanol[355,356].

[99] As described in [95], using 2–2.5 mol of thiol[355,356].

Treatment of the methiodide of a ferrocene Mannich base with aqueous alkali metal sulfides leads to the formation of bis-ferrocenylmethyl sulfide (58%)[339]. The reaction of 4-(1-aminoalkyl)-phenols (**331**) with *carbon disulfide* affords 4-hydroxybenzyl dithiocarbamates (**332**)[357]. This type of reaction is restricted to *p*-phenolic Mannich bases; the hydrogen-bonded hydroxy group of e.g., 2-piperidinomethylphenol is incapable of reacting with carbon disulfide.

[300] L. F. Fieser, M. Fieser, *Reagents for Organic Synthesis*, John Wiley & Sons, New York, 1967, p. 697–703.
[301] A. M. Shur, *Neftekhimiya* **2**, 600 (1962); *C.A.* **58**, 6735 (1963).
[302] D. Beke, C. Szántay, *Chem. Ber.* **95**, 2132 (1962).
[303] M. I. Farberov, G. S. Mironov, *Dokl. Akad. Nauk SSSR* **148**, 1095 (1963); *C.A.* **59**, 5062 (1963).
[304] W. B. Lutz, S. Lazarus, R. I. Meltzer, *J. Org. Chem.* **27**, 1695 (1962).
[305] F. L. Scott, J. C. Riordan, A. F. Hegarty, *Tetrahedron Lett.* **1963**, 537.
[306] F. L. Scott, R. J. MacConaill, J. C. Riordan, *J. Chem. Soc.* [C] **1967**, 44.
[307] P. D. Gardner, H. S. Rafsanjani, *J. Amer. Chem. Soc.* **81**, 3364 (1959).
[308] E. P. Previc, *U.S. Patent* 3461172 (1969); *C.A.* **71**, 101520 (1969).
[309] G. Marr, R. E. Moore, B. W. Rockett, *Tetrahedron Lett.* **1968**, 2517.
[310] F. Troxler, *Helv. Chim. Acta* **51**, 1214 (1968).
[311] J. B. Hester, *J. Org. Chem.* **29**, 1158 (1964).

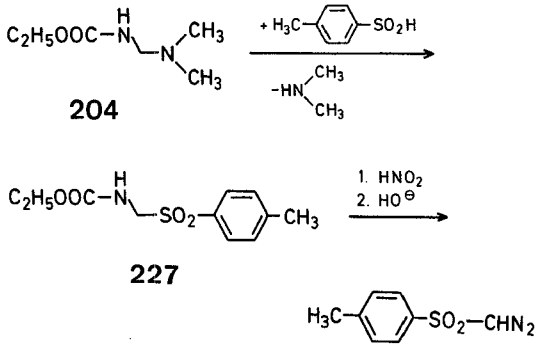


$R^1 = CH_3$, n-C_4H_9, OCH_3,
$R^2 = R^3 = CH_3$; or $R^2 = H$; $R^3 = CH_3$

[100] The Mannich base **331** (1 mol) and carbon disulfide (1 mol) were refluxed in ethanol for 2–5 hr[357].

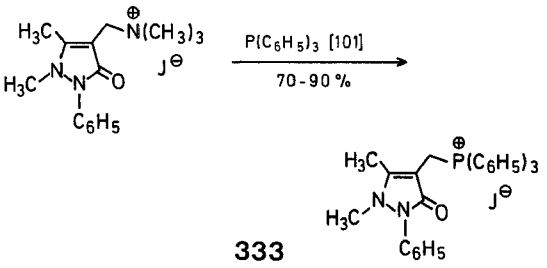
The lack of reactivity of the unsubstituted bases **331** ($R^1 = R^2 = R^3 = H$) is explained by the absence of substituents which could stabilize the intermediate quinone methide.

S-Alkylation of *4-methylbenzenesulfinic acid* (cf. Section 1.5.2.) with ethyl *N*-dimethylaminomethylcarbamate (**204**) and nitrosation of the resultant ethoxycarbonylaminomethyl 4-methylphenyl sulfone (**227**) provides a synthesis of diazomethyl 4-methylphenyl sulfone[223]. The reaction is also applicable to the synthesis of other diazo-sulfones[260].



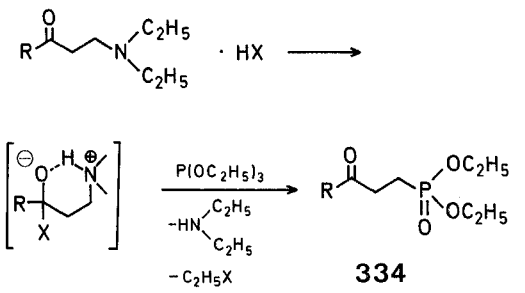
2.3.6. *P*-Alkylation

P-Alkylation using Mannich bases may be carried out on tertiary phosphines (e.g. triethyl- and triphenylphosphine) and trialkyl phosphites (e.g. triethyl phosphite). Good results are obtained from the reaction between phosphines and the Mannich bases derived from ketones, phenols, and N-heterocyclic compounds, either as the free bases or as the methiodides[358]. 2,3-Dimethyl-5-oxo-1-phenyl-4-triphenylphosphoniomethylpyrazoline iodide (**333**) is a good example of a quaternary phosphonium salt thus obtained.



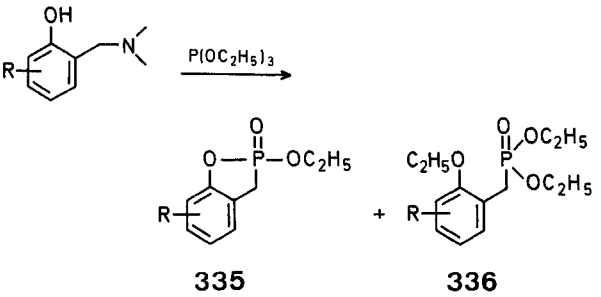
[101] The methiodide of 2,3-dimethyl-4-dimethylaminomethyl-5-oxo-1-phenylpyrazoline and triphenylphosphine (or triethylphosphine) were refluxed in methanol for 4 hr under a nitrogen atmosphere[358].

Diethyl 3-oxoalkanephosphonates (**334**) may be obtained from the reaction of triethyl phosphite with ketonic Mannich bases in dimethylformamide at 100°[297,298].



$R = CH_3$,  ($X^1 = H$, CH_3, OCH_3, Cl)

The proposed mechanism involves nucleophilic attack on the carbonyl group by the anion X with formation of a hydrogen-bonded cyclic transition state; this intermediate is then capable of amine elimination and *P*-substitution. *o*-Phenolic Mannich bases also undergo analogous exchange reactions; however, in this case the phenolic hydroxy group participates in the reaction and O,P-heterocyclic compounds (**335**) are obtained; the corresponding open-chain compounds **336** are only isolated as by-products under special experimental conditions[359,360].



$R = CH_3$, t-C_4H_9, Cl

[312] D. W. Slocum, B. W. Rockett, C. R. Hauser, *Chem & Ind.* **1964**, 1831; *J. Amer. Chem. Soc.* **87**, 1241 (1965).

[313] J. H. Peet, B. W. Rockett, *J. C. S. Perkin Trans. I* **1973**, 106.

[314] H. C. Brown, G. W. Kabalka, M. W. Rathke, M. M. Rogić, *J. Amer. Chem. Soc.* **90**, 4166 (1968).

[315] L. Caglioti, G. Rosini, work in progress.

2-Ethoxy-2-oxo-P^V-1,2-benzoxaphosphole (**335**) is obtained from the methiodide of the Mannich base (4 hr reflux in toluene) in 93% yield, from the hydrochloride (5 hr reflux in xylene) in 55% yield, or from the free base in acetic acid in 58% yield together with **336**. An S_N1 mechanism was proposed, in which decomposition of the base is twenty times slower than the reaction of the phosphorus reagent with the intermediate[359].

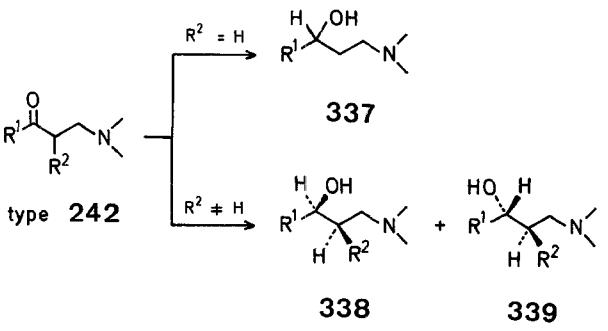
2.4. Reduction of Mannich Bases

Catalytic hydrogenation or reduction with complex metal hydrides of Mannich bases gives rise to two types of products:

- Products formed by hydrogenolytic cleavage of the amino group (substitution by hydrogen, which may also be regarded as an *N*-alkylation, see Section 2.3.1.): R—CH_2—N< → R—CH_3;
- Products formed by reduction of unsaturated groups present in the molecule.

The latter reaction has been carried out with Mannich bases derived from ketones, α,β-unsaturated ketones (vinylogous ketonic bases), and 1-alkynes. *Ketonic Mannich bases* (**242**) have doubtless been most widely investigated in this respect, since the product amino-alcohols **337**, or **338** and **339**, and their *O*-acyl derivatives (cf. Ref.[53, 79, 81]) have interesting pharmaceutical properties.

As can be seen from the reaction scheme, reduction of the carbonyl group in β-amino-ketones containing asymmetric centers (e.g. **242**, $R^2 \neq H$) can lead to product mixtures consisting of two diastereomers.



Only one enantiomer of the racemic pairs of products **338** and **339** is presented here.

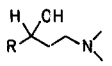
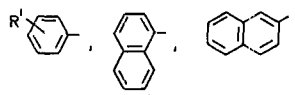
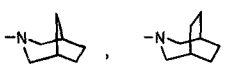
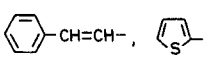
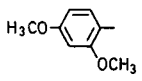
[102] A methanolic solution of sodium borohydride was added in portions to a solution of the Mannich base in methanol at 20–40°. The mixture was then allowed to stand for 12 hr; yield: 97%[361].

Therefore, the reduction of β-amino-ketones of the type **242**, $R^2 = H$, for which the problem of stereospecificity does not exist, will be discussed first.

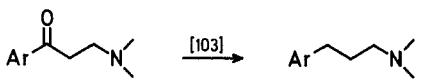
Excellent results are obtained using sodium borohydride in alcohols as a reducing agent; thus, aryl 2-aminoethyl ketones (**242**, R^1 = aryl, $R^2 = H$) are converted into the corresponding β-amino-alcohols (**337**; Table 35, see also Ref.[431, 456]); reduction of the carbonyl group is also selective in the case of 2-aminoethyl styryl ketones (**242**, $R^1 = C_6H_5$—CH=CH—, $R^2 = H$)[361].

In some cases, 2-aminoethyl aryl ketones (**242**, R^1 = Ar, $R^2 = H$) can also be reduced to the corresponding 1-amino-3-arylpropanes[76].

Table 35. Synthesis of Secondary β-Amino-alcohols by Reduction of β-Amino-ketones (**242**, $R^2 = H$)

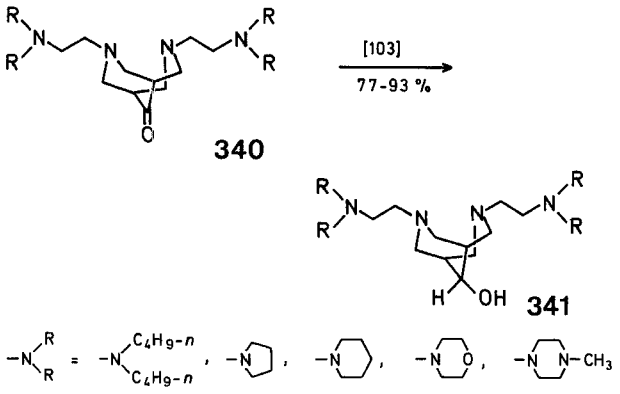
Amino-alcohol  **337**		Yield (%)	References
R	—N<		
	 cycloocta-methylenimine		96, 97
		22–92	98, 361
			
		68[a]	69
		95	76

[a] Hydrogenation in the presence of PtO_2.



[103] The Mannich base and lithium alanate are refluxed in tetrahydrofuran for 24 hr[362], or for 90 min and the mixture is then allowed to stand for 12 hr; yield: 97%[76,362].

Several 3,7-bis-[2-aminoethyl]-9-oxo-3,7-diazabicyclo[3.3.1]nonanes (**340**, "bispidinones") have been reduced to the corresponding 9-hydroxy compounds (**341**) in good yields[362].



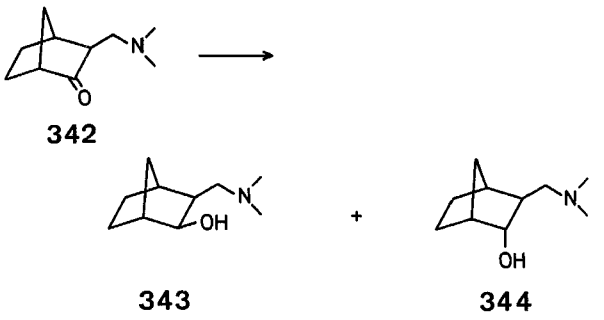
Reduction with hydrogen and complex metal hydrides of β-amino-ketones having an asymmetric C-atom (e.g. **242**, $R^2 \neq H$) has been intensely investigated with respect to the stereochemistry of the reaction[363,364,365] (see also Ref.[366,367]). The reduction of 2-aminoalkyl phenyl ketones (**242**, $R^1 = C_6H_5$, $R^2 \neq H$) with lithium alanate was shown to proceed stereoselectively on the basis of the diastereoisomer ratio obtained (the configurations of the products were also determined). Diastereoisomer **338** (*erythro*) always predominates over **339** (*threo*), and this predominance increases when the α-substituent (R^2) is a phenyl group[364,365].

Reduction of α-substituted β-dimethylaminoalkyl- and β-piperidinoalkyl phenyl ketones (**242**, $R^1 = C_6H_5$, $R^2 \neq H$) with lithium alanate [104].

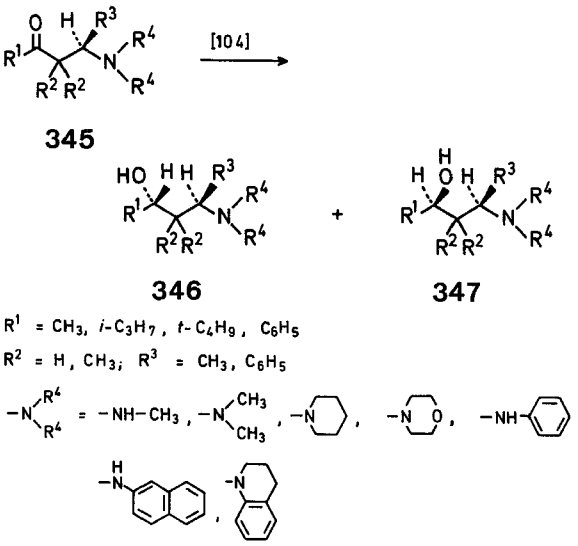
R^2	% **338** (*erythro*)	% **339** (*threo*)
CH_3, $-CH_2-C_6H_5$	54–60	46–40
C_6H_5	78–86	22–14

[104] An ethereal solution of the Mannich base (0.02 mol) was added dropwise to a suspension of lithium alanate (0.02 mol) in anhydrous ether (50 ml); the mixture was refluxed for 1 hr; yield of **338**+**339**: ~90%. The diastereomers can be separated by fractional crystallization of the free bases (from petroleum ether) or of the hydrochlorides (from ethanol/ethyl acetate)[365] (see also Ref.[369]).

The stereochemistry of the reduction of Mannich bases derived from norcamphor, such as 2-*exo*-dimethylamino-3-oxobicyclo[2.2.1]heptane (**342**), was studied using lithium alanate, lithium tri-*t*-butoxyaluminium hydride, and sodium borohydride; the predominance of the diastereomers **343** and **344** obtained depended strongly on the nature of the reducing agent[368,399].



The reduction with complex metal hydrides of 2-aminoalkyl ketones **345**, which posses a center of asymmetry at the position β to the carbonyl group, is usually stereoselective whereby diastereoisomer **346** (*erythro*) predominates over **347** (*threo*) in the product[369].

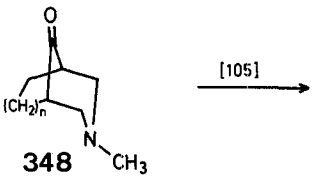


β-Amino-ketones of the type **345**, $R^2 = H$, display lower stereoselectivity in the reduction with lithium alanates than α,α-dimethyl-substituted Mannich bases **345** ($R^2 = CH_3$). It has to be noted that the reduction of *N*-monosubstituted β-amino-ketones (e.g. ketonic Mannich bases obtained using methylamine or aniline) does not display significant stereoselectivity.

The degree of stereoselectivity observed in the catalytic hydrogenation (or reduction by other methods) of azabicycloalkanones of the type **348** and the corresponding quaternary salts depends mainly on the ring size[370].

[316] E. M. Austin, H. L. Brown, G. L. Buchanan, *Tetrahedron* **25**, 5509 (1969)

[317] K. Higashi, E. Imoto, *Kôgyô Kagaku Zasshi* **61**, 1043 (1958); *C.A.* **55**, 22210 (1961).



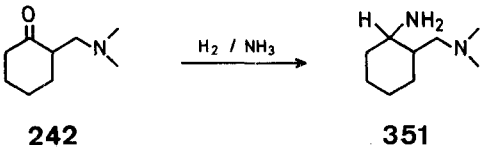
348

349 350

n = 1	81–98%	2–19%
n = 2	4–44%	60–96%
n = 3	1–9%	91–99%

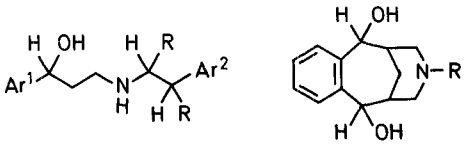
[105] Compounds **348** were hydrogenated in isopropanol or acetic acid in the presence of platinum at room temperature; hydrogenation of the quaternary salts derived from **348** required a temperature of 120°. Other reduction conditions: sodium borohydride in methanol/water (3 hr at room temperature); sodium in isopropanol/toluene (reflux for 2–3 hr)[370] (see also Ref.[147]).

Several other α-substituted β-amino-ketones (**242**; see Table 36 and Ref.[433]) have been reduced to the alcohols without configurational assignment of the products and configurational analysis of the product mixtures. 2-Aminomethylcyclohexanones [**242**, $R^1—R^2 = —(CH_2)_4—$] have been subjected to reductive amination to give 1-amino-2-aminomethylcyclohexanes (**351**)[371], the *O*- and *N*-acyl derivatives of which are of pharmacological interest.



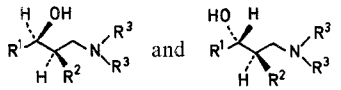
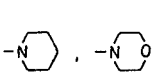
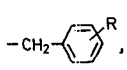
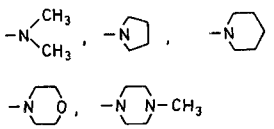
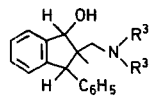
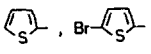
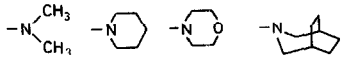
242 351

Other examples of such reduction are provided by β-amino-ketones having a center of asymmetry in the amine moiety (amphetamine or similar residue), which are hydrogenated over 5% palladium on barium sulfate[92] to give β-amino-alcohols of the type **352**, and by tricyclic diketones of the type **124** (section 1.4.4.), which are reduced by lithium alanate[372] to give pharmacologically interesting 1,7-dihydroxy-2,3,4,5,6,7-hexahydro-1*H*-2,6-methano-4-benzazonines (**353**).

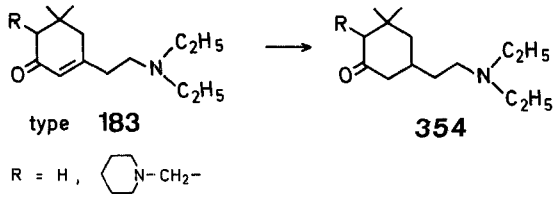


352 353

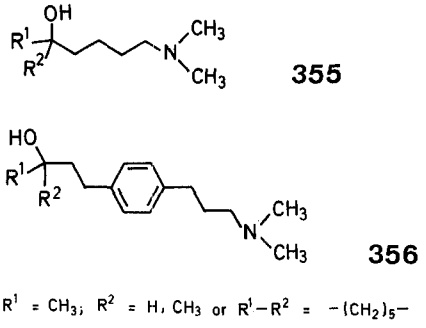
Table 36. Synthesis of Secondary β-Amino-alcohols by Reduction of β-Amino-ketones (**242**, $R^2 \neq H$) [without regard to stereochemistry]

Alcohols  338 and 339			Reducing Agent	Yield (%)	References
R^1	R^2	$-N(R^3)_2$			
$(C_6H_5)_2C(X)-$ 	CH_3	$-N(CH_3)_2$	$NaBH_4$, $LiAlH_4$	30–67	53
	$-(CH_2)_4-$				371
	CH_3		$NaBH_4$	45–70	98
	n-C_3H_7, n-C_4H_9, 		$NaBH_4$	good	79, 81
and alcohols 					
	CH_3		$NaBH_4$	34–87	84, 361

Selective hydrogenation of the *C=C double bond* in "vinylogous" ketonic Mannich bases such as 1-(2-dialkylaminoethyl)-5,5-dimethyl-3-oxocyclohexenes (**183**; see Section 1.4.8.) to give δ-aminoketones of the type **354** [3-(2-aminoethyl)-cyclohexanones] may be achieved using Raney nickel as a catalyst[204].



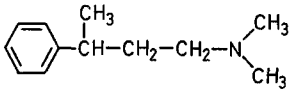
Hydrogenation of the *triple bond* in some Mannich bases derived from 1-alkynes (see Section 1.4.6.) to give amino-alcohols of the types **355** and **356** has been achieved using platinum (in ethanol)[373] or Raney nickel[186] as catalysts.



2.5. Reaction of Mannich Bases with Organometallic Compounds

A convenient synthetic route to tertiary β-amino-alcohols (**357**) is provided by the aminomethylation of suitable *ketones* and reaction of the resultant Mannich bases (**242**) with Grignard or organolithium reagents. (Table 37; see also Ref.[430,431,457]). Usually an excess of organometallic reagent is employed.

An example of the further synthetic use of the β-amino-alcohols thus obtained is the dehydration of 4-dimethylamino-2-hydroxy-2-phenyl-butane (**357**, $R^1=C_6H_5$, $R^2=R^3=CH_3$) followed by hydrogenation to give the pharmacologically interesting 1-dimethylamino-3-phenylbutane[375].

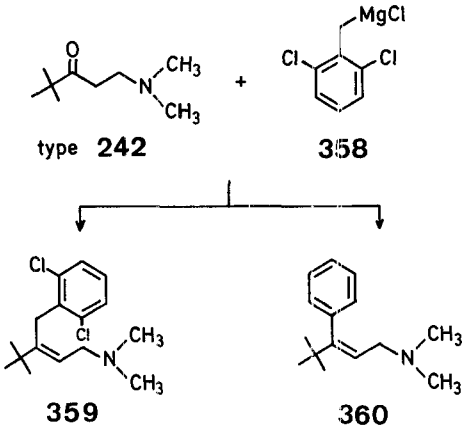


The reaction of 2,6-dichlorobenzylmagnesium chloride (**358**) with *t*-butyl 2-dimethylaminoethyl ketone (**242**, $R^1=t\text{-}C_4H_9$) affords not only alkene **359**, which could be expected to arise by dehydration of the product alcohol, but also product **360**, which contains two Cl-atoms and one CH_2 group less than **359**. The reaction of the corresponding 2-

Table 37. Synthesis of Tertiary β-Amino-alcohols (**357**) by Reaction of β-Amino-ketones (**242**, R^2=H) with Organometallic Compounds

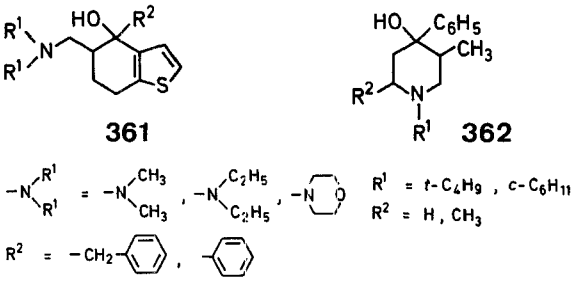
Alcohols **357**			Organometallic Reagent	Yield (%)	References
R^1	$-N^{R^2}_{R^2}$	R^3			
t-C_4H_9	$-N(CH_3)_2$	$-CH_2-C_6H_4(Cl)$	Grignard	70–80	374
C_6H_5	$-N(CH_3)_2$	CH_3	Grignard	65	375
X-C_6H_4 (X = 2-CH_3, 4-CH_3, 4-OCH_3, 4-F)	$-N(CH_3)_2$	$-CH_2-C_6H_5$, $-CH_2$-pyridyl	Li-org., Grignard	70–80	366, 367, 376
R-C_6H_4, naphthyl, naphthyl	$-N$-bicyclo	CH_3, C_2H_5, $-CH_2-C_6H_5$, c-C_6H_{11}, C_6H_5, $C_6H_4(CH_3)$	Grignard	16–70	100
H_3CO-C_6H_4, $(H_3CO)_2C_6H_3$, $(H_3CO)_3C_6H_2$	$-N(CH_3)_2$, $-N(C_2H_5)_2$, $-N$-pyrrolidine, $-N$-morpholine	3,4-methylenedioxyphenyl	Li-org.	34–89	71
2-furyl, 2-thienyl	$-N$-bicyclo	$-CH_2-C_6H_5$, C_6H_5, $C_6H_4(CH_3)$	Grignard	22–82	100
2-thienyl	$-N$-morpholine	C_6H_5	Grignard	60	377

aminoethyl phenyl ketone (**242**, $R^1 = C_6H_5$) does not afford a product analogous to **360**[378].



Stereochemical investigations of the reaction of β-amino-ketones containing asymmetric C-atoms have been carried out using both open-chain and cyclic Mannich bases.

In the synthesis of tertiary alcohols **361**[88] and **362**[380,381] from the corresponding ketones and Grignard reagents, a strong preference for the formation of one of the two configurational isomers of **361** and **362**, respectively, was observed.



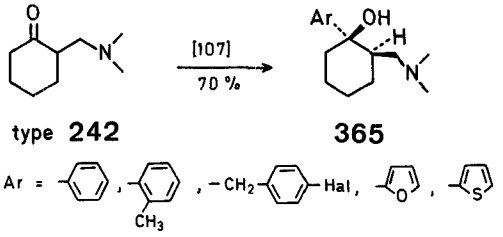
The stereochemistry of the reaction of aryl and methyl 2-aminoalkyl ketones substituted in the position α to the carbonyl group **242**, ($R^1 = C_6H_5$, CH_3, $R^2 \neq H$) with methyl-, phenyl, benzyl-, and 2-pyridylmethylmagnesium halides has been fully investigated[268,363,376,379,382]. The configurations and the diastereomer ratios obtained were determined[268,382].

was refluxed for 90 min. The product was purified from the diastereoisomer (when present) by fractional crystallization of the free base from light petroleum or ethanol or of the picrate or hydrochloride from ethanol or ethyl acetate/ethanol[382].

The reaction with phenyl-ketonic Mannich bases (**242**, $R^1 = C_6H_5$) is 100% stereospecific, affording only **363**, whereas that with methyl-ketonic bases (**242**, $R^1 = CH_3$) displays high steric yields, giving predominantly **364**. These results indicate that the methyl or phenyl group of the Grignard reagent always enters from the same side of the plane R—CO—C^α, leading preferentially to the diastereoisomers observed[382].

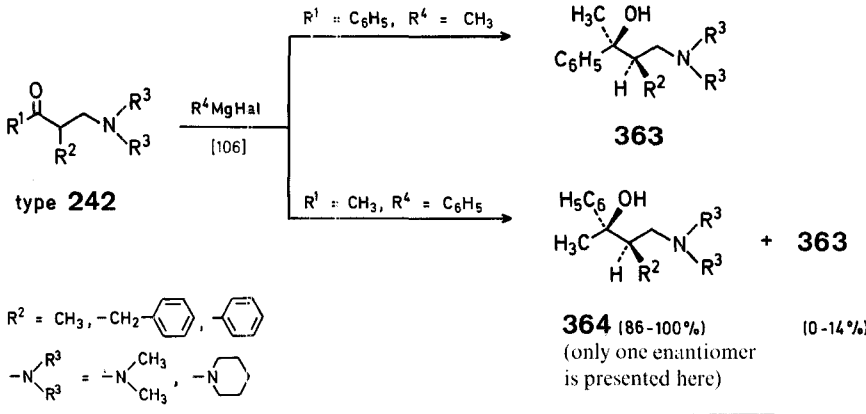
Preliminary studies on β-amino-ketones having an asymmetric C-atom in the β-position or in the alkylamino group also indicate high stereospecificity in the Grignard reaction; participation of the amine *N*-atom in the reaction was proposed to account for this fact[382].

The reaction of aryllithium reagents with Mannich bases derived from cyclohexanone are also stereospecific and afford a single product (**365**); the structure having the aryl and aminomethyl groups *trans* to each other was assigned to the product[383] (cf. also Ref.[459]) in agreement with the results described above.



[107] The 2-aminomethylcyclohexanone (0.1 mol) and aryllithium (0.19 mol) in anhydrous ether (115 ml) were refluxed for 1 hr[383].

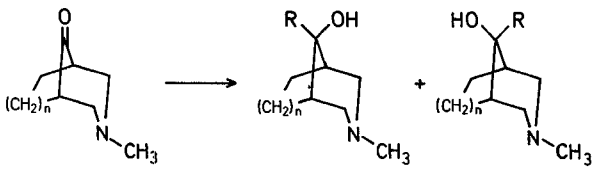
Azabicycloalkanones **348** have been subjected to reaction with several organometallic compounds[384,385]. The products are azabicycloalkanols **366** and **367**; the stereochemistry of the reaction is strongly affected by the ring size of **348**[384].



[106] A solution of the Mannich base (0.01 mol) in ether (30 ml) was added over 30 min to an ethereal solution (40 ml) of the Grignard reagent (0.025 mol). The reaction mixture

[318] H. Hellmann, J. L. W. Pohlmann, *Liebigs Ann. Chem.* **643**, 43 (1961).

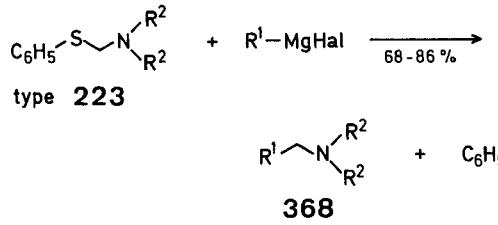
[319] H. O. House et al., *J. Org. Chem.* **30**, 2513 (1965).



348	366	367
n=1	100%	0%
n=2	31–39%	61–69%
n=3	0%	100%

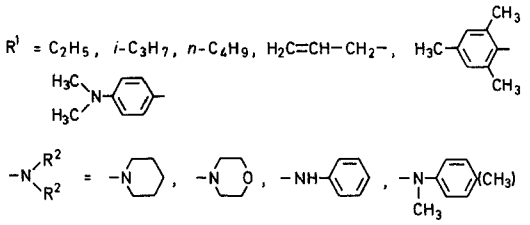
Other reactions of organomagnesium reagents with various Mannich bases (Table 38) have been carried out without investigating the stereochemistry; the amino-alcohols obtained were often studied from the pharmacological point of view, sometimes after *O*-acylation[79,88,269,379], or dehydration[81] (see also Ref.[458]) to yield aminoalkenes.

The reaction of *aminomethyl phenyl sulfides* (**223**), obtained by *S*-aminomethylation of thiophenol (Section 1.5.2.), with aliphatic or aromatic Grignard reagents provides a method for the preparation of alkylamines (including benzylamines) (**368**) having an alkyl chain of n+1 C-atoms from organic halides having a chain length of n C-atoms[256].



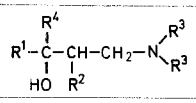
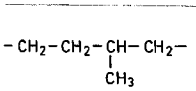
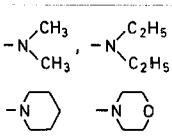
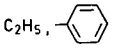
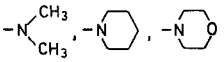
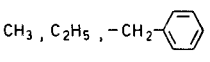
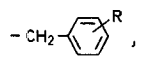
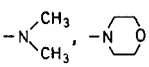
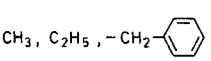
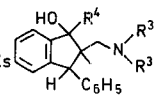
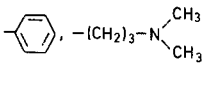
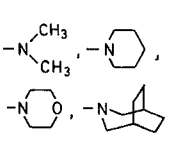
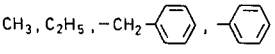
type **223**

368



Similar results have been obtained in the reactions of Grignard reagents with tertiary Mannich bases derived from *aniline* (**298,** Section 2.3.2.) or from *ammonia* (**220,** Section 1.5.2.)[386].

Table 38. Synthesis of Tertiary β-Amino-alcohols by Reaction of β-Amino-ketones (**242**, $R^2 \neq H$) with Grignard Reagents (without Regard of Stereochemical Questions)

Alcohols				Yield (%)	References
R^1	R^2		R^4		
				17–25	58
	CH_3		C_2H_5, 		98
	n-C_3H_7		CH_3, C_2H_5, 		79, 269
			CH_3, C_2H_5, 		
and alcohols				good	81
	CH_3		CH_3, C_2H_5, 	10–68	84, 100

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[321] H. Hellmann, J. L. W. Pohlmann, *Liebigs Ann. Chem.* **642**, 35 (1961).
[322] H. L. Brown, G. L. Buchanan, A. C. W. Curran, G. W. McLay, *Tetrahedron* **24**, 4565 (1968).
[323] E. M. Austin, H. L. Brown, G. L. Buchanan, R. A. Raphael, *Tetrahedron* **25**, 5517 (1969).
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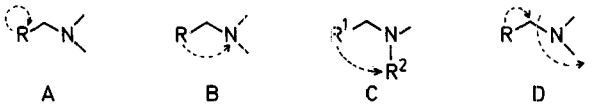
[327] A. Kamal, A. A. Qureshi, I. Ahmad, *Tetrahedron* **19**, 681 (1963).
[328] A. Kamal, Asadullah, *Pakistan J. Sci. Ind. Res.* **9**, 316 (1966).
[329] I. Fleming, M. H. Karger, *J. Chem. Soc.* [C] **1967**, 226.

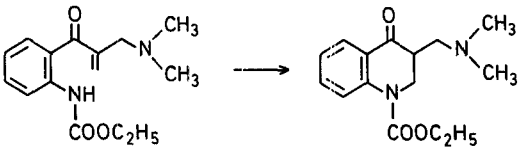
2.6. Cyclization Reactions of Mannich Bases

Mannich bases are useful intermediates for several types of cyclization reactions. These cyclizations are divided here into two groups:

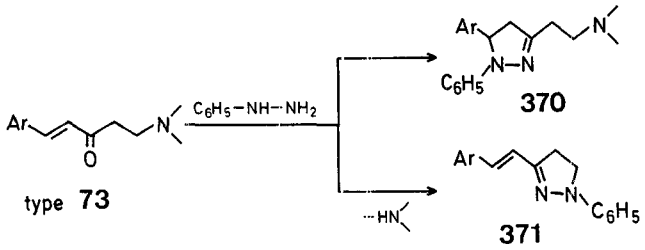
- Reactions taking place without elimination of the amino group, and which occur within the group R of the Substrate (Type A), to the N-atom (Type B), or to another position of the amino group (Type C); in the two latter cases, the reaction affords N-heterocyclic compounds.
- Reactions taking place with elimination of the amino group, and involving ring closure at the methylene C-atom (Type D).



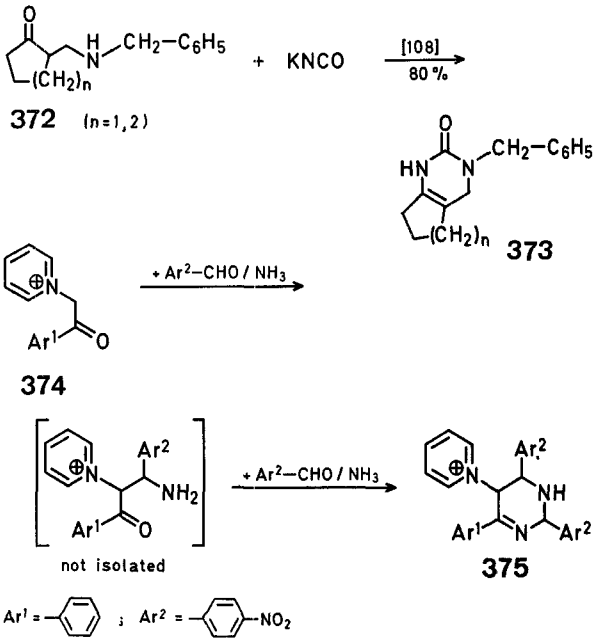
The cyclization of 2-dimethylaminomethyl-3-oxo-3-(2-ethoxycarbonylaminophenyl)-propene (type **58**) to give 3-dimethylaminomethyl-1-ethoxycarbonyl 4-oxo-1,2,3,4-tetrahydroquinoline **(369)** proceeds without participation of the amino group (Type A)[74].



The reaction of 2-aminoethyl styryl ketones (**73**) with phenylhydrazine can proceed without participation of the amino group (Type A) to give 3-(2-aminoethyl)-5-aryl-1-phenyl-Δ^2-pyrazolines (**370**), or with elimination of the amino group (Type D) to give 1-phenyl-3-styryl-Δ^2-pyrazolines **(371)**[387].



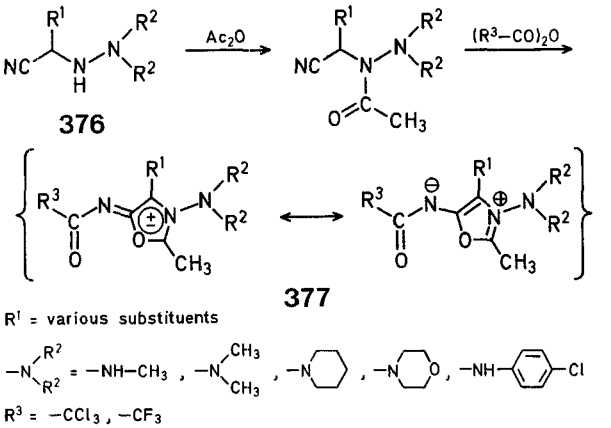
Examples of reactions of the Type B, proceeding with incorporation of the amino *N*-atom into a heterocyclic ring, are the cyclizations of 2-aminomethylcycloalkanones (**372**) with potassium cyanate[388], and of *N*-phenacylpyridinium salts (**374**) with aldehydes and ammonia[389] to afford tetrahydropyrimidine derivatives **373** and **375**, respectively, in good yields.



[108] A saturated solution of the Mannich base (0.01 mol) and potassium cyanate (0.012 mol) in water were allowed to stand for a few min at room temperature[388].

Compound **375** may pyrolyze the pyridino group on refluxing in methanol to the corresponding dihydropyrimidine, which is then dehydrogenated by the excess nitrobenzaldehyde present to give the 2,4,6-triarylpyrimidine.

Further examples of reactions of the Type B are provided by the cyclocondensations of α-hydrazinonitriles **376** (obtained from hydrogen cyanide, aldehydes, and hydrazines) by *N*-acetylation and reaction with carboxylic anhydrides to give 5-amino-1,3-oxazolium betains **(377)**[213].



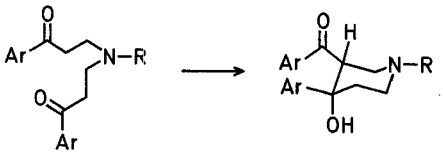
An analogous synthesis involving *N*-nitrosation instead of the above described *N*-acetylation reaction has been suggested as a method to obtain the corresponding 1,2,3-oxadiazole derivatives[213] (see also Ref.[442,443]).

Examples of cyclization according to reaction Type C are numerous. 4-Hydroxypiperidines (**379**) have been synthesized from bis-ketonic Mannich bases **378** (bis-[3-aryl-3-oxopropyl]-amines), which are obtained from aryl β-dialkylaminoethyl ket-

[330] A. Risaliti, U. De Martino, *Ann. Chim. (Roma)* **53**, 819 (1963).

[331] M. von Strandtmann, M. P. Cohen, J. Shavel, *J. Org. Chem.* **30**, 3240 (1965); *Tetrahedron Lett.* **1965**, 3103.

ones by amine exchange or directly via Mannich synthesis using primary alkylamines[64,267,390,391] (see Table 39).



378 **379**

The mechanism[390] and stereochemistry[64] of these reactions have been investigated. The cyclization reaction has been shown to be stereospecific, the products having the configuration shown in formula **379**.

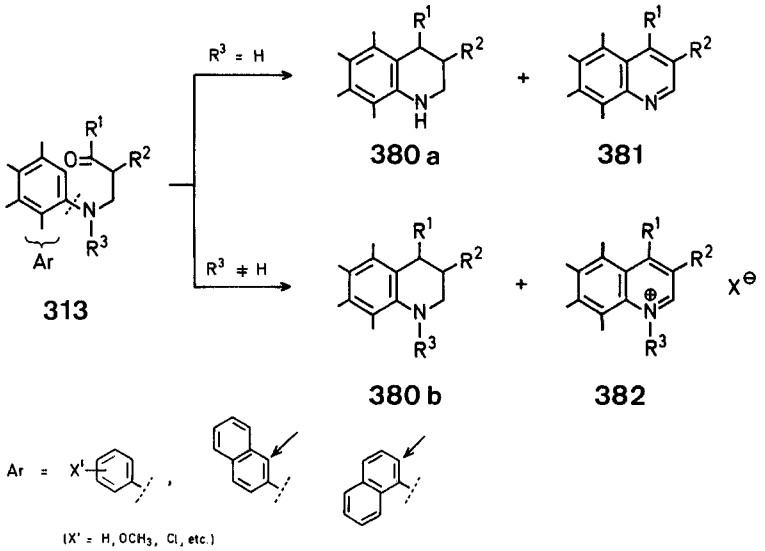
Cyclization of β-arylamino-ketones **313** affords both 1,2,3,4-tetrahydroquinoline derivatives **380** and, in equal amounts, quinoline derivatives **381**; when $R^3 \neq H$, quinolinium salts **382** are obtained instead of **381** (Table 40). The reagents used are polyphosphoric acid[343,344,345] or hydrochloric acid in ethanol[343,344]. Only quinoline **381** without the corresponding tetrahydro derivative **380** is obtained when polyphosphoric acid in the presence of trityl chloride[343,344] is used as the reagent.

Table 39. Synthesis of 3-Aroyl-4-aryl-4-hydroxypiperidines (**379**) by Cyclization of Bis-[3-aryl-3-oxopropyl]-amines (**378**)

Ar	R	Reaction Conditions	Yield (%)	References
	H			390
	*n*-C_4H_9, *c*-C_6H_{11}	[109]	95–98	267
	C_2H_5, *n*-C_3H_7, *n*-C_4H_9,	[110]	51–67	64
 X = H, 3-NO_2, 3-OCH_3, 4-OCH_3, 4-F	 (X = H, Cl, OCH_3)			391

[109] 1-Diethylamino-3-oxo-3-phenylpropane hydrochloride and the primary amine in aqueous ethanol (1:1) were allowed to stand at room temperature[267].

[110] Propylamino-3-oxo-3-phenylpropane or compound **378** (the latter obtained directly by Mannich synthesis) was allowed to react with aqueous sodium hydroxide at room temperature for 30 min[64].



[332] F. Andreani, R. Andrisano, C. Della Casa, M. Tramontini, *J. Chem. Soc.* [C] **1970**, 1157; *Tetrahedron Lett.* **1968**, 1059.

[333] P. T. S. Lau, G. F. Grillot, *J. Org. Chem.* **28**, 2763 (1963).

[334] I. E. Pollak, G. F. Grillot, *J. Org. Chem.* **32**, 3101 (1967).

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[336] G. Decodts, M. Wakselman, M. Vilkas, *Tetrahedron* **26**, 3313 (1970).

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[341] E. A. Mistryukov, N. I. Aronova, V. F. Kucherov, *Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk* **1961**, 932; *C.A.* **55**, 27310 (1961).

[342] S. Chiavarelli, H. F. Töffler, L. V. Fennoy, R. Landi-Vittory, P. Mazzeo, *Il Farmaco, Ed. Sci.* **20**, 408 (1965).

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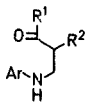
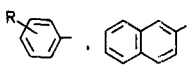
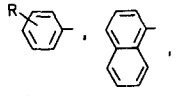
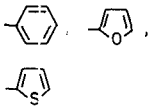
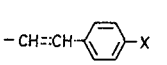
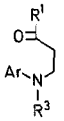
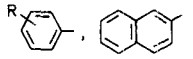
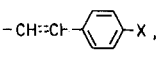
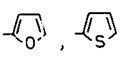
Table 40. Cyclization of β-Arylamino-ketones (**313**) to 1,2,3,4-Tetrahydroquinolines (**380**), Quinolines (**381**), and Quinolinium Salts (**382**)

β-Arylamino-ketones			Reaction Conditions	Products	Yield (%)	References
 **313** (R^3 = H)						
Ar	R^1	R^2				
	CH_3	H	[111], [112]	**380** **381**	25–50 45–90	343, 344, 392
		H		**380** **381**	25–40 17–50	75, 344, 348, 350
		H	[114]	**380** **381**	25–40 25–40	348, 351
	X = H, OCH_3, Cl					
		$-(CH_2)_{3,4}-$	[113]	**380** **381**	25–50 25–95	343, 344, 345
	CH_3, 	CH_3		**380** **381**	25–50 40–68	344, 345
 **313** (R^2 = H)						
Ar	R^1	R^3				
	CH_3		[113]	**382**[a]	25	392
		CH_3		**380** **382**[b]	40 40	348
		CH_3	[114]	**380** **382**[c]	30–40 30–45	348, 352
	X = OCH_3, Cl					
						

[a] Perchlorate.
[b] Chlorozinkates.
[c] Chlorides, chlorozinkates, and picrates.

[111] Polyphosphoric acid (2.5 ml of H_3PO_4, d = 1.75, and 4 g of P_2O_5) and β-arylamino-ketone (1 g) were heated at 70–100° for 2–3 hr[343,344,345].

[112] The β-arylamino-ketone was refluxed in 1% ethanolic hydrogen chloride for 1–2 hr[343,344].

[113] A mixture of polyphosphoric acid and β-arylamino-ketone as in [111] but containing triphenylmethyl chloride was stirred for 30 min at room temperature, or was heated at 100° for 1 hr[343].

[114] An ethanolic solution of β-arylamino-ketone (0.01 mol) and tin(IV) chloride pentahydrate ($SnCl_4 \cdot 5\,H_2O$; 0.01 mol) (the presence of arylamine hydrochloride was not always necessary) was refluxed for 1–2 hr; the chlorostannate salt partially precipitated. The mixture was then made alkaline with sodium hydroxide and the quinoline derivative extracted with ether[348]. Quinolinium salts (e. g. chlorides **382**) were obtained from the chlorostannates by destannation in boiling water.

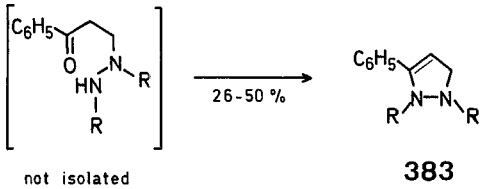
Under reaction conditions [111], the proposed mechanism involves migration of a hydride ion from the position 2 of an intermediate 1,2-dihydroquinoline derivative to the cationic position 4 of a protonated molecule of dihydroquinoline[343,345].

Tin(IV) chloride pentahydrate in ethanol [114][75,348,350,351,352] has also been successfully used as cyclizing agent; however, this salt does not possess oxidizing properties such as those of trityl chloride; thus, the formation of tetrahydroquinolines **380** is not inhibited[348].

In some cases[392], synthesis of β-arylamino-ketones **313** by an exchange reaction, and cyclization in the presence of iron(III) chloride can be carried out without isolation of **313**; the yields of quinolines **381** are often higher than 50%, showing that iron(III) chloride, unlike tin(IV) chloride, exerts an oxidizing action.

Analogous treatment of 2-aryl-2-arylaminoalkyl ketones (obtained by Mannich reaction of ketones with

benzaldehydes and arylamines) affords 2-phenylquinolines[393], whereas the cyclization of aryl 2-hydrazinoethyl ketones gives 3-phenyl-Δ^3-pyrazolines (**383**) in good yields[106] (see also Ref.[461]).

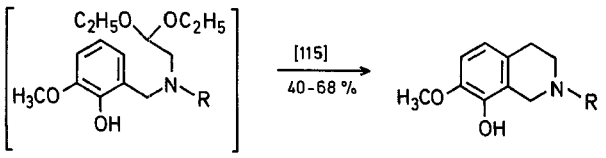


not isolated

383

R = CH_3, C_2H_5, i-C_3H_7

The synthesis of 1,2,3,4-tetrahydroisoquinolines **384** via aminomethylation of phenols using 2,2-diethoxyalkylamines, followed by cyclization and catalytic hydrogenation[394], represents another example of cyclizations of the Type C.



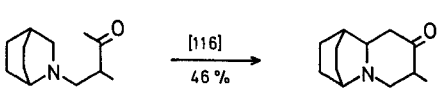
not isolated

384

R = H, CH_3,

[115] *Mannich Reaction.*· A solution of phenol, amine, and aqueous formaldehyde in ethanol was allowed to stand at room temperature for 24 hr. *Cyclization and Hydrogenation:* The unpurified Mannich base was dissolved in 6*N* hydrochloric acid. The mixture was allowed to stand at room temperature for 15–36 hr, palladium on charcoal was then added and the mixture hydrogenated at room temperature[394].

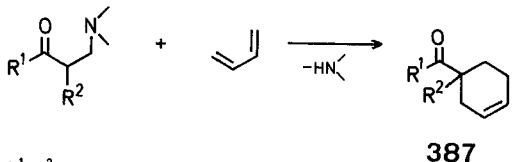
Cyclization of 2-(2-methyl-3-oxobutyl)-2-azabicyclo[2.2.2]octane (**385**; obtained by aminomethylation of butanone with 2-azabicyclo[2.2.2]octane and formaldehyde) to give 8-methyl-9-oxo-2,5-ethanooctahydroquinolizine (**386**) can be accomplished by dehydrogenation with mercury(II) acetate[51].



385 **386**

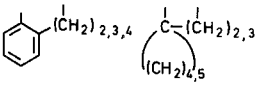
[116] Compound **385** was heated with mercury(II) acetate in acetic acid at 70° for 6 hr[51].

Cyclizations of the Type D are represented, for example, by the synthesis of cyclohexene derivatives (**387**) from Diels-Alder reactions of dienes with the vinyl derivatives formed by elimination of amine from Mannich bases.



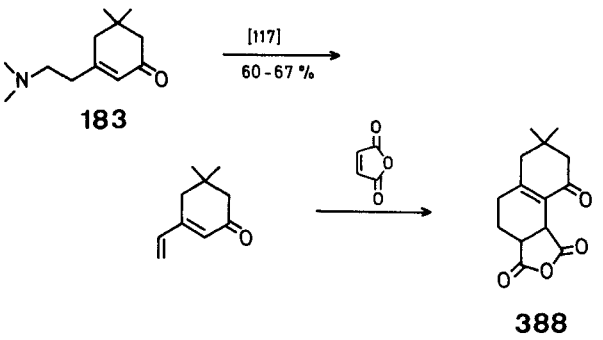
387

R^1, R^2 = Ar–CH=CH–, H or

R^1–R^2 = 

The reaction is performed with the free base in toluene at 160° (sealed tube)[59,86], or by refluxing suspensions of the hydrochloride in toluene[395,396]. It is even applicable to the synthesis of cyclohex-3-enyl styryl ketones (**387**, $R^1 = C_6H_5$—CH=CH—), due to the lack of reactivity of the styryl C=C double bond in this Diels-Alder reaction[396]. The use of Mannich bases derived from cycloalkanones in the above reaction leads to the formation of spiroketones[59,86].

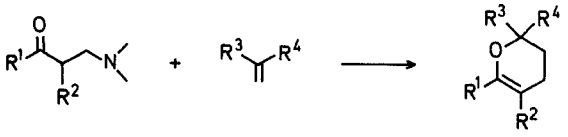
The diene intermediates formed by deamination of Mannich bases of the type **183** (derived from cyclic α,β-unsaturated ketones; cyclic "vinylogous ketonic" Mannich bases) react with dienophiles such as maleic anhydride to give the tricyclic adduct (**388**)[397].



183 **388**

[117] Compound **183** was refluxed with sodium acetate in acetic acid for 5 min, or was heated on a steam bath for 3 hr. Maleic anhydride and the unsaturated ketone were then heated without solvent for 30 min; yield: 90%[397].

Mannich bases derived from ketones can also behave as masked heterodienes in the reaction with dienophiles. The α,β-unsaturated ketone formed by elimination of the amino group undergoes cycloaddition with the dienophile to give dihydro-4*H*-pyrans (**389**)[86,278] (see also the dimerization reaction of vinyl ketones formed by deamination of ketonic Mannich bases, formula **250**, Section 2.2.; see also Ref.[85,278,289]).



389

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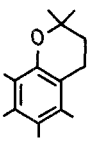
2-Amino-1-phenylalkyl ketones undergo the reaction even in the presence of dienes[278]. *o*-Phenolic Mannich bases also react as masked heterodienes to give chromans (**390**)[398,399,400].

The use of enamines as dienophiles in reactions of Mannich bases derived from 4-hydroxycoumarin, 3-hydroxynaphthoquinone, or 3-hydroxypyridine leads to the formation of condensed dihydropyran derivatives (e.g. **391** from 1-aminocyclohexenes and 2-aminomethyl-3-hydroxypyridines)[401]; in the presence of water, the hydroxy compound corresponding to **391** is obtained (see also Ref.[460]).



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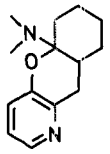
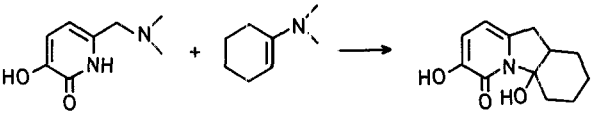


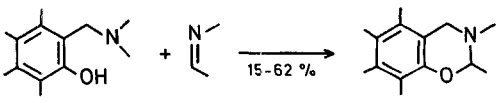
391

The reaction of 1-aminocyclohexenes with Mannich bases derived from 3-hydroxy-2-(1*H*)-pyridone affords 4a,7-dihydroxy-6-oxo-1,2,3,4,4a,6,10,10a-octahydropyrido[1,2-*a*]indoles (**392**)[176].



392

Condensed 1,3-oxazine derivatives (**393**) can be obtained from the reaction of *o*-phenolic Mannich bases with imines or aldoximes as dienophiles. Compound **394** has been obtained[402] from an 4-amino-5-hydroxyindole and 6,7-dimethoxy-3,4-dihydroisoquinoline.



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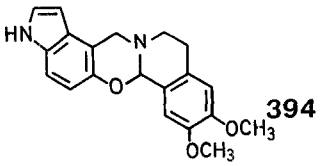
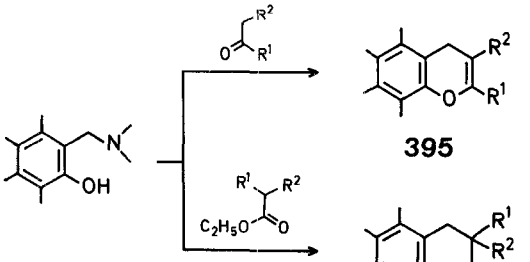


394

4*H*-Chromenes (**395**) and 3,4-dihydrocoumarins (**396**) have been obtained from the reaction of *o*-phenolic Mannich bases with ketones having two H-atoms in one of the α-positions or with alkyl carboxylates, respectively, having at least one H-atom in the α-position (Table 41). In the reaction of *o*-phenolic Mannich bases with ketones, the intermediate open-chain benzylation products (e.g. **302,** Section 2.3.2.) could in some cases be isolated and cyclized (e.g. to **303**) using phosphorus oxychloride[337].



395

396

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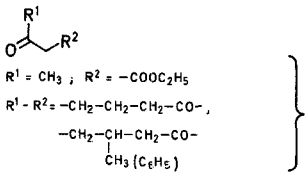
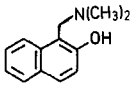
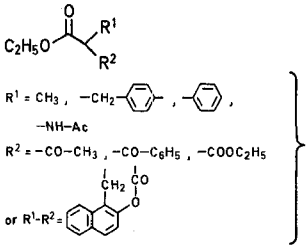
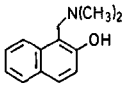
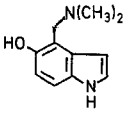
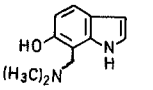
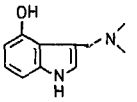
Table 41. Synthesis of 4*H*-Chromenes (**395**) and 3,4-Dihydrocoumarins (**396**) from *o*-Phenolic Mannich Bases and Alkyl Ketones or Alkyl Carboxylates, respectively

Ketone or Alkyl Carboxylate	Mannich Base	Reaction Conditions	Products	Yield (%)	References
		[118]	**395** **395**	50 26–61	403 321
		[119]	**396**	31–92	325, 403
$R^1 = CH_3$; $R^2 = NO_2$		[120]	**396**	20	310
$R^1 = COOC_2H_5$, $R^2 = -NH-CHO$		[120]	**396**	90	310
$R^1, R^2 = =P(C_6H_5)_3$		[121]	**396**	55	326

[118] The ketones and the Mannich base were heated in chlorobenzene at 65° for 3 days[321].

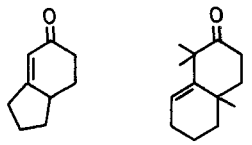
[119] The Mannich base, the ester, and magnesium ethoxide were refluxed in chlorobenzene for 40 min while nitrogen was bubbled through the mixture[325].

[120] The Mannich base, the ester, and powdered sodium hydroxide in dioxan or toluene were refluxed for several hours under a nitrogen atmosphere[310].

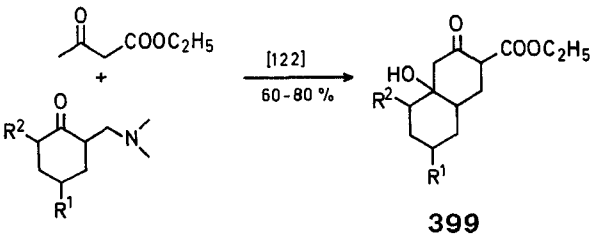
[121] The ester and the Mannich base in toluene were refluxed under a nitrogen atmosphere for 6–7 hr[326].

In the course of such chromene and dihydrocoumarin syntheses, elimination of carboxyl groups[403] or of the triphenylphosphinyl group in phosphoranes[326] were sometimes observed.

The δ-dioxo compounds (types **282** and **285**, Section 2.3.2.) obtained by *C*-alkylation of alkyl ketones or alkyl 3-oxoalkanoates with ketonic Mannich bases are useful starting materials for another type of cyclization, leading to cyclohexenone and cyclohexanone derivatives. Thus, bicyclic ketones **397** and **398** may be prepared from cyclopentanone and 4-aminobutanones[319], and from cyclohexanone and 5-amino-2-methylpentan-3-ones[46], respectively. Compounds **399** were directly synthesized from ethyl acetoacetate and Mannich bases derived from cyclohexanones[58] (see also Ref.[432]).



397 (75%) **398**



$R^1 = H$; $R^2 = CH_3$; or

$R^1 = -CH_2-CH(CH_3)-C_3H_7-n$, $-CH_2-CH(C_2H_5)-C_3H_7-n$; $R^2 = H$

399

[122] The Mannich base and ethyl acetoacetate in an ethanolic solution of sodium ethoxide were allowed to stand for 17 days at room temperature[58].

[383] A. F. Casy, N. J. Harper, J. R. Dimmock, *J. Chem. Soc.* **1964**, 3635.

[384] H. O. House, W. M. Bryant, *J. Org. Chem.* **30**, 3634 (1965).

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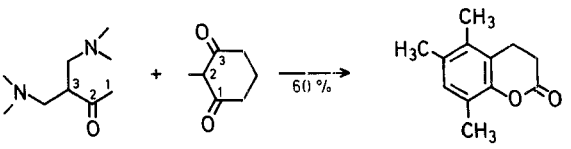
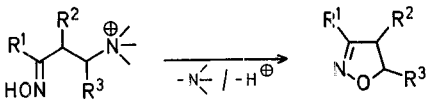
The reaction between the bis-base derived from acetone and 2-methylcyclohexan-1,3-dione is more complex; the 3,4-dihydrocoumarin **400** was suggested to be formed via a bicyclic intermediate involving positions 2 and 4 in both reagents, followed by the opening of the diketone ring[404].



400

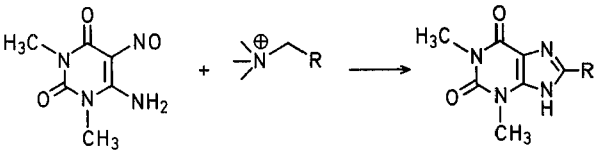
Another synthesis involving substitution of the amino group is the cyclization of Mannich bases derived from ketoximes (as the methiodides) to afford Δ^2-1,2-oxazolines (**401**; Table 42).



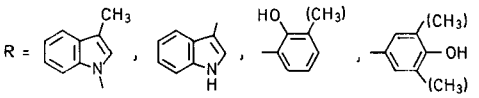
401

Some further examples of cyclizations of Type D are as follows:

– The reaction of several Mannich bases with 6-amino-1,3-dimethyl-2,4-dioxo-5-nitrosotetrahydropyrimidines affords[407] purines **402**.

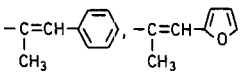
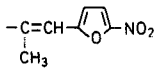


402



Dihydrofuran derivatives of the types **403** and **404** have been obtained from ferrocene Mannich bases[312,313] and from an *o*-phenolic Mannich base of a thiocolchicine derivative[408], respectively.

Table 42. Cyclization of β-Amino-ketoximes to Δ^2-1,2-Oxazolines

Δ^2-1,2-Oxazolines (**401**)			Yield (%) [Conditions]	References
R^1	R^2	R^3		
	H	H	27–50 [123]	305
	H	H	good [123]	405
				
	D	H	53[a]	406
	CH_3	H	26[b]	276
	H	CH_3	85[b]	276

[a] 100% of D-derivative.
[b] Optically active product.

[123] The methiodide of the β-amino-ketoxime was refluxed in ethanolic sodium ethoxide for 6 hr, or was heated in aqueous sodium hydroxide for 1 hr at 50°[305,405].

The mechanism of the reaction has been studied using deuterated[406] and optically active[276] oximes. Isotopic exchange was not observed and the optical activity was retained in the products, thus precluding an elimination-addition mechanism (shown to be operative in other substitution reactions).

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[390] N. Uchino, *Bull. Chem. Soc. Japan* **32**, 1009, 1012 (1959).
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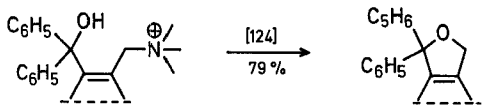
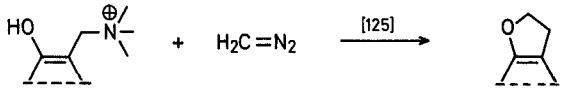
[392] B. I. Ardashev, E. S. Kagan, V. V. Mezheritskii, T. F. Sidorova, *Khim. Geterocikl. Soed. Akad. Nauk Latv. SSR* **1966**, 250; *C.A.* **65**, 2217 (1966).
[393] H. J. Roth, E. Schumann, *Arch. Pharm.* **303**, 268 (1970).
[394] J. M. Bobbitt, C. P. Dutta, *J. Org. Chem.* **34**, 2001 (1969).
[395] R. Andrisano, A. S. Angeloni, F. Del Moro, M. Tramontini *Ann. Chim. (Roma)* **55**, 968 (1965).
[396] R. Andrisano, A. S. Angeloni, M. Tramontini, *Ann. Chim. (Roma)* **55**, 143 (1965).
[397] J. H. Roth, G. Langer, *Arch. Pharm.* **301**, 707 (1968).
[398] J. Brugidou, H. Christol, *C.R. Acad. Sci.* **256**, 3149, 3323 (1963); *Bull. Soc. Chim. France* **1966**, 1974.
[399] J. Málek, M. Černý, *Synthesis* **1972**, 217.
[400] Not used.
[401] M. von Strandtmann, M. P. Cohen, J. Shavel, *Tetrahedron Lett.* **1965**, 3103.



403



404

[124] The methiodide of the Mannich base was treated with sodium in liquid ammonia and then refluxed in monoglyme for 6 days.

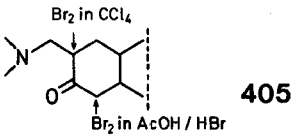
[125] The methiodide of the Mannich base was allowed to react with diazomethane in methanol/dichloromethane at 5° for 2 days[408].

The synthesis of five-membered O,P-heterocyclic compounds (**335**, Section 2.3.6.) from *o*-phenolic Mannich bases and triethyl phosphite[360], as well as the intramolecular cyclization of Mannich bases derived from 2-(1-oxopropyl)-furans to give 6-oxo-5,6-dihydro-4*H*-cyclopenta[*b*]furans[83] (**70**, Table 9) are also noteworthy examples of cyclization of Type D.

2.7. Miscellaneous Reactions of Mannich Bases

Azo coupling of Mannich bases containing amino-aryl groups is used in the synthesis of dyes (cf. Sections 1.4.2. and 1.4.4.).

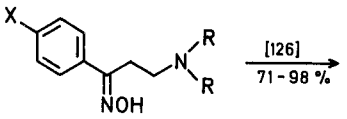
Bromination of 2-aminomethylcycloalkanones, e.g. androstane derivatives (**405**), occurs at positions 2 or 4, depending on the reaction medium; subsequent dehydrohalogenation is used in the synthesis of 2-aminomethylandrostene derivatives[409].

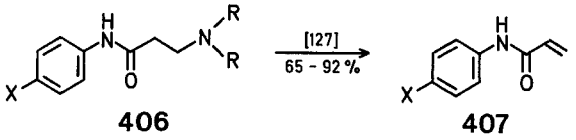


405

Bromination of 5,7-bis-[aminomethyl]tropolones takes place in position 5, azo coupling in position 7[206].

Oxime-[274] and *hydrazone formation*[304] of Mannich bases derived from 9-oxo-3,7-diazabicyclo[3.3.1]-nonanes ("bispidinones") and oxime formation of ketonic Mannich bases[276,306,405,410] have been studied with regard to the *syn-anti* stereochemistry of the oximino group. The *Beckmann rearrangement* of amino-ketoximes has been investigated[276,306,405,410]. Beckmann rearrangement of Mannich bases derived from acetophenone oximes and deamination of the resultant 3-aminopropanoic acid anilides (**406**) affords acrylanilides (**407**) in good yields.





406 407

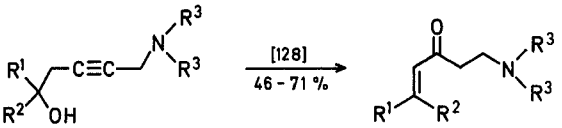
X = H, NO_2, OCH_3, Br

[126] An anhydrous ethereal solution of the β-amino-ketoxime and a benzene solution of phosphorus(III) chloride were mixed with cooling and the mixture was allowed to stand at 0° for 1 hr. The products were isolated as their methiodides[410].

[127] The methiodide of amide **406** was heated in aqueous sodium hydroxide for 1 hr at 50°[306].

Decarboxylation of 9-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylic acids (**123**)[184,411] and 1,7-dioxo-2,3,4,5,6,7-hexahydro-1*H*-2,6-methano-4-benzazonine-2,6-dicarboxylic acids (cf. **124**)[149] has been carried out in good yield by refluxing the starting materials in 25% hydrochloric acid for 16–18 hr; the reaction also allows the substitution of the carboxyl group by deuterium[411].

Hydration of the *C≡C triple bond* in Mannich bases (**408**) derived from 4-hydroxy-1-alkynes in the presence of mercury(II) salts affords α,β-unsaturated β′-amino-ketones (**409**)[373] (cf. Ref.[184]).



408 409

$R^1 = R^2 = CH_3$, C_2H_5; or

$R^1 = H$, $R^2 = n\text{-}C_3H_7$, $i\text{-}C_3H_7$; or

$R^1\text{-}R^2 = -(CH_2)_{4,5}-$, $-CH_2-CH_2-O-\overset{CH_3}{\underset{CH_3}{C}}-CH_2-$

$-N\begin{matrix}R^3\\R^3\end{matrix} = -N\begin{matrix}CH_3\\CH_3\end{matrix}$, $-N\begin{matrix}C_2H_5\\C_2H_5\end{matrix}$, $-N$

[128] Mercury(II) sulfate was added in portions (every 30 min) to a stirred solution of the Mannich base in 10% sulfuric acid. The stirred mixture was heated at 60–63° for 6 hr[373].

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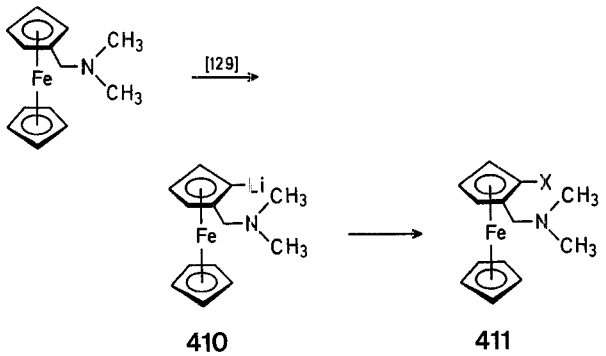
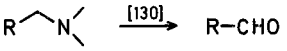
Metallation of aminomethylferrocenes with buthyllithium[312,412,413] takes place at the position adjacent to the aminomethyl group, which appears to activate the substrate for the reaction[312]. In derivative **410**, the Li-atom can be substituted by chlorine[414] or deuterium, and by carbonyl- or hydroxy groups[312,415], or the diphenylphosphinyl group[416] to give products **411** in good yields.



[129] A solution of butyllithium in hexane was added during 10 min to an ethereal solution of the Mannich base with stirring; the mixture was stirred for an additional hour[312].

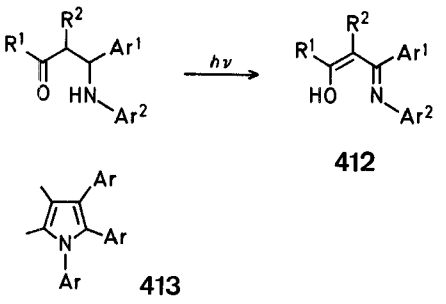
N-Acylations of secondary ketonic (including bicyclic) Mannich bases have been carried out with the usual acylation reagents, with tosyl chloride[26], and with ethyl chlorocarbonate[142]. The reaction of secondary nitroalkylamines (e.g. **167**) with nitric acid[193] affords the corresponding *N*-nitro nitroalkylamines.

Oxidation of the aminomethyl group in Mannich bases with manganese(IV) oxide affords aldehydes. The reaction is particularly useful in the ferrocene series, affording ferrocene-aldehydes in 5–55% yields[417].



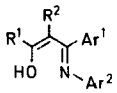
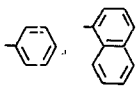
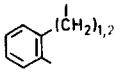
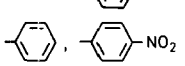
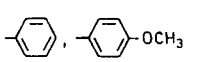
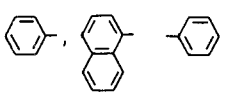
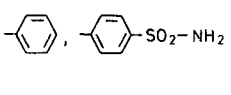
[130] The Mannich base (1 mol) and manganese(IV) oxide (10–20 mol) were allowed to react in chlorohydrocarbon solvents at 20–80° for 3–60 hr[417].

The *photochemical reactivity* of several 2-arylaminoalkyl ketones has been investigated[418–421]; irradiation in methanol or tetrahydrofuran for 6–24 hr affords imines **412** as the main products (Table 43). By-products observed include deaminoalkylation products[419] (which in some cases may even be the main products) and 1-arylpyrroles (**413**), which are formed by fragmentation reactions[418,420].



Some 2- and 3-substituted 3-amino-1-oxo-1-phenylpropanes have been *photocyclized* to give 2-amino-1-hydroxy-1-phenylcyclopropanes in good yield[421].

Table 43. Synthesis of Aryl 2-Hydroxy-1-alkenyl Ketone *N*-Arylimines (**412**) by Photodehydrogenation of 2-Arylaminoalkyl Ketones

Imines  **412**				Yield (%)	References
R^1	R^2	Ar^1	Ar^2		
$-(CH_2)_{3,4}-$				20–50	418
				24–60	418, 420
				7–70	21, 418, 419

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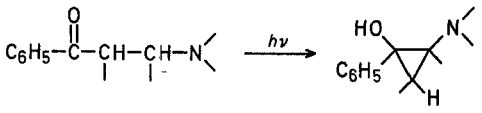
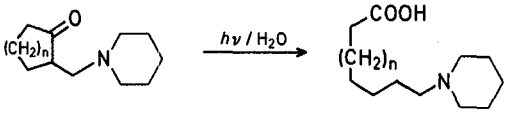


Mannich bases derived from cycloalkanones undergo *photolysis* in aqueous medium to give ω-aminocarboxylic acids (e.g. **414**) in yields of 3–20%[422].



n = 1-4

414

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