Translated from *Uspekhi Khimii*, 53, 971-1013 (1984) U.D.C. 542.91+547.235+547.284

Advances in the Chemistry of β-Aminoketones

G.A.Gevorgyan, A.G.Agababyan, and O.L.Mndzhoyan

Data on the aminomethylation reaction (the Mannich reaction) for the period 1970-1980 are examined and a systematic account is given. The synthesis of β-aminoketones from various ketones (dialkyl ketones, alkyl aryl ketones, heterocyclic alkyl ketones, and cyclic ketones, as well as diketones) is discussed.
The bibliography includes 229 references.

CONTENTS

I. Introduction 561
II. Aminomethylation of ketones 561
III. The Mannich reactions with aldehydes 576

I. INTRODUCTION

The interest in β-aminoketones (Mannich bases) has been stimulated recently by the following factors: (a) β-aminoketones are intermediates in the synthesis of α,β-unsaturated ketones, β-aminoalcohols, and heterocyclic compounds; (b) β-aminoketones are potentially biologically active compounds.

The main method of synthesis of β-aminoketones is based on the aminomethylation of ketones. The extensive literature on the aminomethylation reaction, called the Mannich reaction, has been systematically represented throughout in review articles[1-13], and monographs[14,15]. A review[16] is devoted to advances in the study of the Mannich reaction during the period 1960–1970.

In our own review article[17], we considered the aminomethylation reaction using α-aminoacids as the amino-components.

It is known that β-aminoacids possess a broad spectrum of biological activity. Many of them have found applications in medical practice. Thus the hydrochlorides of 4-(n-propoxy)- and 4-(n-butoxy)-β-piperidinopropiophenones (falicaine and dyclonine) as well as the hydrochloride of 4-(n-propoxy)-β-hexamethyleneiminopropiophenone (hexacaine) are used in medical practice as local anaesthetics[18-21], the hydrochloride of 4-methyl-α-methyl-β-piperidinopropiophenone (mydocalm) is used as an anticonvulsant[22], and the hydrochloride of 6-[β-(3-phenylpyrrolidino)propionyl]-1,4-benzodioxan (pyrroxan) is an α-adrenoblocking agent[23,24].

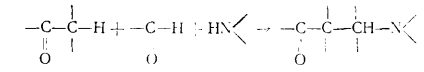
Furthermore, antibacterial[25-29], anti-inflammatory[30,31], antitumour[26,32-37], analgesic[37,38], psychotropic[39] and other properties[40-47] have been discovered in a large number of β-aminoketones.

The present review is devoted to the available literature data on the aminomethylation reactions of various ketones accumulated during 1970–1980 (and for diketones also up to 1970).

For clarity and to ensure brevity of exposition, we thought it useful to quote the biological activities of β-aminoketones in a separate column in the Tables.

II. AMINOMETHYLATION OF KETONES

One of the convenient methods of synthesis of β-aminoketones is the Mannich reaction, which consists of the condensation of a ketone containing at least one hydrogen atom in the α-position with an aldehyde (usually formaldehyde) and an amine:

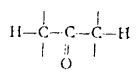


Numerous communications have been devoted to the study of the mechanism of this reaction[1,6-8,10,38,48].

1. Dialkyl Ketones

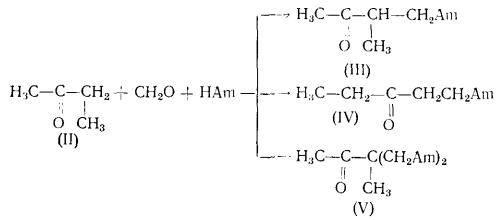
A number of studies have been made of the aminomethylation of asymmetric dialkyl ketones[49-63]. Despite the fact that the Mannich reaction has been studied for a long time, the problem of selectivity for asymmetric ketones has still not been fully solved. Some data[49] are now recognised as erroneous.

There are mobile hydrogen atoms in the α- and α'-positions in the molecules of dialkyl ketones of type (I), which suggests different modes of aminomethylation:



(I)

When ethyl methyl ketone (II) is aminomethylated, a mixture of three aminoketones (III)–(V) is formed[51]:

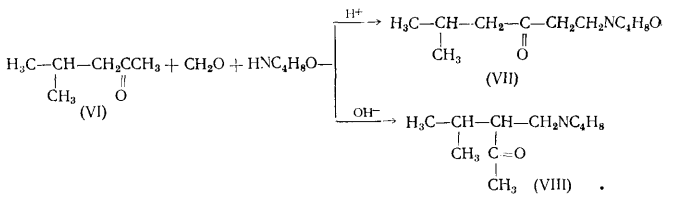


Am = $N(C_2H_5)_2$, NC_5H_{10}.

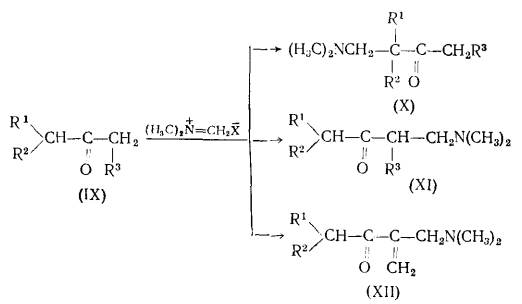
It has been shown that, with decrease of the pH of the medium, the yields increase: on heating ethyl methyl ketone, paraformaldehyde, and diethylamine in ethanol at pH 8–9 for 6 h, the overall yield of the mixture of aminoketones is 28.6%, while at pH 1 it is 43%. The formation of compound (IV) has been demonstrated by specific synthesis and also mass-spectrometrically[52].

The relation between the yields of the final products and the pH of the medium has also been considered[53].

The aminomethylation of 4-methyl-2-pentanone (VI) in ethanol in an acid medium leads to a mixture of 1-morpholino-5-methylhexanone (VII) and 1-morpholino-2-isopropyl-3-butanone (VIII) (in proportions of 69:31) with an overall yield of 81%, while in a basic medium a mixture of compounds (VII) and (VIII) is obtained with the latter predominating [(VII):(VIII) = 8:92]; the overall yield is 43%:



It has now become possible to direct aminomethylation to a particular α-carbon atom in an asymmetric ketone using immonium salts as the reagents. Thus the aminomethylation of the ketone (IX) [54–57] using the immonium salt $(CH_3)_2\overset{+}{N}=CH_2X^-$ (0.05 M, X = CF_3CO_2 or ClO_4) in trifluoroacetic acid at 72 °C leads to selective attack on the more substituted α-carbon atom with formation of compound (X):[56]



$R^1 = R^3 = H, CH_3$; $R^2 = CH_3, C_2H_5$, n-C_4H_9

$R^1 + R^2 = (CH_2)_n$, $n = 3–5$.

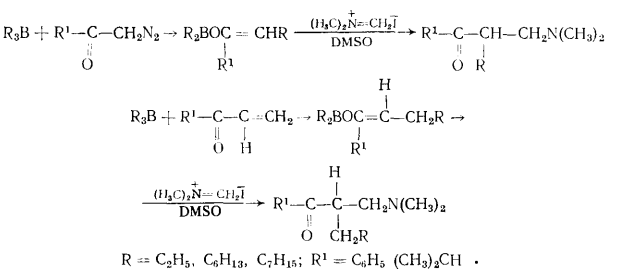
Table 1. The regioselective synthesis of the β-aminoketones (X) and (XI) from asymmetric ketones $RCOCH_3$ and immonium salts[55].

Immonium salt	R	Overall yield, %	(X):(XI)
Solvent F_3C-COOH			
$(CH_3)_2\overset{+}{N}=CH_2CF_3COO^-$	$C_6H_5CH_2$	95	85:15
ditto	CH_3CH_2	85	80:20
»	$(CH_3)_2CH$	90	85:15
»	cyclopentyl	90	95:5
»	cyclohexyl	70	69:31
Solvent CH_3CN			
$(C_3H_7)_2\overset{+}{N}=CH_2ClO_4^-$	cyclopentyl	80	0:100
ditto	$(CH_3)_2CH$	95	0:100
»	cyclohexyl	90	0:100

On increase of the concentration of the immonium ion to 2 M, the reaction product is compound (XI), which is formed, according to the authors, as a result of the isomerisation of the aminoketone (X).† In acetonitrile at 72 °C and in the presence of a 2 M concentration of the immonium ion, the reaction product is compound (XI), whose formation is accompanied by that of the aminoketone (XII), which contains the vinyl group. The sterically hindered dipropyl(methylene)ammonium salt reacts specifically with the methyl group in alkyl methyl ketones in acetonitrile (Table 1).

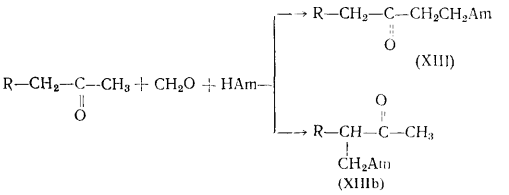
From the experimental data, the authors conclude that the regioselectivity is greatly influenced by the size of the group at the nitrogen atom, the solvent, the concentration of the immonium salts, and the counterion.

Enol borinates also react regiospecifically with dimethyl(methylene)ammonium iodide in dimethyl sulphoxide (DMSO).[54] The reaction constitutes an effective method of synthesis of Mannich bases from α-diazoketones or α,β-unsaturated ketones and aldehydes:



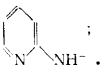
R = C_2H_5, C_6H_{13}, C_7H_{15}; $R^1 = C_6H_5$ $(CH_3)_2CH$.

Despite the possibility of aminomethylation at both methylene groups of the substituted acetone molecule[58–63], the products of aminomethylation at the methyl group have been characterised[58] [compound (XIIIa)], while other workers[59–61] characterised the products of aminomethylation at the methylene group [compound (XIIIb)]:

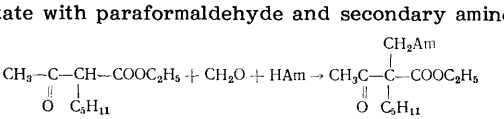


(a) R = $CH_2CH_2COOC_2H_5$, CH_2CH_2CN, $CH_2CH{=}C(Cl){-}CH_3$, $CH_2CH_2C_6H_4OCH_3$-*m*;

$CH_2CH_2{-}C(C_7H_4{-}OH\text{-}o)_2CH_3$; Am = $N(C_2H_5)_2$, NC_5H_{10}, $N(C_3H_7)_2$

(b) R = C_6H_5,  ; Am = $N(CH_3)_2$, $N(C_2H_5)_2$ NC_4H_8O

Optically active Mannich bases (XIV) have been obtained in 36–50% yield by the reaction of (+)-ethyl 2-methylbutylacetoacetate with paraformaldehyde and secondary amines[62]:



Am = $N(CH_3)_2$, $N(C_2H_5)_2$, $N(C_3H_7)_2$, $N(n\text{-}C_5H_{11})_2$, NC_5H_{10}, NC_4H_8O, $N(CH_2CH_2OH)_2$.

The above justifies the conclusion that, regardless of the pH of the medium, the aminomethylation of asymmetric dialkyl ketones leads to the formation of the α- and α′-aminomethyl derivatives and that in an acid medium the reaction involves

†In our view, the direct formation of compound (XI) cannot be excluded.

preferentially the less substituted α-carbon atom, while in an alkaline medium it involves the more substituted α-carbon atom. It has been suggested that the observed relation between the regioselectivity of the aminomethylation and the reaction conditions reflects the change in the relative rates of the enolisation and addition stages.

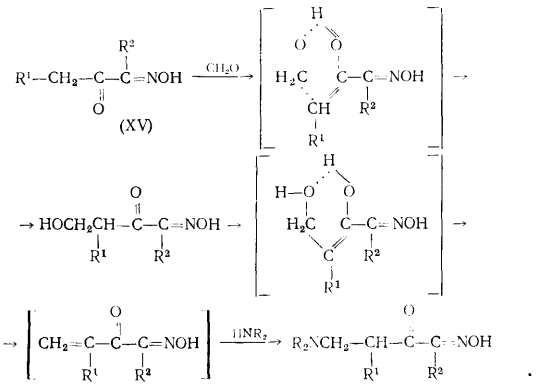
2. Isonitrosoketones

A number of studies have been made of the aminomethylation of α-isonitrosoketones[64-67]. It has been shown that the products of the aminomethylation of α-isonitrosoketones (XV) are mono-, di-, and tri-substituted derivatives (Table 2).

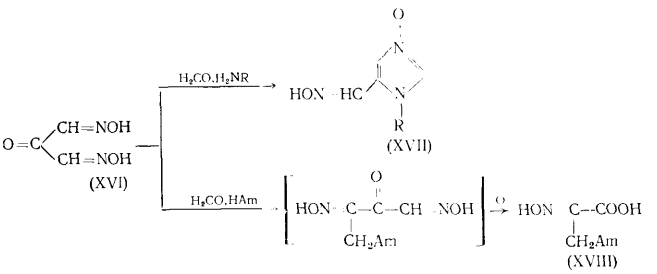
Table 2. The Mannich reaction involving substituted isonitrosoketones.

Initial ketone	Aminomethylation product	Yield, %	Refs.
$CH_3CH_2-C(=O)-C(=NOH)-CH_3$	$CH_3-CH(CH_2Am)-C(=O)-C(=N-OH)-CH_3$ Am = $N(CH_3)_2$, NC_4H_8, NC_5H_{10}	47—75	[64]
$CH_3-C(=O)-C(=NOH)-R^1$ R^1 = CH_3, C_6H_5, $COOC_2H_5$	$AmCH_2-CH(-C(=O)-C(=NOH)-R^1)-AmCH_2$ Am = $N(CH_3)_2$, $N(C_2H_5)_2$, NC_4H_8, NC_4H_8O, NC_5H_{10}	31—90	[64]
$CH_3-C(=O)-CH(-NOH)$	$AmCH_2-CH(-C(=O)-CH=NOH)-AmCH_2$ Am = $N(C_2H_5)_2$, NC_4H_8O, NC_5H_{10}	26—70	[65]
$C_5H_{10}NCH_2-CH(-C(=O)-CH=NOH)-C_5H_{10}NCH_2$	$C_5H_{10}NCH_2-CH(-C(=O)-C(=NOH)-CH_2Am)-C_5H_{10}NCH_2$ Am = $N(C_2H_5)_2$, NC_5H_{10}	35, 51	[65]

Hahn and Bartnik[64] proposed a probable reaction mechanism consisting of the following stages: (1) condensation of the formaldehyde with the CH acid component in which the amine behaves as a basic catalyst; (2) dehydration of the hydroxymethyl derivative formed; (3) nucleophilic addition of the amine to the double bond facilitated by the vicinity of the carbonyl group.

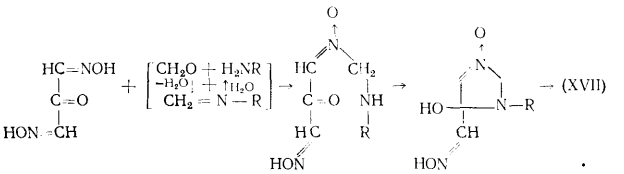


The mode of reaction of di-isonitrosoacetone (XVI) with formaldehyde and primary and secondary amines has been investigated. The reaction products are respectively derivatives of 5-(hydroxyiminomethyl)imidazole 3-*N*-oxide (XVII) and the oxime of aminopyruvic acid (XVIII):[67]



R = CH_3, C_2H_5, C_6H_{11}, $C_6H_5CH_2$, *p*-$CH_3OC_6H_4$, *p*-$C_2H_5OC_6H_4$
Am = NC_4H_8O, NC_5H_{10}.

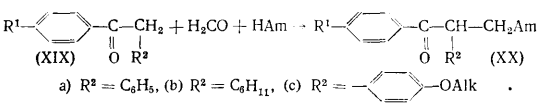
The authors explain the formation of compound (XVII) in the following way:



This is consistent with the data obtained by Lettau[68-72] for the condensation of isonitrosoketones with aldehydes and primary amines.

3. Alkyl Aryl Ketones

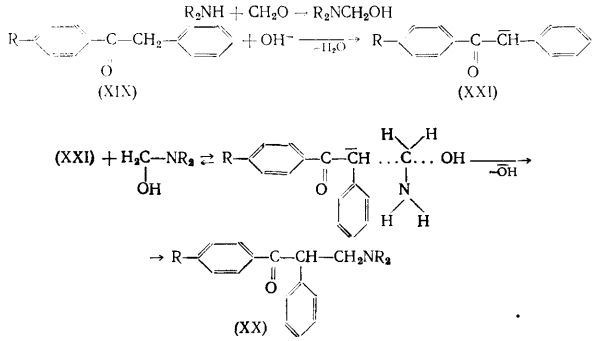
In order to investigate the problem of structure–reactivity relation, a large group of β-aminoketones (XX) have been synthesised by the Mannich reaction from substituted benzyl phenyl and cyclohexylmethyl phenyl ketones (XIX) (Table 3):[38,73-80]



a) $R^2 = C_6H_5$, (b) $R^2 = C_6H_{11}$, (c) R^2 =

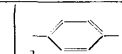
It is known that the course of the Mannich reaction and the yields of products are significantly influenced by the pH of the medium[3,81]. The results of studies in recent years fully confirm this hypothesis[38,51,73-77]. Thus the yield does not exceed 28% in the condensation of the ketone (XIXa), paraformaldehyde, and pyrrolidine in an acid medium (pH 1–2) on heating for 30 h. On the other hand, in a

basic medium (pH 8–9) heating in the course of 4 h ensures a 70–90% yield of the aminoketone (XX):



(XIX) (XXI) (XX)

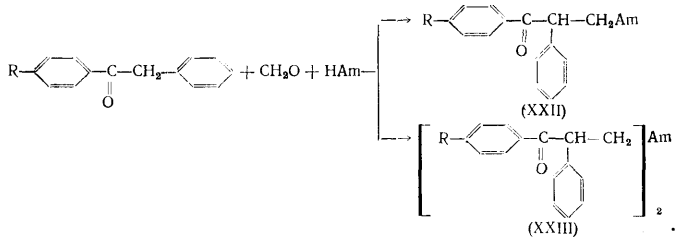
Table 3. Aminomethylation of benzyl phenyl and cyclohexylmethyl phenyl ketones.

R^1–C(=O)–CH_2R^2		R^1–C(=O)–$CHCH_2Am$ (R^2)	Yield, %	Biological activity	Refs.
R^1	R^2	Am			
H, HO, n-alkoxy-(C_1–C_7), iso-C_3H_7O, iso-$C_5H_{11}O$	C_6H_5	NC_5H_{10}	38–92	analgesic, anaesthetic	[73]
H, HO, n-alkoxy-(C_1–C_5), iso-$C_5H_{11}O$	C_6H_5	NC_4H_8O	46–89	—	[73]
H, HO n-alkoxy-(C_1–C_7), iso-C_3H_7O, iso-$C_5H_{11}O$	C_6H_5	NC_4H_8	28–91	ana.' analgesic	[74]
H	 R^3 = H, HO, n-alkoxy-(C_1–C_5), iso-C_3H_7O, iso-C_4H_9O, iso-$C_5H_{11}O$	NC_4H_8	32–62	ditto	[75]
H, n-alkoxy-(C_1–C_5)	C_6H_5	NC_6H_{12}	61–75	anti-inflammatory, antipyretic	[76]
H, HO, F, C_4H_9O, iso-C_3H_7O		NC_5H_{10}, NC_6H_{12}, HN–$CH(CH_3)_2$	43–91	ditto	[77]
H, n-alkoxy-(C_1–C_5), iso-C_3H_7O, iso-$C_5H_{11}O$	C_6H_5	$HNCH_3$, HNC_4H_9	47–80	loss of analgesic activity	[78]

In all probability the reaction proceeds via the S_N2 mechanism[38]. Presumably, with increase of the pH of the medium, the concentration of the carbanion (XXI) increases, which tends to increase the rate of reaction.

The opposite relation is observed in the aminomethylation of the ketones (XIXb).[77] Thus, when a reaction mixture consisting of equimolar amounts of cyclohexylmethyl phenyl ketone, paraformaldehyde, and hexamethyleneimine is heated for 15 h at pH 1.0 in dioxan, the yield is 83%, while at pH 7.0–8.0 it does not exceed 25–30%. In this case the reaction apparently proceeds via the electrophilic substitution mechanism (S_E).

When primary amines are used, the disubstituted derivative (XXIII) is formed together with the monosubstituted products (XXII):[75]



(XXII) (XXIII)

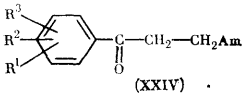
It is known that the biological activity of β-aminoketones is significantly influenced by the presence and position of an alkoxy-group in the benzene ring, the structure of the amino-group, and also the substituent in the α-position[18].

Pharmacological studies of the salts of the aminoketones (XXa, Am = NC_5H_{10}) showed that the methoxy- and ethoxy-derivatives completely lack a surface-anaesthetic activity. An increase of the length of the alkoxy-group to four carbon atoms results in the appearance of a moderate activity, which weakens as the length of the hydrocarbon chain is increased further to six atoms[45]. The hypotensive activity of these compounds increases with increase of the length of the alkoxy-group from methoxy- to pentoxy, after which it falls. The replacement of piperidine by pyrrolidine in the molecule of compounds (XXa) results in the appearance of both terminal and conductor anaesthesia. Some of them approach dicain as regards their anaesthetic activity and morphine as regards their analgesic activity[73].

The anti-inflammatory activity of the aminoketones (XX) has been investigated as a function of their capacity to arrest the haemolysis of rat erythrocytes. It has been shown that *in vitro* they all suppress the haemolysis of erythrocytes at a concentration of 10^{-3}–10^{-4} M and, after an increase in the length of the chain of the alkoxy-group, at 10^{-5}–10^{-9} M.[31]

A change in the position of the alkoxy-group, as in compound (XXc, Am = pyrrolidine), and also the replacement of the cyclic amine by a primary amine (methylamine, butylamine) lead to the loss of analgesic activity[75,78]. The replacement of the phenyl group in the α-position by the cyclohexyl group, as in compound (XXb), is not reflected in the anti-inflammatory activity of the compounds, but some of them acquire antipyretic properties[77].

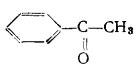
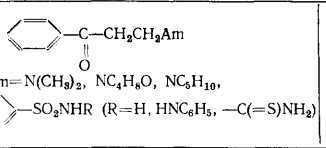
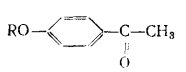
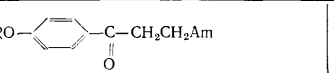
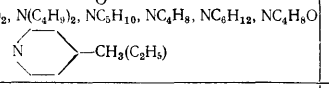
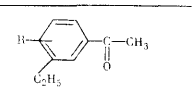
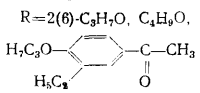
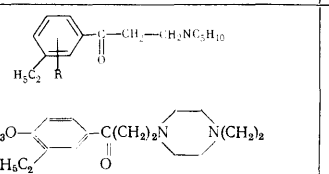
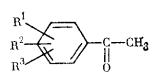
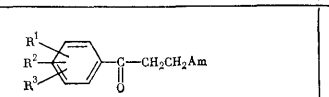
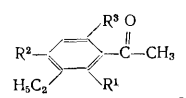
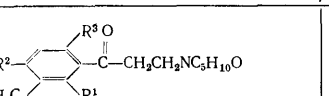
In order to investigate the relation between the chemical structure and biochemical activity, Schrotter and co-workers also synthesised a large group of β-aminoketones (XXIV) (Table 4):[82–87]



(XXIV)

Piperidino-derivatives are the most active among the aminoketones (XXIV, R^1 = H, R^2 = 4-alkoxy-, R^3 = C_2H_5) and the intensity of the anaesthesia increases up to $R^2 = n\text{-}C_3H_7O$, remains constant up to $R^2 = n\text{-}C_6H_{13}O$, and then falls[83]. On the other hand, the maximum duration of the activity of the compound has been noted for the *n*-heptoxy-derivative. Compounds with iso-groups are inferior to the *n*-alkoxy-derivatives both as regards the intensity of the anaesthesia and the duration of the activity. It has been noted that, when the methyl or ethyl group is introduced into the 4-position of the piperidine residue, the strength and duration of the activity increase. The replacement of the 4-alkoxy-group in aminoketones (XXIV) by an alkoxy-group

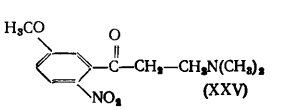
Table 4. Aminomethylation of acetophenones.

Initial ketone	Aminomethylation product	Yield, %	Biological activity	Refs.
	 Am=$N(CH_3)_2$, NC_4H_8O, NC_5H_{10}, HN– –SO_2NHR (R=H, HNC_6H_5, $-C(=S)NH_2$)	31—88	—	[88—90, 111]
 R=CH_3CO, C_4H_9CO, n-alkyl-(C_1—C_{10}), iso-C_3H_7, iso-C_4H_9, iso-C_5H_{11}, $C_4H_9O(CH_2)_2$, $C_5H_{11}O(CH_2)_2$, $C_6H_{13}O(CH_2)_2$, $C_2H_5O(CH_2)_4$, $C_3H_7O(CH_2)_4$, $C_4H_9O(CH_2)_4$	 Am=$N(CH_3)_2$, $N(C_4H_9)_2$, NC_5H_{10}, NC_4H_8, NC_6H_{12}, NC_4H_8O 	29—63	local anaesthetic, bacteriostatic	[82, 87]
 R=2(6)-C_3H_7O, C_4H_9O, 		41—63	ditto	[83—85, 94]
 R^1=Cl, Br, NO_2, iso-C_3H_7, OH; R^2=H, HO, CH_3, n-alkoxy-(C_1—C_6), $C_2H_5O(CH_2)_4O$, $C_3H_7O(CH_2)_4O$, $C_4H_9O(CH_2)_4O$; R^3=H, CH_3, CH_3O, Br, NO_2	 Am=$N(CH_3)_2$, $N(C_2H_5)_2$, $N(C_4H_9)_2$, NC_4H_8, NC_4H_8O, NC_5H_{10}, NC_6H_{12}	55—89	local anaesthetic	[86, 87, 98, 99, 112]
 R^1=C_3H_7, C_4H_9, H; R^2=H, C_3H_7, C_4H_9; R^3=H, C_3H_7, C_4H_9		*	ditto	[87]

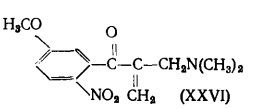
*The yields are given in grams.

[R^2 = 4-Alko-$(CH_2)_nO$; n = 2, 4] made it possible to obtain substances with the same activity but a greater duration of the latter[84]. Antiparasitic and antibacterial properties have been found in some aminoketones of the (XXIV) series[85,87].

The aminomethylation of substituted acetophenones has also been studied[43,88—116] (Tables 4—6). It has been shown that, when 5-methoxy-2-nitroacetophenone reacts with formaldehyde and dimethylamine hydrochloride in 1-butanol, β-dimethylaminomethyl-5-methoxy-2-nitropropiophenone (XXV) is formed[95,96]:

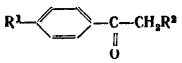

(XXV)

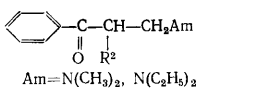
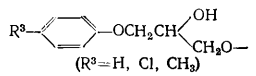
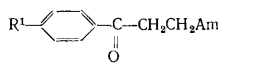
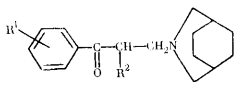
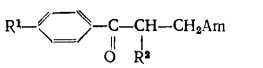
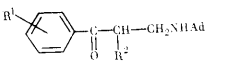
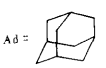
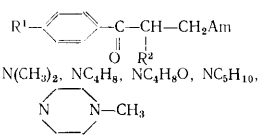
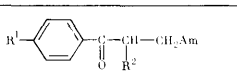
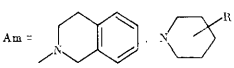
Subsequently, Back established that the aminomethylation of 2-nitro- and 2-ethoxycarbonyl-aminoacetophenones leads to the formation of 2-nitro- and 2-ethoxycarbonylamino-α-dimethylaminomethylacrylophenones (XXVI) in addition to the expected propiophenone derivatives[92,94]:


(XXVI)

The authors explained the formation of compound (XXVI) by the fact that, under the conditions of the Mannich reaction,

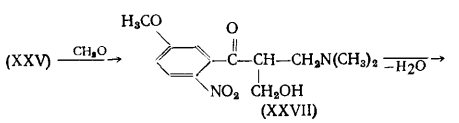
Table 5. Aminomethylation of α-substituted acetophenones.



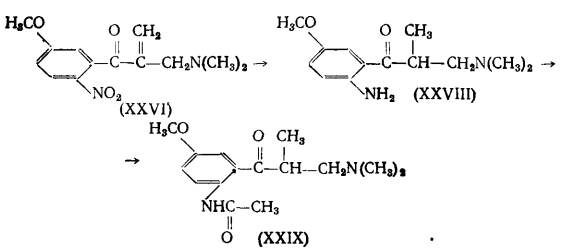
R^1	R^2	Reaction product	Yield, %	Biological activity	Refs
H	H, CH_3, C_6H_5	 Am=$N(CH_3)_2$, $N(C_2H_5)_2$	54—89	antimicrobial	[30]
Phenoxy-, substituted phenoxy-,  (R^3=H, Cl, CH_3)	H	 Am=$N(C_2H_5)_2$, $N(C_4H_9)_2$, NC_4H_8O, NC_5H_{10}	*	local anaesthetic	[100]
4-F, 4-Cl, 4-Br, 2(4)-benzyloxy-, 4-fluorobenzyloxy-, 2,2-dimethylaminomethoxy-	H, CH_3, C_2H_5, C_3H_7		42—72	anticough	[101]
Hal, NO_2, iso-C_3H_7	H, CH_3, C_2H_5	 Am=$N(CH_3)_2$, NC_5H_{10}, NC_6H_{12}	*	hypotensive	[91, 102]
H, NO_2, Hal, OH	H, lower alkyl	 	20—40	antimicrobial	[103, 104]
H, CH_3, HO, F, F_3C, C_4H_9, NO_2, CH_3, C_2H_5, CH_3SO, CH_3SO_2	H, CH_3, C_3H_7, C_4H_9	 Am=$N(CH_3)_2$, NC_4H_8, NC_4H_8O, NC_5H_{10},	20—76	stimulators of central nervous system	[106]
H, F	—	  R = 2(3, 4)-CH_3, 4-C_6H_5	55—85	ditto	[40, 106]

*The yields are given in grams.

the *C*-hydroxymethyl compound (XXVII) is formed from compound (XXV) and its dehydration leads to compound (XXVI):

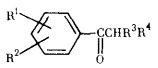


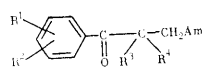
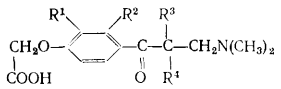
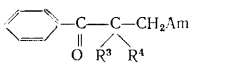
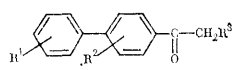
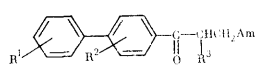
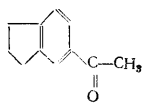
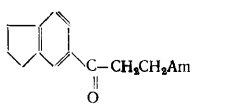
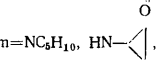
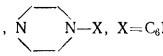
This has been confirmed by both physicochemical analytical methods and by various reactions of compound (XXVI).[92,94] Thus catalytic hydrogenation of compound (XXVI) and acetylation of the reduction product (XXVIII) lead to the formation of 2-acetamido-5-methoxy-α-methyl-β-dimethylaminopropiophenone (XXIX):



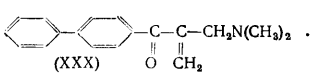
The formation of an acrylophenone derivative has been described also by Mann et al.[97] in relation to compound (XXX) as an example:

Table 6. Aminomethylation of substituted acetophenones.



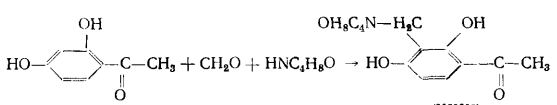
R^1, R^2	R^3, R^4	Reaction product	Yield, %	Biological activity	Refs.
Cl, CH_3, CH_3O, C_2H_5O	H, CH_3	 Am = NC_5H_{10}; NC_4H_8O	42—59	stimulators of central nervous system	[40]
H, Cl	H, CH_3, C_2H_5		22—93	diuretic	[43]
H, CH_3	H, CH_3, OCH_3	 Am=NC_4H_8, NC_5H_{10}	62—91	—	[110]
 R^1=H, Cl, NO_2, CH_3O; R^2=H, NO_2, CH_3; R^3=H, CH_3, C_6H_5		 Am = $N(CH_3)_2$, NC_5H_{10}	9—81	—	[97]
		 Am=NC_5H_{10}, HN—, —X, X=C_6H_5, *o*-(Cl, F, CH_3, CH_3O)C_6H_4, *m*-ClC_6H_4, *p*-(Cl, F)C_6H_4, CH_3, CH_2CH_2OH, $COOC_2H_5$, $CH_2C_6H_5$, 	*	sedative	[108]

*The yields are given in grams.

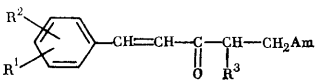

(XXX)

3,4,5-Trisubstituted acetophenones containing nitro-groups in the 3- and 5-positions are aminomethylated with difficulty (with a yield of 8—12%).[98]

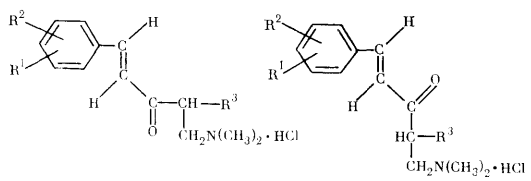
In the case of resacetophenone, the aminomethyl group enters the ring of compound (XXXI):[109]


(XXXI)

The aminoketones (XXXII) have been obtained by the condensation of substituted styryl ketones, paraformaldehyde, and amine hydrochlorides[26,34,36,60,107,117—128] (Table 7):


(XXXII)

According to infrared spectroscopic data, 4-dimethylaminomethyl-1-phenyl-1-ionen-3-ones (XXXII, $R^3 = C_5H_{11}$) exist in the *S-cis*- and *S-trans*-forms[118]:

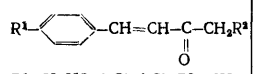
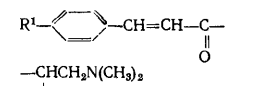
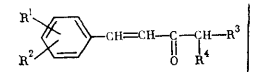
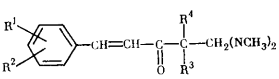
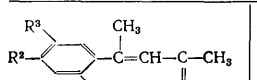
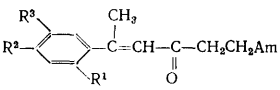
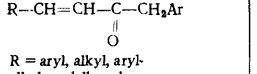
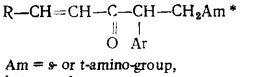
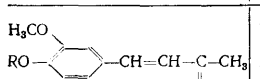
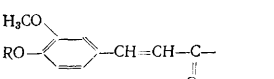
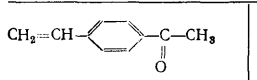
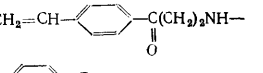

S-trans-(XXXII) *S-cis*-(XXXII)

Compounds (XXXII) possess various biological properties[26,34,36,60,107,120,122,123]. In particular, many hydrochlorides of derivatives of 5-dimethylamino-1-substituted phenylpent-1-en-3-ones [XXXII, R^1 = H or 2(3)-Cl; R^2 = H or 4(6)-Cl; $R^3 = (CH_2)_4CH_3$] exhibit pronounced cytotoxic properties[34,36,122].

Their antimitochondrial properties have been investigated[120,122]. It has been shown that their hydrochlorides manifest a high inhibiting activity, while the methiodides lack these properties. The antimitochondrial properties of the products of the deamination of the aminoketones (XXXII)

have also been studied and it has been shown that the unsaturated ketones are inactive in this respect[120].

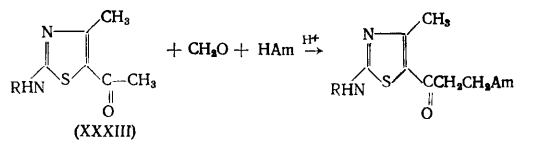
Table 7. Aminomethylation of styryl ketones.

Initial ketone	Aminomethylation product	Yield, %	Refs.
 R^1=H, HO, 2-Cl, 4-Cl, R^2=CH_3, n-C_5H_{11}		37—43	[26, 36, 120]
 R^1=H, 2-(3,4-)Cl, $N(CH_3)_2$; R^2=H, 4(6)Cl; R^3=H, n-C_5H_{11}; R^4=H, CH_3	 R^1=R^2=H; R^3=n-C_5H_{11}; R^4=CH_3	29—56	[36, 107, 118—123]
 R^1=H, CH_3; R^2=CH_3O, C_2H_5O; R^3=H, iso-C_3H_7	 Am=$N(CH_3)_2$, $N(C_2H_5)_2$, NC_4H_8, NC_4H_8O, NC_5H_{10}	43—50	[124, 125]
 R = aryl, alkyl, aryl-alkyl, arylalkenyl Ar = aryl with various substituents	 Am = s- or t-amino-group, heterocycle	**	[126]
 R=H, Ac		**	[127]
	 R=H, OH, CH_3, CH_3O, COOH, NO_2	24—62	[128]

*Possess antimicrobial and antimitotic activity.
**The yields are given in grams.

4. Heterocyclic Methyl Ketones

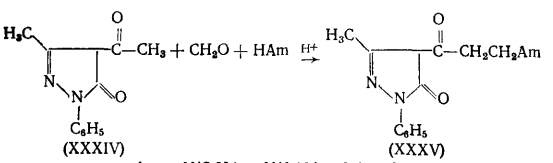
A number of studies have been made on the aminomethylation of heterocyclic methyl ketones[41,101,129—134]. It has been shown[130] that 2-substituted 5-acetyl-4-methylthiazoles (XXXIII) can be aminomethylated in concentrated hydrochloric acid or in a 2:1 acetic acid–dioxan mixture with a yield of 40–90%. The aminomethylation in ethanol, acetic acid, and dimethylformamide was unsuccessful:



(XXXIII)

R = H, $CH_3C(=O)$—, $C_6H_5C(=O)$—, m-$NO_2C_6H_4C(=O)$—, $ClCH_2C(=O)$—, Cl_3CH—$C(=O)$—, CH_3CH=CH—; Am = $N(CH_3)_2$, $N(C_2H_5)_2$, $N(iso\text{-}C_3H_7)_2$, NC_4H_8O, NC_5H_{10}

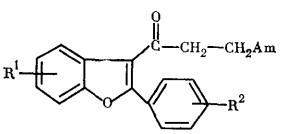
The aminoketones (XXXV) have been obtained in 60% yield by the aminomethylation of 4-acetyl-3-methyl-1-phenyl-2-pyrazolin-5-one (XXXIV) in ethanol in the presence of hydrochloric acid[131]:



(XXXIV) (XXXV)

Am = $N(C_2H_5)_2$, $N(C_6H_5)_2$, NC_4H_8O

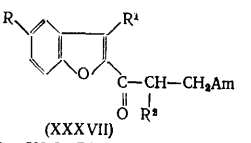
A method of synthesis of pharmacologically active aminomethyl derivatives of 3-acetylbenzofuran (XXXVI) has been patented[132]:



(XXXVI)

R^1 = H, a halogen, or lower alkyls: R^2 = H, a halogen, lower alkyls, or an alkoxy-group; Am = lower alkylamines, pyrrolidine, morpholine, piperidine, hexamethyleneimine, piperazine, or *N*-methylpiperazine.

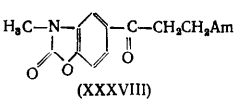
The aminoketones (XXXVII) have been synthesised by the condensation of substituted 2-acetylbenzofurans with formaldehyde and amines[134]:



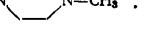
(XXXVII)

R = Cl, Br, CH_3O; R^1 = H, CH_3; R^2 = H, CH_3, C_2H_5; Am = $N(CH_3)_2$, $N(C_2H_5)_2$, NC_5H_{11}

β-Aminoketones of the benzoxazolinone series (XXXVIII), which exhibit an analgesic activity, have been obtained in 60–80% yield[41]:

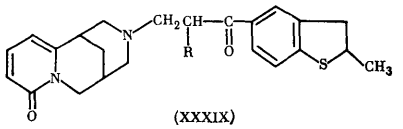


(XXXVIII)

Am = $N(CH_3)_2$, NC_4H_8O, NC_5H_{10}, 

Aminoketones derived from cytisine (XXXIX), whose cholinolytic activity exceeds that of cytisine itself, have

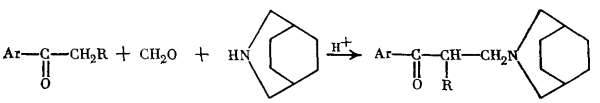
been obtained from substituted acetylthioindanones[133]:



(XXXIX)

R = H, CH_3 .

The aminoketones (XL), obtained by the interaction of substituted acetophenones or propiophenones with paraformaldehyde and the hydrochloride of 3-azabicyclo[3.2.2]-nonane in ethanol with added hydrochloric acid, possess an anticough activity[101]:



(XL)

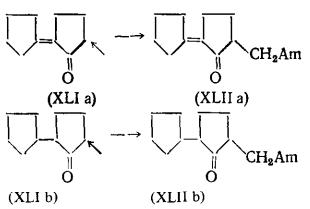
Ar = 3-pyridyl, 2-thienyl, 3-indolyl, or 1-(*N*-methyl-4-piperidinyl)-5-methyl-4-pyrazolyl; R = H or CH_3.

The aminomethylation of certain acetyl derivatives of steroids has been described[135–137].

5. Cyclic Ketones

A large number of publications have been devoted to the aminomethylation of cycloalkanones and their various derivatives[30,56,138–164], on the one hand, and heterocyclic ketones[167–204], on the other. Table 8 lists the substituted cyclopentanones and the corresponding Mannich bases.

Roth and Thassler showed that the aminomethylation of 2-cyclopentylidene and 2-cyclopentyl-cyclopentanones (XLI, a and b) in isopropyl alcohol results in the formation of the aminoketones (XLII, a and b) as the sole products[138]:



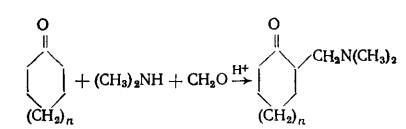
(XLI a) (XLII a)

(XLI b) (XLII b)

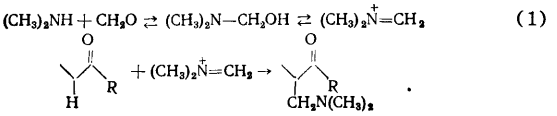
Am = $N(CH_3)_2$, NC_4H_8, NC_4H_8O, NC_5H_{10}, NHC_6H_{11}, $NHCH_2C_6H_5$.

Table 9 lists the cyclohexanone derivatives and their aminomethylation products.

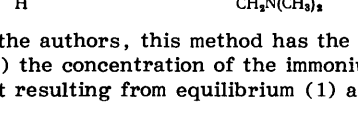
The aminomethylation of cyclohexanone and cyclopentanone involving the direct use of an immonium ion[143,144] generated in the reaction mixture has been studied:



$n = 0, 1$

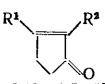
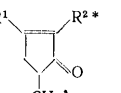
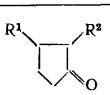
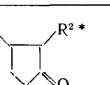
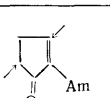
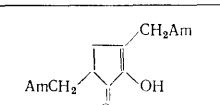
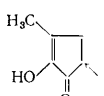
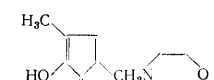
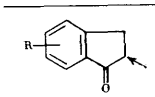
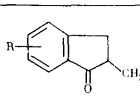


(1)



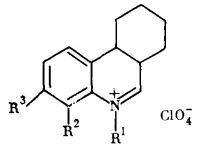
According to the authors, this method has the following advantages: (1) the concentration of the immonium ion is higher than that resulting from equilibrium (1) and the reaction is thus faster; (2) lower temperatures can be used; (3) an aprotic medium can be employed.

Table 8. Aminomethylation of cyclopentenones and cyclopentanones.

Initial ketone	Aminomethylation product	Yield, %	Refs.
 R^1=CH_3, C_6H_5, 4-FC_6H_4, $C_6H_5CH_2$, $CH_2CO_2C_2H_5$, *N,N*-diethylacetamido, acetylmorpholino-	 Am=$N(C_2H_5)_2$, NC_4H_8O, NC_4H_8, HNC_3H_7, HNC_6H_5, 	**	[30]
 R^1=CH_3, C_6H_5; R^2= alkyl (C_1—C_8)	 Am=$N(CH_3)_2$, HNC_4H_9, NC_4H_8O, NC_5H_{10}	**	[30]
	 Am=NC_4H_8, NC_4H_8O, NC_5H_{10}	61—73	[139]
		34.0	[140]
 R = CH_3, C_2H_5, iso-C_3H_7, Cl, Br, CH_3O	 Am=$N(CH_3)_2$, NC_4H_8, NC_5H_{10}, NC_4H_8O	60—75	[151]

*Exhibits analgesic and anti-inflammatory activity.
**The yields are given in grams.

The condensation of cyclohexanone with paraformaldehyde and secondary amines in the presence of an inorganic acid in 1-butanol leads to quaternary substituted tetrahydrophenanthridinium salts (XLIII):[145,146]

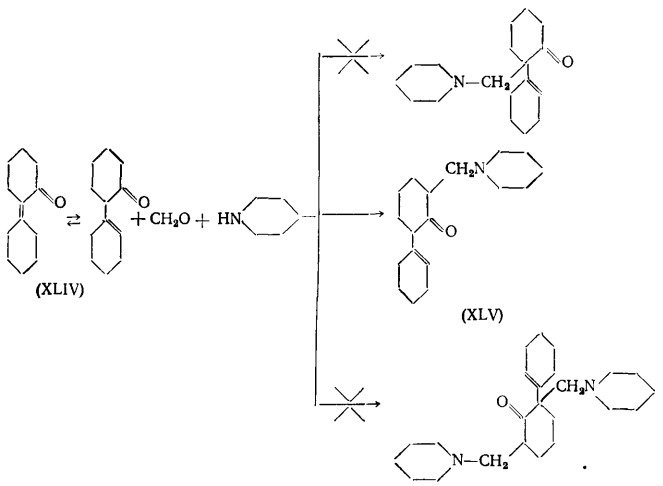


(XLIII)

R^1 = CH_3, C_2H_5, C_6H_5, $C_6H_5CH_2$; R^2 = R^3 = H; R^2 + R^3 = C_6H_5 .

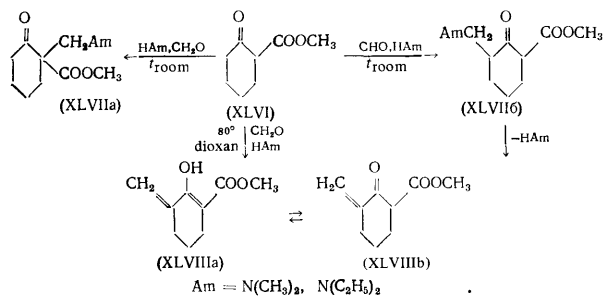
Although the aminomethylation of the 2-(cyclohex-1-enyl)-cyclohexanone (XLIV) molecule is possible in both the 2- and 6-position, the authors[147] showed that in benzene the only

product is the aminoketone (XLV):



(XLIV) (XLV)

Depending on the temperature and the duration of heating, the aminomethylation of 2-methoxycarbonylcyclohexanone (XLVI) proceeds via two different pathways[148]:

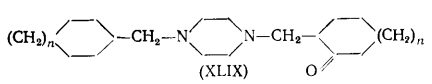


(XLVIIa) (XLVI) (XLVIIб) (XLVIIIa) (XLVIIIb)

Am = $N(CH_3)_2$, $N(C_2H_5)_2$

The above scheme shows that, at room temperature in dioxan, a mixture of compounds (XLVIIa) and (XLVIIb) in proportions of 55 : 45 is formed, while at 80 °C in dioxan compound (XLVIIIa), which is the enolic form of the deamination product of the Mannich base (XLVIIIb), is produced.

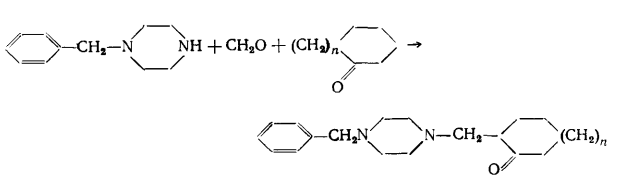
The synthesis of symmetrical Mannich bisbases (XLIX) has been studied[149]:



(XLIX)

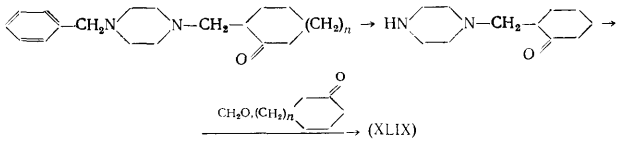
$n = 0, 1$.

Data have also been published on the synthesis of asymmetric Mannich bisbases. Having first protected one of the nitrogen atoms in the piperazine molecule by a benzyl group, the authors obtained a monosubstituted product:



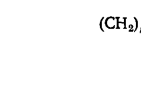
$n = 0, 1$

Having then removed the protecting group, the product was reintroduced into the Mannich reaction and the expected bisbase (XLIX) was obtained:



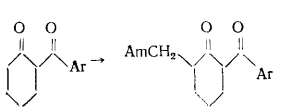
(XLIX)

Table 9. Aminomethylation of cyclohexanone and its derivatives.

Initial ketone	Reaction product	Yield, %	Biological activity	Refs.
R=CH_3, C_6H_{11}, C_6H_9, C_6H_5, $C_6H_5CH_2$, $COOCH_3$, —	Am=$N(CH_3)_2$, $N(C_2H_5)_2$, HNC_6H_5, NC_4H_8O, NC_5H_{10},	40—98	—	[56, 117, 147—149]
R=H, CH_3, $CHCl_2$	Am=NC_4H_8, NC_4H_8O, HC_5H_{10},	*	spasmolytic	[151]
R^1=H, Cl, F, CH_3, CH O; R^2=H, Cl; R^3 H, CH_3O; R^4, R^5 -H, CH_3	Am=$HNCH_3$, HNC_2H_5, $N(CH_3)_2$, HNC_6H_{11}, $N(C_2H_5)_2$, NC_4H_8, NC_5H_{10}, NC_6H_{12}, $NHCH_2CH=CH_2$,	5—81	analgesic, tranquilising	[42]
 R=F, Cl, CH_3, CH_3O	Am=$HNNH_2CH(CH_3)C_6H_5$, $HNCH(CH_3)CH_2C_6H_5$	30—67	action on central nervous system	[165]

*The yields are given in grams.

2-Aroylcyclohexan-1-ones (L) react under the conditions of the Mannich reaction with certain amines to form 6-aminomethyl-2-aroylcyclohexan-1-ones:[150]



(L)

Ar = C_6H_5, $C_6H_4OCH_3$-p, $C_6H_2(OCH_3)_3$-3, 4, 5; Am = NC_5H_{10}, $N(CH_3)_2$.

The aminomethylation of 3-aminocyclohex-2-en-1-one (LI) by piperidine hydrochloride and formaldehyde proceeds in accordance with the scheme[153]

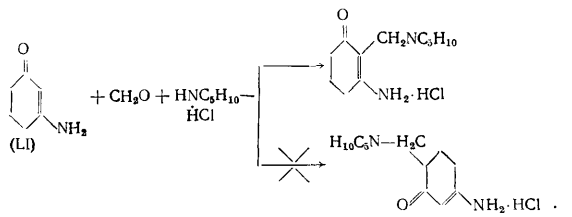
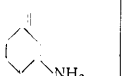
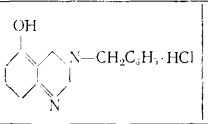
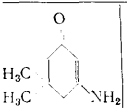
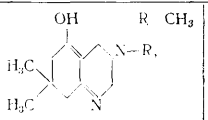
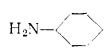
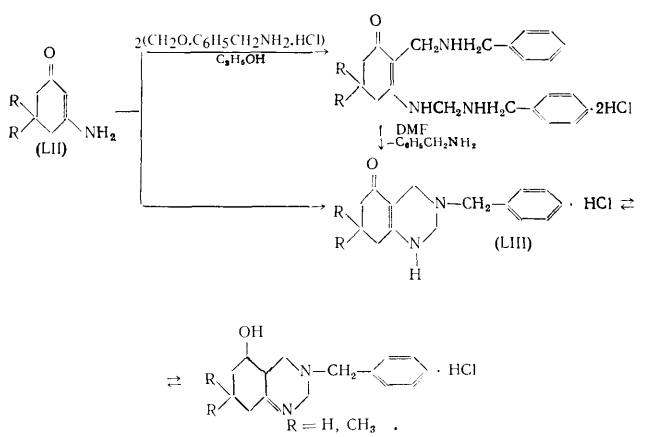


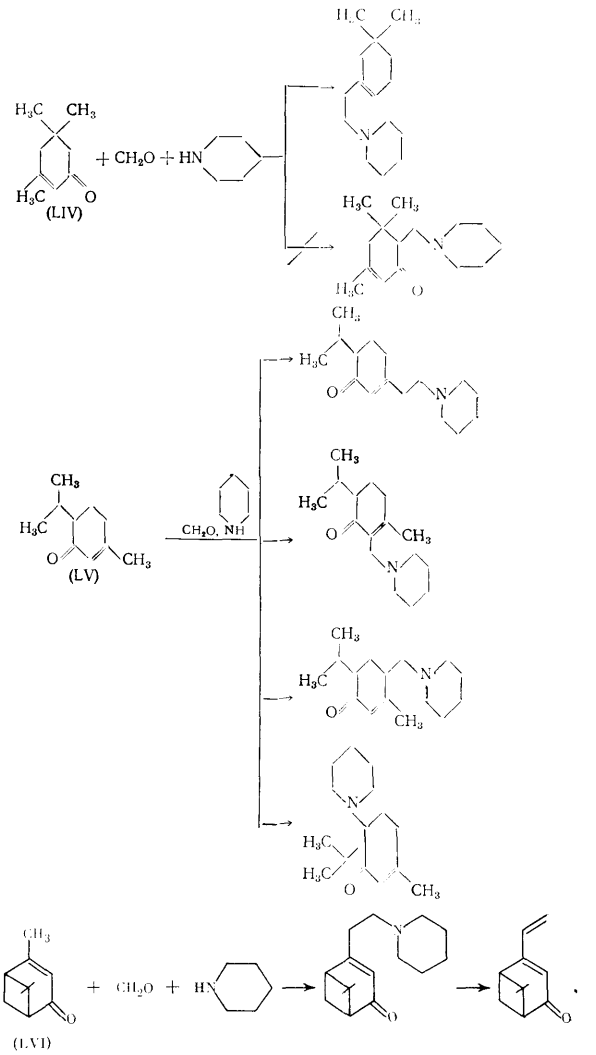
Table 10. Aminomethylation of substituted cyclohex-2-en-1-ones.

Enamine	Amine hydrochloride	Quinazoline derivatives	Yield, %
	$H_2NCH_2C_6H_5$		55,0
	H_2N-CH_3		42,0
		ditto, R = 	46,0
	$H_2N-CH_2-C_6H_5$	» , $R = CH_2C_6H_5$	64,0

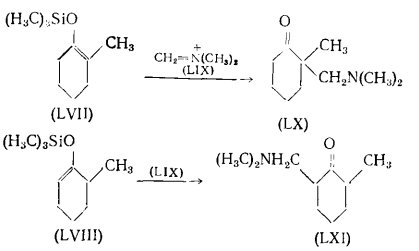
It has been shown that the product of the reaction of substituted cyclohex-2-enones (LII) with benzylamine hydrochloride (and other primary amines) and formaldehyde is a quinazoline derivative (LIII) (Table 10):[153]



The formation of vinylogues on aminomethylation of isophorone (LIV), piperitone (LV), and 2-pinen-4-one (LVI):

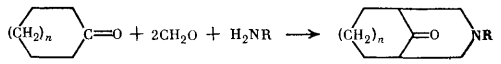


The regioselectivity of the reactions of the trimethylsilyl ethers of the enolic forms of cyclohexenone (LVII) and (LVIII) with the carbonium-immonium ion $[CH_2=\overset{+}{N}(CH_3)_2]$ (LIX) to form the Mannich bases (LX) and (LXI) in 65 and 78% yields respectively has been investigated and the authors established that compound (LXI) consists of a 2 : 1 mixture of stereoisomers[157].



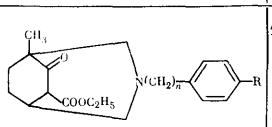
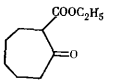
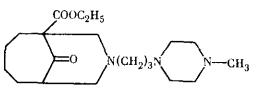
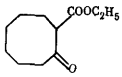
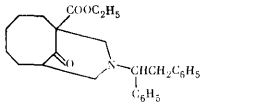
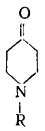
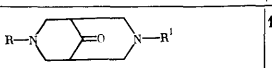
The condensation of substituted cyclic ketones with two moles of paraformaldehyde and one mole of a primary amine in acetic acid[158–160,162] or methanol[161] leads to the bicyclic

compound (LXII) (Table 11).

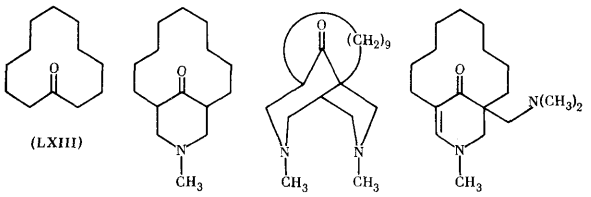


(LXII)

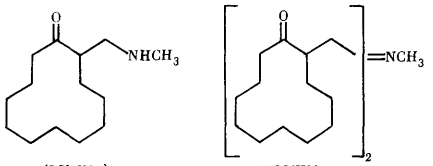
Table 11. The formation of bispidines on aminomethylation.

Initial ketone	Aminomethylation product	Yield, %	Biological activity	Refs.
	 $n = 1, 2$; R = H, F	10—27	analgesic, anti-inflammatory, hypotensive	[162]
		20	ditto	[162]
		8	»	[162]
 R=CH_3, $CH_2C_6H_5$, $(CH_2)_2C_6H_5$, *uзо*-C_3H_7	 R^1=$CH_2C_6H_5$, $(CH_2)_2C_6H_5$, C_6H_{13}, $(CH_2)_2OH$, alkyl(C_1-C_4), cyclopentyl, $(CH_2)_3N(CH_3)_2$, cyclohexyl	15—61	antiarrhythmic	[159-161]

Interesting data have been published on the aminomethylation of the cyclododecanone (LXIII).[163] Refluxing with formaldehyde and methylamine for two days resulting in the formation of a mixture of substances whose separation led to the isolation of the azabicyclopentadecanone (LXIV), the bispyridinediazatricyclopentadecanone (LXV), and the dihydropyridin-4-one (LXVI). On heating for less than two days, the products are the aminoketones (LXVIIa) and (LXVIIb):



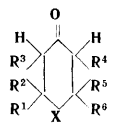
(LXIII) (LXIV) (LXV) (LXVI)

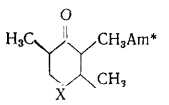
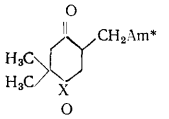
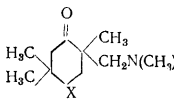
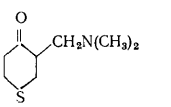
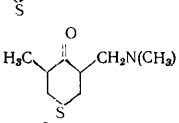
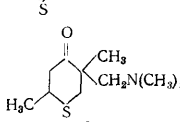
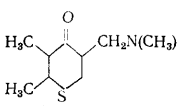


(LXVIIa) (XLVIIb)

Golovin and co-workers carried out a major study of the aminomethylation of saturated cyclic γ-ketones by formaldehyde and various amines as a function of the number and positions of the alkyl substituents relative to the carbonyl group and also the character of the heteroatom X in the ring (X = O, S, or N) [167-169,172-178] (Table 12).

Table 12. Aminomethylation of γ-ketones.

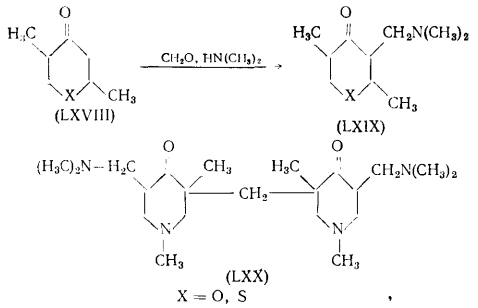


R^1	R^2	R^3	R^4	R^5	R^6	X	Aminomethylation product	Yield, %	Refs.
H	H	CH_3	H	H	CH_3	S, NCH_3		37—75	[167,168]
CH_3	CH_3	H	H	H	H	S,O, NCH_3		51—68	[169,172]
H	H	CH_3	H	CH_3	CH_3	O,S		56—61	[173]
H	H	H	H	H	H	S		56,5	[174]
H	H	CH_3	H	H	H	S		57	[175]
H	CH_3	H	CH_3	H	H	S		64	[178]
H	H	H	CH_3	H	CH_3	S		10—21	[177]

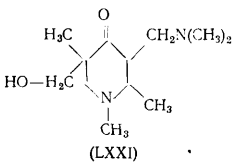
*Am = $N(CH_3)_2$, $N(C_2H_5)_2$, $N(C_3H_7)_2$, $N(C_4H_9)_2$, NC_4H_8, NC_4H_8O, NC_5H_{10}, NC_6H_{12}.

In the aminomethylation of 1,2,5-trimethylpiperidin-4-one (LXVIII, X = NCH_3), bis(1,2,5-trimethyl-3-dimethylaminomethyl-4-oxopiperidinyl)methane (LXX) was isolated together

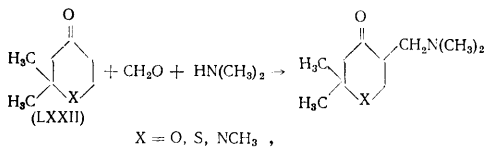
with the main reaction product (LXIX):[167-169]



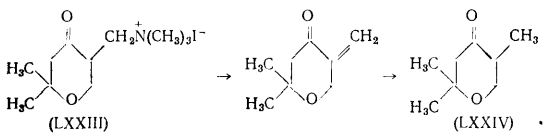
When the above reaction is carried out with a twofold excess of paraformaldehyde, 3-dimethylaminomethyl-5-hydroxymethyl-1,2,5-trimethyl-4-piperidinone (LXXI) is mainly formed:



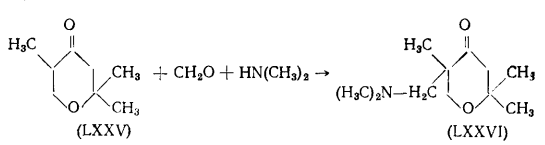
In order to elucidate the influence of two methyl groups in the β-position relative to the carbonyl group on the regioselectivity of the Mannich reaction, it was shown later[169] that, regardless of the nature of the entering aminomethyl group, the aminomethylation of compound (LXXII) proceeds with participation of only the methylene group located on the opposite side of the heterocycle relative to the methyl substituents:



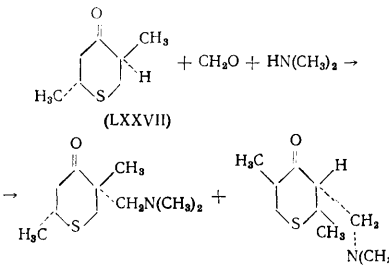
Additional proof of the structure of the Mannich bases has been obtained[170] by exhaustive Hofmann methylation. For example, the methiodide of the aminoketone (LXXIII) has been converted by reductive deamination into the known 2,2,5-trimethyl-4-oxotetrahydropyran (LXXIV):[171]



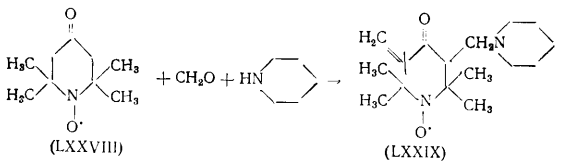
The study of the structural specificity of the aminomethylation of 2,2,5-trimethyl-4-oxotetrahydropyran (LXXV) showed that the reaction is directed exclusively to the tertiary carbon atom adjoining the carbonyl group and leads to the formation of the corresponding 5-dimethylaminomethyl derivatives (LXXVI):[173]



The study of the products of the aminomethylation of *trans*-2e, 5e-dimethyl- and *cis*-3e, 5e-dimethyl-tetrahydro-1-thiopyran-4-ones (LXXVII) showed that only monoaminoketones with an axial orientation of the aminomethyl group are formed. The absence of bisaminomethyl bases from the reaction products in this instance can be explained by the impossibility of the entry of a second axial aminomethyl group next to the carbonyl group as a consequence of the *meta*-axial interaction[176]. It has been shown that the orientation of the aminomethylation depends exclusively on the structure of the initial ketone, namely on the number and positions of the alkyl substituents in the ring:



It is of interest that the aminomethylation of 2,2,6,6-tetramethyl-4-oxopiperidine-1-oxide (LXXVIII) results in the formation of compound (LXXIX) in 94% yield[179,180]:



As early as 1952, Wiley[181] described the condensation of 4-pyrone with dimethylamine hydrochloride and formaldehyde in ethanol; the reaction product was identified as the monoaminoketone (LXXX). It was shown subsequently that both mono- and bis-dimethylaminomethylpyrones (LXXX) and (LXXXI) are formed[182]:

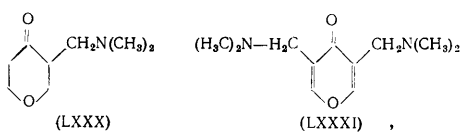
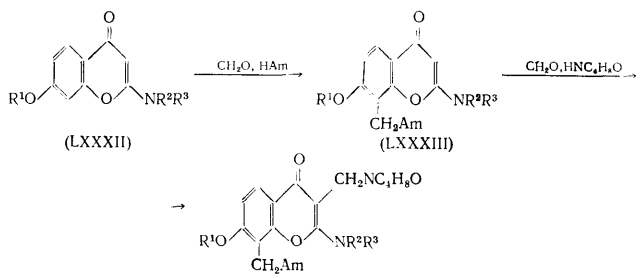


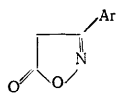
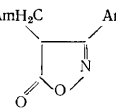
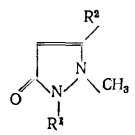
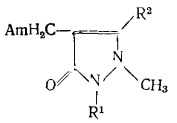
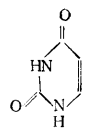
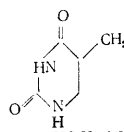
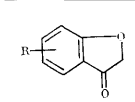
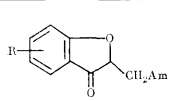
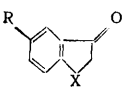
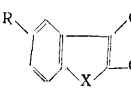
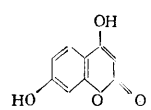
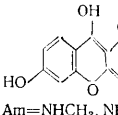
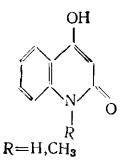
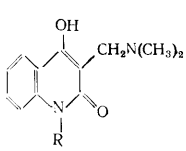
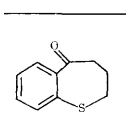
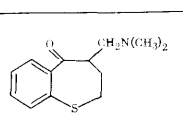
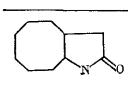
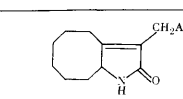
Table 13 lists the products of the aminomethylation of isoxazoles[183,184], pyrazoles[185], uracils[186], coumaranones[187], and other heterocyclic ketones[188-192]. A number of studies have been made on the aminomethylation of chromans, isochromans, and pyrans[193-204].

It has been shown[195] that the aminomethylation of chromans takes place in the 3-position. However, according to other data[196], in the case of 2-dialkyl-amino-7-hydroxychroman (LXXXII, R = H) substitution takes place in the 8-position with formation of compound (LXXXIII) and only the subsequent aminomethylation is in the 3-position with formation of compound (LXXXIV):



$R^1 = H$; Am = NC_4H_8O, NC_5H_{10}, , $NR^2R^3 = N(CH_3)_2$, $N(C_2H_5)_2$, NC_5H_{10}, $N(CH_3)C_2H_5$, $N(C_2H_5)C_6H_5$;
$R^1 = CH_3$, Am = NC_4H_8O; $NR^2R^3 = N(C_2H_5)_2$, NC_4H_8, NC_5H_{10}.

Table 13. The Mannich reaction involving heterocyclic ketones.

Initial ketone	Aminomethylation product	Yield, %	Refs.
 Ar=C_6H_5, p-$NO_2C_6H_5$, p-ClC_6H_4, p-$CH_3OC_6H_4$, p-$CH_3C_6H_4$	 Am=$N(CH_3)_2$, $N(C_2H_5)_2$, NC_4H_8, NC_4H_8O, NC_5H_{10}	70—96	[183, 184]
 R^1=CH_3, C_6H_5; R^2=H, CH_3	 Am=NC_4H_8O, $N(CH_2CH_2Cl)_2$	66—100	[185]
	 Am=NHC_4H_9, NHC_6H_{11}, $N(CH_3)_2$, NHC_6H_5, NHC_6H_4R(R=p-Cl, m-CH_3, p-CH_3O, p-NO_2)	30—98	[186]
 R=5-Cl, CH_3, NO_2, 7-Cl, CH_3	 Am=$N(CH_3)_2$, NC_4H_8O, NC_5H_{10}, $N(C_2H_5)_2$	22—78	[187]
 X=O, S, Se; R=H,CH_3	 Am=$N(CH_3)_2$, NC_4H_8, NC_5H_{10}	**	[188]
	 Am=$NHCH_3$, NHC_2H_5, NHC_3H_7, $NHCH_2CH{=}CH_2$, NC_5H_{10}	**	[189]
 R=H,CH_3		80	[190]
		23	[191]
	 Am=$N(CH_3)_2$, NC_4H_8O	**	[192]

*Using $>N^+ = CH_2Cl^-$ in acetonitrile at 20 °C.
**The yields are given in grams.

The side product (LXXXV) was also isolated:

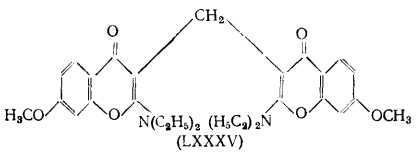
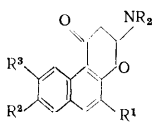
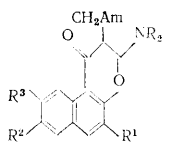
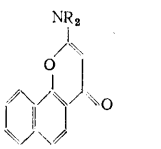
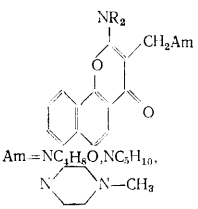
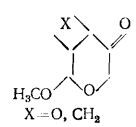
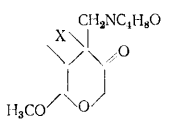
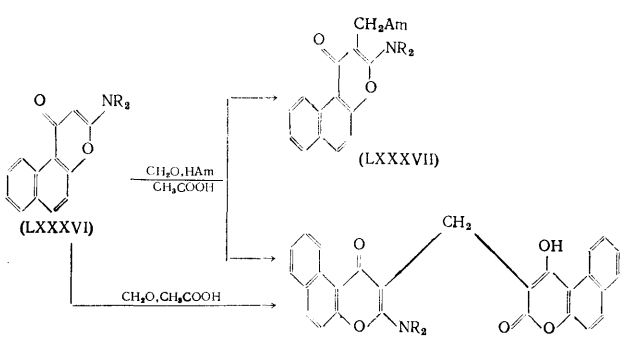

(LXXXV)

Table 14. Aminomethylation of 3-amino-1-oxo-1*H*-naphtho-[2,1-*b*]pyrans.

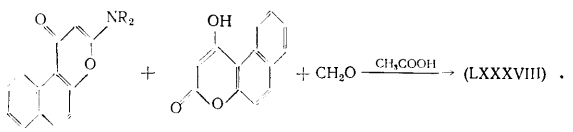
Initial ketone	Aminomethylation product	Yield, %	Biological activity	Refs.
 R^1=H, CH_3O; R^2=H,CH_3,Br, OAc;R^3=H,CH_3,OH,CH_3O, OAc;NR_2=$N(CH_3)_2$, $N(C_2H_5)_2$,$N(CH_3)C_2H_5$, NC_4H_8,NC_5H_{10}	 Am=NC_4H_8O,NC_5H_{10}	28—62	anti-convulsant	[201]
 NR_2=$N(CH_3)_2$, $N(C_2H_5)_2$, $N(CH_2)C_2H_5$	 Am=NC_4H_8O,NC_5H_{10},	21—54	neuro-tropic	[202]
 X=O, CH_2		70;88	—	[204]

The aminomethylation of 3-dialkylamino-1-oxo-1*H*-napntho-[2,1-*b*]pyrans (LXXXVI) in acetic acid leads to 2-dialkylaminomethylamino-1-oxo-1*H*-naphtho[2,1-*b*]pyrans (LXXXVII), which exhibit an anticonvulsant activity[198,199] (Table 14).

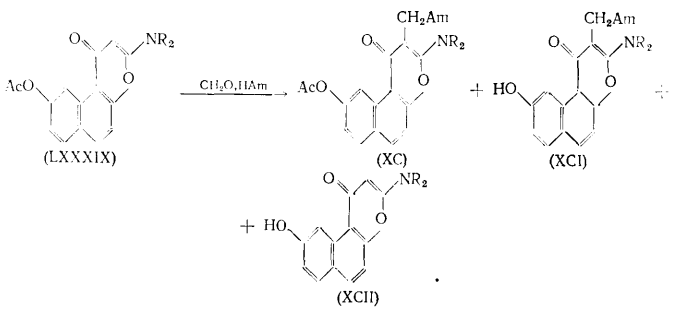

(LXXXVI) (LXXXVII) (LXXXVIII)

NR_2 = $N(CH_3)_2$, $N(C_2H_5)_2$, N (iso-C_3H_7)$_2$, NC_4H_8, NC_5H_{10}, $N(CH_2CH{=}CH_2)_2$, $N(CH_3)CH_2C_6H_5$, $N(C_2H_5)CH_2C_6H_5$;
Am = NC_4H_8O, NC_5H_{10} .

In the presence of an excess of acetic acid, 3-dialkylamino-2-{1-hydroxy-3-oxo-3*H*-naphtho[2,1-*b*]pyran-2-ylmethyl}-1-oxo-1*H*-naphtho[2,1-*b*]pyran (LXXXVIII) is formed as a side product. Its structure has been demonstrated by specific synthesis:



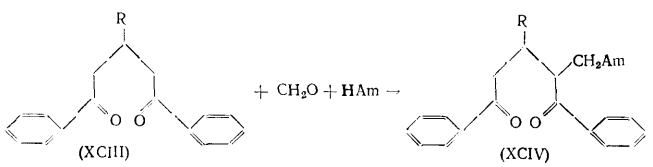
The aminomethylation of compound (LXXXIX) yielded a mixture of the three compounds (XC), (XCI), and (XCII):



6. Diketones

Comparatively few studies have been devoted to the aminomethylation of diketones[205–221] (Table 15).

Thus Tilichenko and co-workers showed that the aminomethylation of the diketones (XCIII) yields only the monoaminomethyl derivatives (XCIV):[205–212]



The condensation of 1-(2-oxocyclohexyl)-1,3-diphenyl-3-propanone (XCV) with formaldehyde and dimethylamine hydrochloride results in the formation of a mixture of 2-dimethylaminomethyl-1-(2-oxocyclohexyl)-1,3-diphenyl-3-propanone (XCVI) and 1-(3-dimethylaminomethyl-2-oxocyclohexyl)-1,3-diphenyl-3-propanone (XCVII):[209]

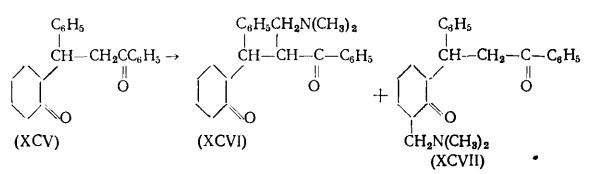
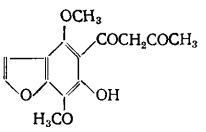
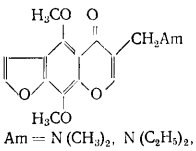
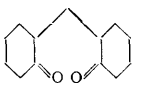
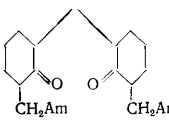
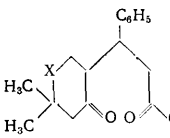
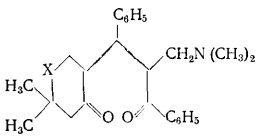
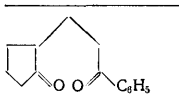
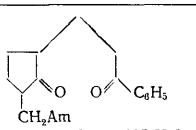
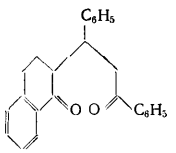
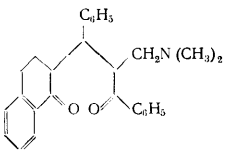
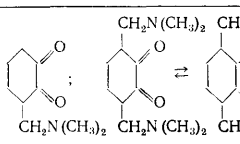
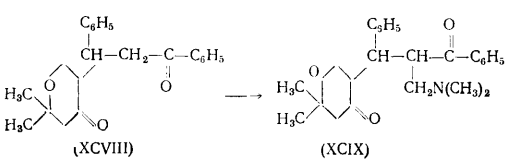


Table 15. The Mannich reaction involving diketones.

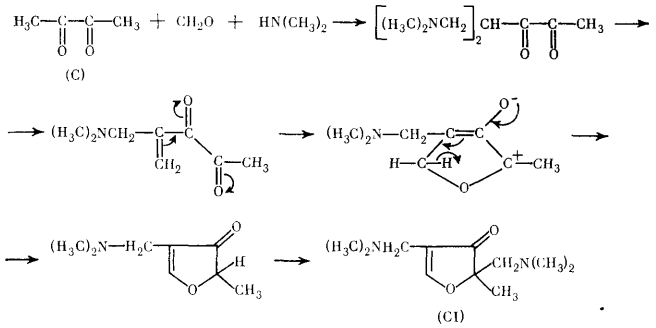
Initial ketone	Aminomethylation product	Yield, %	Refs.
	 Am = N $(CH_3)_2$, N $(C_2H_5)_2$, NC_5H_{10}		[219]
	 Am = N $(CH_3)_2$, N $(C_2H_5)_2$	48—100	[212]
 X = O, S, CH_2		70—83	[210, 211]
	 Am = N $(CH_3)_2$, NC_4H_8O	50; 70	[211]
		59	[211]
		24	[213]

On the other hand, the aminomethylation of 1-(α,α-dimethyltetrahydro-γ-pyron-β'-yl)-1,3-diphenyl-3-propanone (XCVIII) in the ring is not observed; only 2-dimethylaminomethyl-1-(α,α-dimethyltetrahydro-γ-pyron-β'-yl)-1,3-diphenyl-3-propanone (XCIV) is produced[210,212]:

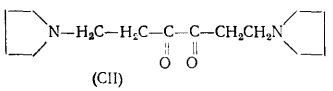


When the Mannich reaction is carried out with butane-2,3-dione (C), the character of the product obtained depends on the nature of the amino-component[213]. Thus the product

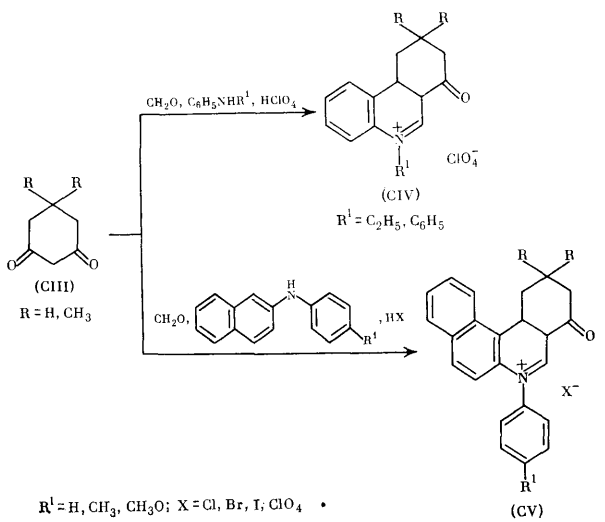
of the condensation of butane-2,3-dione with paraformaldehyde and dimethylamine is 2-methyl-2,4-bis(dimethylaminomethyl)-3-furanone (CI) in 18% yield, whose formation can be represented as follows:



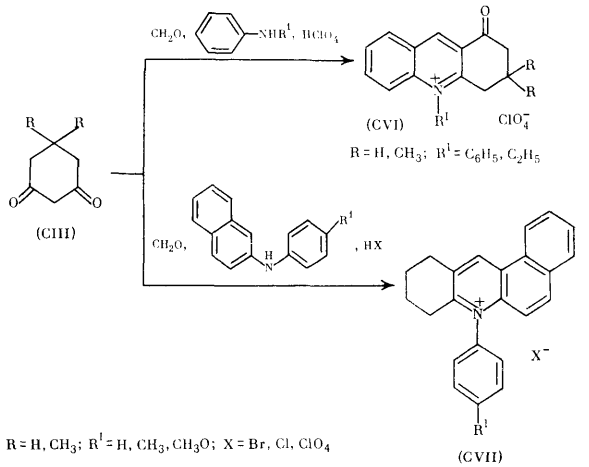
When compound (C) reacts with pyrrolidine, the diaminoketone (CII) is formed in 44% yield:



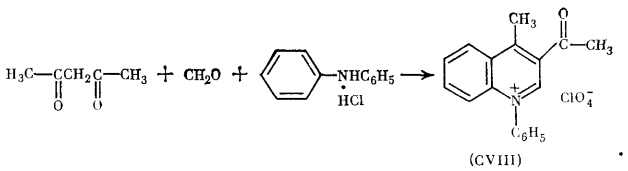
Secondary aromatic amines of the benzene series cyclise with paraformaldehyde and dimedone (CIII, R = CH_3) in the presence of perchloric acid to form the *N*-substituted quaternary 9,9-dimethyl-7-oxo-7,8,9,10-tetrahydrophenanthridinium salts (CIV). Phenyl(*p*-X-phenyl)-2-naphthylamines cyclise in the presence of hydrochloric, hydrobromic, and perchloric acids to form *N*-aryl-substituted 2,2-dimethyl-4-oxo-1,2,3,4-tetrahydrobenzo[*a*]phenanthridinium salts (CV):



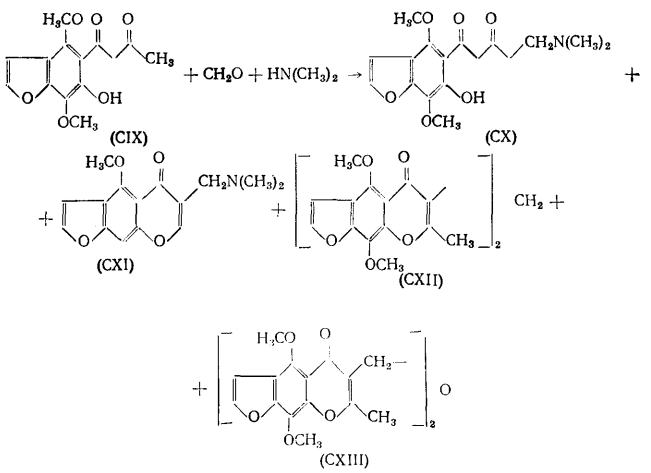
The condensation of diphenylamine and *N*-ethylaniline with formaldehyde and cyclic β-diketones (CIII) leads to the formation of *N*-substituted 1-oxo-1,2,3,4-tetrahydroacridinium salts (CVI). The authors' more detailed studies of the products of the reaction with 2-arylaminonaphthalenes showed that the cyclisation involves the most reactive α-position of the naphthalene ring, which leads to the formation of quaternary 11-oxo-8,9,10,11-tetrahydrobenzo[*a*]acridinium salts (CVII):[215]



Acetylacetone reacts with formaldehyde and diphenylamine in the presence of perchloric acid to form 3-acetyl-1-phenyllepidinium perchlorate (CVIII):[216]



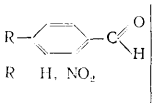
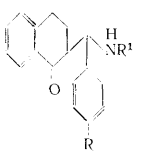
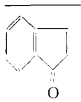
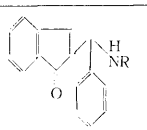
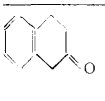
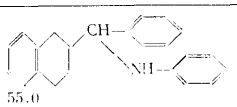
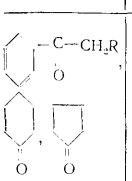
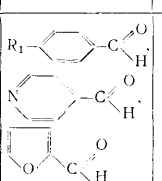
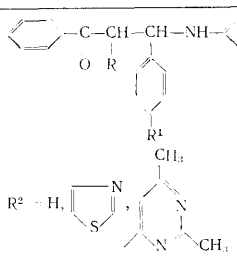
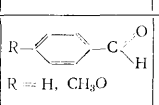
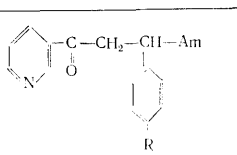
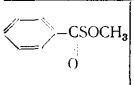
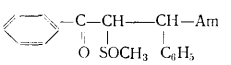
The aminomethylation of ω-acetylkhellinone (CIX) leads to the formation of the cyclisation product (CXI) and the dimerisation products (CXII) and (CXIII) in addition to the main product (CX):[217–219]



III. THE MANNICH REACTIONS WITH ALDEHYDES

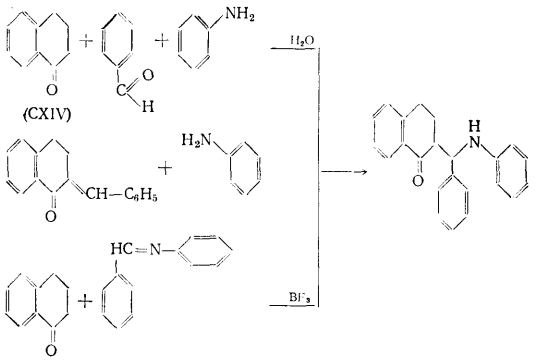
A number of studies have been devoted to the aminomethylation of ketones by various aldehydes[111,166,222–226] (Table 16).

Table 16. The Mannich reaction involving various aldehydes.

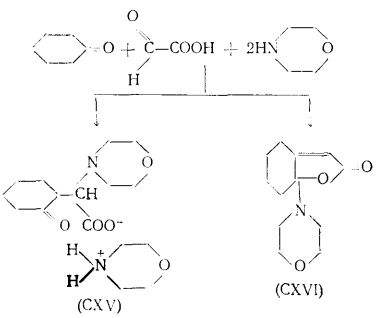
Initial ketone	Initial aldehyde	Aminomethylation product [yield, %]	Refs.
	 R = H, NO_2	 52–100* R^1 = C_6H_5, $C_6H_5OCH_3$-*p*	[222]
		 93, 97* R = C_6H_5, $C_6H_4OCH_3$-*n*	[222]
	ditto	 55.0	[166]
 R = H, CH_3	 R^1 = H, CH_3O, NO_2	 R^2 = H, 31–94	[111]
	 R = H, CH_3O	 20–100 Am = NHC_3H_5, NHC_5H_{11}, NC_5H_{10}, NC_4H_8O, $NHCH_2C_6H_5$, $NH(CH_2)_2C_2H_5$	[223]
		 74–91 Am = NC_4H_8, NC_4H_8O, $N(CH_3)_2$	[224]

*The reaction was carried out in the presence of a catalyst (BF_3).

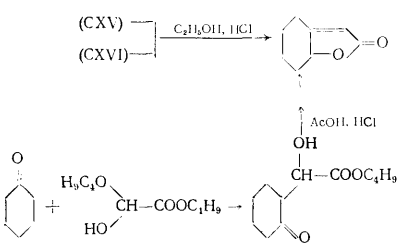
In particular, when the α-tetralone (CXIV) is condensed with benzaldehyde and amines, substitution takes place in the 2-position, which has been demonstrated by specific synthesis[218]:



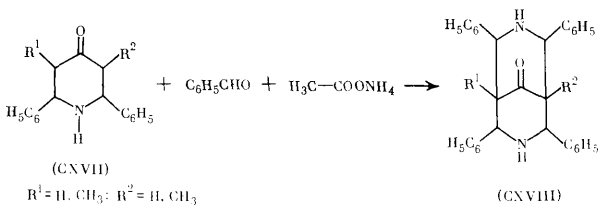
On the other hand, the condensation of cyclohexanone, morpholine, and glyoxalic aldehyde results in the formation of a mixture of products (CXV) and (CXVI):[214]



The formation of compounds (CXV) and (CXVI) has been demonstrated as follows:



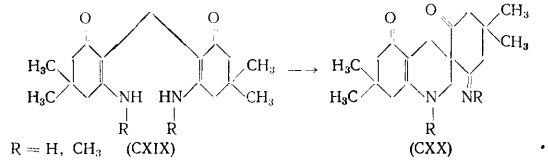
When benzaldehyde is used in the Mannich reaction instead of formaldehyde, the substituted piperidinones (CXVII) are converted into aza- and diaza-bicyclo[3.3.1]nonan-9-ones (CXVIII):[226]



It has been shown[226] that compound (CXVII, $R^1 = R^2 = CH_3$) does not form a bicyclic product despite the presence of two axial α-hydrogen atoms. Steric hindrance generated by the tertiary carbon atoms C(3) and C(5) operates in this instance.

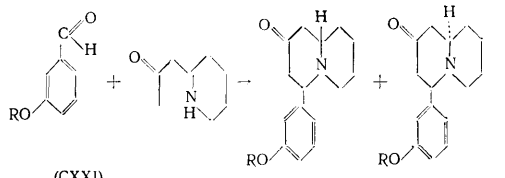
Not three but only two components, one of which plays the role of both the amino- and the CH-acid component, can enter into the Mannich reaction. Similar condensations,

i.e. intramolecular Mannich reactions, have been investigated in other studies[227-229]. In particular, it has been shown that methylenebisenaminoketones (CXIX) condense with formaldehyde to form the spiro-compounds (CXX):[227]



R = H, CH_3 (CXIX) (CXX)

The condensation of isopelletierine (CXXXI) with 3-methoxybenzaldehyde in an aqueous medium leads to the formation of *trans*- and *cis*-quinolizidines (CXXII) and (CXXIII) in proportions of 1:6, while the reaction with 3-hydroxybenzaldehyde leads almost exclusively to *trans*-quinolizidine (CXXIV).[229] On the other hand, in methanol the reaction proceeds with formation of compounds (CXXII) and (CXXIII) in proportions of 5:1. It has been shown that the interaction of compound (CXXI) with an arylaldehyde in an alkaline medium leads to the formation of *cis*-4-aryl-quinolizidin-2-one, which then isomerises to the corresponding *trans*-form:



(CXXI) (CXXII), R = CH_3 (CXXIII)
R = H, CH_3 (CXXIV), R = H

The data presented in this review on the synthesis of β-aminoketones show that more detailed studies of the Mannich reaction would be useful. This is due to the extensive possibilities for its application in organic synthesis and in particular in the specific synthesis of compounds with a potential biological activity.

REFERENCES

1. F.F.Blick, in Symposium, "Organic Reactions", Vol.1 (Edited by R.Adams) (Translated into Russian), Inostr.Lit., Moscow, 1948, p.399.
2. E.R.Alexander and E.J.Underhill, J.Amer.Chem. Soc., 1949, **71**, 4014.
3. S.V.Lieberman and E.C.Wagner, J.Org.Chem., 1949, **14**, 1001.
4. H.Karbe, Arch.Pharm., 1950, **283**, 38.
5. E.C.Wagner, J.Org.Chem., 1954, **19**, 1862.
6. H.Hellmann and G.Opitz, Angew.Chem., 1956, **68**, 265.
7. T.F.Cummings and J.R.Shelton, J.Org.Chem., 1960, **25**, 419.
8. H.J.Roth, Arch.Pharm., 1961, **294**, 623.
9. V.M.Belikov, Yu.N.Belokon', M.M.Dolgaya, and N.S.Martinkova, Izv.Akad.Nauk SSSR, Ser.Khim., 1967, 1721.
10. B.B.Thompson, J.Pharm.Sci., 1968, **57**, 715.
11. W.L.Nobles and N.D.Potti, J.Pharm.Sci., 1968, **57**, 1097.
12. V.M.Belikov, Ju.N.Belokon, M.M.Dolgaja, and N.S.Martinkova, Tetrahedron, 1970, **26**, 1199.
13. R.Neidlein, Apoteker-Zeitung, 1977, **117**, 1215.
14. B.Reichert, "Die Mannich Reaktion", Springer-Verlag, Berlin, 1959.
15. H.Hellman and G.Opitz, "α-Aminoalkylierung", Verlag-Chemie, Weinheim, 1960.
16. M.Tramontini, Synthesis, 1973, **12**, 705.
17. A.G.Agababyan, G.A.Gevorgyan, and O.L.Mndzhoyan, Uspekhi Khim., 1982, **51**, 678 [Russ.Chem.Rev., 1982(4)].
18. A.N.Kudrin and V.G.Vorob'ev, "Aminoketony" (Aminoketones), Izd.Meditsina, Moscow, 1970.
19. E.Profft, "Die Falikaine, ihre Chemie, Pharmakologie, Sowie Anwendung in der Medizin", Berlin, 1954.
20. B.E.Abrew and A.B.Richards, J.Pharm.Exp.Ther., 1955, **155**, 419.
21. H.J.Florestano and M.E.Tahler, J.Amer.Pharm. Assoc., 1956, **45**, 320.
22. J.Porszasz, K.Nador, K.Gibiszer-Porszasz, and T.Barankay, Acta Physiol.Sci.Hung., 1960, **18**, 149; Chem.Abs., 1961, **55**, 13637.
23. O.M.Avakyan, "Veshchestva Deistvuyushchie na Simpato-Adrenalovuyu Sistemu" (Substances Acting on the Sympathetic-Adrenal System), Izd.Akad. Nauk Arm.SSR, Erevan, 1980, p.129.
24. S.S.Krylov and N.T.Starykh, Farmakol i Toksikol., 1973, **36**, 396.
25. H.Schönenberger, T.Bastug, L.Bindl, A.Adam, D.Adam, A.Petter, and W.Zwez, Pharm.Acta Helv., 1969, **44**, 691.
26. J.R.Dimmock, C.B.Nyathi, and P.J.Smith, J.Pharm. Sci., 1978, **67**, 1543.
27. H.Schönenberger and T.Bastug, Arzneimittel-Forsch., 1970, **20**, 386.
28. H.Schönenberger and T.Bastug, Arzneimittel-Forsch., 1971, **21**, 68.
29. H.Schönenberger and P.Lippert, Pharmazie, 1970, **25**, 617.
30. BRD P.2241588 (1974); Chem.Abs., 1974, **80**, 108064.
31. N.A.Apoyan, Zh.B.Sayadan, and V.G.Sarkisyan, Biol.Zhur.Armenii, 1974, **27**, 37.
32. W.Werner, W.Jungstand, and W.Gutsche, Arzneim-Forsch., 1970, **20**, 246.
33. W.Jungstand, W.Gutsche, and K.Wohlrabe, Arzneim-Forsch., 1971, **21**, 404.
34. C.B.Nyathi, V.S.Gupta, and J.R.Dimmock, J.Pharm.Sci., 1979, **68**, 1383.
35. W.Werner, W.Jungstand, W.Gutsche, and K.Wohlrabe, Pharmazie, 1977, **32**, 341.
36. J.R.Dimmock and W.G.Taylor, J.Pharm.Sci., 1975, **64**, 241.
37. E.V.Vlasenko, Z.S.Mkrtchyan, and A.S.Edilyan, Biol.Zhur.Armenii, 1972, **25**, 125.
38. G.A.Gevorgyan, Abstract of Candidate's Thesis in Chemical Sciences, Institute of Fine Organic Chemistry, Academy of Sciences of the Armenian SSR, Erevan, 1972.
39. R.N.Schut, F.E.Ward, and R.Rodriguez, J.Medicin. Chem., 1972, **15**, 301.
40. H.P.S.Chawla, B.C.Gautam, R.S.Kapil, N.Anand, G.K.Patnak, M.M.Vohra, and O.P.Schrivastava, J.Medicin.Chem., 1970, **13**, 480.
41. J.C.Cazin, D.Lesieur, Ch.Lespagnol, M.Cazin, P.Lemaire, and C.Brunet, Europ.J.Med.Chem.Chim. Therap., 1976, **11**, 33.
42. W.M.Welch, C.A.Harbert, R.Sarges, P.Stratten, and A.Weissman, J.Medicin.Chem., 1977, **20**, 699.
43. D.A.Koechel and O.G.Rankin, J.Medicin.Chem., 1978, **21**, 764.
44. C.Brunet, M.Cazin, and J.C.Cazin, Arzneim-Forsch., 1980, **30**, 1285.

45. V.G.Vorob'ev, N.G.Maksimova, G.A.Gevorgyan, and I.F.Katorgina, Krovoobrashchenie, 1975, **8**, 8.
46. A.Delacourte, F.Boutteau, G.Biserte, M.Cazin, J.C.Cazin, C.C.Brune, J.Lesieur, and M.Luyckx, Acta Therap., 1980, **6**, 121.
47. D.A.Gilder, W.Fain, and L.L.Simpson, J.Pharm. Exptl.Ther., 1976, **198**, 255.
48. M.I.Farberov and G.S.Mironov, Kinetika i Kataliz, 1963, **4**, 526.
49. G.L.Buchanan, A.C.W.Curran, and T.R.Wall, Tetrahedron, 1969, **25**, 5503.
50. F.Henin and J.P.Pele, Synthesis, 1980(11), 895.
51. O.L.Mndzhoyan and G.A.Gevorgyan, Arm.Khim. Zhur., 1973, **26**, 219.
52. Ts.E.Agadzhanyan, R.T.Grigoryan, and E.B.Grigoryan, Arm.Khim.Zhur., 1971, **24**, 213.
53. K.Komeda, T.Chang, I.Ichimoto, and H.Ueda, J.Agr.Chem.(Japan), 1972, **46**, 289.
54. J.Hooz and J.N.Bridson, J.Amer.Chem.Soc., 1973, **95**, 602.
55. Y.Jasor, M.J.Luche, M.Gaudry, and A.Marguet, Chem.Comm., 1974, 253.
56. Y.Jasor, M.J.Luche, M.Gaudry, and A.Marguet, Tetrahedron, 1977, **33**, 295.
57. M.Gaudry, Y.Jasor, and B.K.Trung, Org.Synth., 1980, **59**, 153.
58. BRD P.2251976 (1974); Chem.Abs., 1974, **81**, 25087.
59. J.R.Dimmock, D.K.Kowal, W.A.Turner, P.J.Smith, L.M.Noble, and W.K.Pannekoek, J.Pharm.Sci., 1978, **67**, 401.
60. Zh.G.Akopyan and G.L.Papayan, Arm.Khim.Zhur., 1977, **30**, 963.
61. B.P.1199731 (1970); Chem.Abs., 1970, **73**, 120344.
62. J.K.Astik and K.A.Thaker, J.Inst.Chemists (India), 1975, **47**, 69.
63. US P.3637597 (1972); Chem.Abs., 1972, **76**, 128959.
64. W.E.Hahn and R.Bartnik, Roczniki Chem., 1973, **47**, 2089.
65. W.E.Hahn and R.Bartnik, Roczniki Chem., 1974, **48**, 475.
66. W.E.Hahn and R.Bartnik, Roczniki Chem., 1974, **48**, 345.
67. R.Bartnik, W.E.Hahn, and B.Orlowska, Roczniki Chem., 1976, **50**, 1875.
68. H.Z.Lettau, Z.Chem., 1970, **10**, 211.
69. H.Z.Lettau, Z.Chem., 1970, **10**, 338.
70. H.Z.Lettau, Z.Chem., 1970, **10**, 431.
71. H.Z.Lettau, Z.Chem., 1970, **10**, 462.
72. H.Z.Lettau, Z.Chem., 1971, **11**, 10.
73. G.A.Gevorgyan, N.Z.Pakhlevanyan, S.N.Asratyan, and O.L.Mndzhoyan, Arm.Khim.Zhur., 1971, **24**, 32.
74. G.A.Gevorgyan, N.Z.Pakhlevanyan, S.N.Asratyan, and O.L.Mndzhoyan, Arm.Khim.Zhur., 1971, **24**, 333.
75. G.A.Gevorgyan, L.M.Petrosyan, N.Z.Pakhlevanyan, E.V.Vlasenko, A.S.Edilyan, and O.L.Mndzhoyan, Arm.Khim.Zhur., 1973, **26**, 584.
76. G.A.Gevorgyan, N.A.Apoyan, L.P.Podol'skaya, L.K.Durgaryan, and O.L.Mndzhoyan, Khim.-Farm. Zhur., 1979, **13**(7), 68.
77. G.A.Gevorgyan, A.G.Agababyan, N.A.Apoyan, L.P.Podol'skaya, and O.L.Mndzhoyan, Khim.-Farm. Zhur., 1977, **11**(4), 20.
78. G.A.Gevorgyan, A.G.Agababyan, A.S.Azlivyan, E.V.Vlasenko, and O.L.Mndzhoyan, Khim.-Farm. Zhur., 1979, **13**(10), 32.
79. G.A.Gevorgyan, E.V.Vlasenko, N.A.Apoyan, and O.L.Mndzhoyan, "Tezisy Dokladov IV Vsesoyuznogo Simpoziuma po Tselenapravlennomu Izyskaniyu Fiziologicheski Aktivnykh Veshchestv. Riga, 1981" (Abstracts of Reports at the IVth All-Union Symposium on the Specific Search for Physiologically Active Substances, Riga, 1981), p.84.
80. L.V.Khazhakyan, S.K.Khachatryan, and G.A.Gevorgyan, "Tezisy XVI Respublikanskoi Nauchno-Tekhnichesko Konferentsii Aspirantov Obshchestvennoi Aspirantury, Erevan, 1979" (Abstracts of Reports at the XVIth All-Republic Science and Engineering Conference of Postgraduates, Erevan, 1979).
81. M.I.Farberov and G.S.Mironov, Zhur.Prikl.Khim., 1962, **35**, 2483.
82. E.Schrötter, Z.Chem., 1970, **10**, 183.
83. E.Schrötter and H.Schubert, Pharmazie, 1970, 25, 395.
84. E.Schrötter and E.Högel, Pharmazie, 1973, **28**, 189.
85. E.Högel and E.Schrötter, Pharmazie, 1973, **28**, 636.
86. E.Schrötter and M.Tschäpe, Pharmazie, 1976, **31**, 21.
87. E.Schrötter and W.Weuffen, Pharmazie, 1976, 31, 314.
88. D.Delchev and P.Todorova-Abramova, Farmatsiya, 1970, **20**, 6.
89. L.Strekowski, Synth.Struct., 1975, 287.
90. BRD P.236357 (1957); Chem.Abs., 1975, **83**, 148565.
91. G.Grizard, L.Cronenberger, and H.Pacheco, Bull. Soc.chim.France, 1973, 1070.
92. W.Back, Arch.Pharm., 1970, **303**, 465.
93. W.Back, Arch.Pharm., 1970, **302**, 491.
94. W.Back, Arch.Pharm., 1971, **304**, 27.
95. K.Makino and H.Takahashi, J.Biochem.(Tokyo), 1955, **42**, 559; Chem.Abs., 1956, **50**, 1183.
96. Y.Joh, J.Biochem.(Tokyo), 1965, **58**, 248; Chem. Abs., 1966, **64**, 631.
97. N.Mann, W.Back, and H.Mutschler, Arch.Pharm., 1973, **306**, 625.
98. J.Veinbergs, I.Jakobsons, and V.Grinsteins, Izv. Akad.Nauk Latv.SSR, Ser.Khim., 1974, 724.
99. W.Werner, Arch.Pharm., 1976, **309**, 1011.
100. T.Kurihara, H.Takeda, and H.Sato, Tohoku Yakka Daigaku kenkyu Nempo, 1978, 53; Chem.Abs., 1980, **92**, 15480.
101. V.P.Arya, C.L.Kaul, and K.S.Grewal, Arzneim-Forsch., 1977, **27**(II), 1648.
102. US P.3888901 (1975); Chem.Abs., 1975, **83**, 192356.
103. R.A.Magarian and W.G.Sorenson, J.Medicin.Chem., 1976, **19**, 186.
104. B.P.1181520 (1970); Chem.Abs., 1970, 72, 110903.
105. P.Parimoo and W.L.Nobles, J.Pharm.Sci., 1970, **59**, 1038.
106. A.M.Eirin, L.Santana, E.Ravina, F.Fernandes, E.Sanchez-Abarca, and J.M.Calleja, Europ.J.Medicin. Chem., Chim.Therap., 1978, 13(6), 533.
107. J.R.Dimmock and L.M.Smith, J.Pharm.Sci., 1980, **69**, 575.
108. French P.2138488 (1973); Chem.Abs., 1973, 79, 5170.
109. H.E.Hagen, A.W.Frahm, E.Brandes, and H.R.Roth, Arch.Pharm., 1970, **303**, 988.
110. H.Böhme and B.Clement, Arch.Pharm., 1979, 312, 527.
111. H.J.Roth and I.Allmer, Arch.Pharm., 1970, 303, 275.
112. R.Narayan and R.A.Kulkarni, Indian J.Pharm.Sci., 1979, **41**, 176.

113. US P.3992313 (1976); Chem.Abs., 1977, **87**, 1394496.
114. L.V.Morozova and T.N.Oparina, "Materialy X Nauchnoi Itogovoi Konferentsii" (Proceedings of the Xth Conference on Scientific Results), Perm, Vol.110; Trudy Perm.Gos.Med.Inst., 1972, 39.
115. W.Werner, J.prakt.Chem., 1972, **314**, 577.
116. R.R.Ison and M.M.A.Hassan, J.Pharm.Sci., 1973, **62**, 1388.
117. J.R.Dimmock and W.A.Turner, Canad.J.Pharm.Sci., 1974, **9**, 33; Chem.Abs., 1974, **81**, 25242.
118. J.R.Dimmock and W.G.Taylor, J.Pharm.Sci., 1974, **63**, 69.
119. J.R.Dimmock, W.C.L.Wong, and L.C.Marjorie, Canad.J.Pharm.Sci., 1976, **11**, 35; Chem.Abs., 1976, **84**, 173447.
120. J.R.Dimmock, N.W.Hamon, K.W.Hindmarsh, D.G.Mills, L.E.Negrave, G.H.Rank, and A.J.Robertson, J.Pharm.Sci., 1976, **65**, 482.
121. J.R.Dimmock, P.J.Smith, L.M.Noble, and W.J.Pannekoek, J.Pharm.Sci., 1978, **67**, 1536.
122. N.W.Hamon, D.L.Bassendowski, D.E.Wright, J.R.Dimmock, and L.M.Noble, J.Pharm.Sci., 1978, **67**, 1539.
123. J.R.Dimmock, N.W.Hamon, L.M.Noble, and D.E.Wright, J.Pharm.Sci., 1979, **68**, 1033.
124. A.D.Palekar and R.A.Kulkarni, J.Indian Chem. Soc., 1971, **48**, 354.
125. R.P.Rao and R.A.Kulkarni, Curr.Sci., 1972, **41**, 603.
126. BRD P.2193616 (1974); Chem.Abs., 1974, **80**, 133242.
127. A.Psarrea-Sandris, Ann.pharm.(France), 1974, **32**(12), 685.
128. H.Kamogawa, K.Kubota, and B.Nanasawa, Bull. Chem.Soc.Japan, 1978, **51**(2), 561; Chem.Abs., 1978(88), 137013.
129. L.Fisnerova et al., Coll.Czech.Chem.Comm., 1974, **39**, 624.
130. D.Suciu, J.prakt.Chem., 1971, **313**, 193.
131. E.A.Soliman, M.M.Abdalla, M.M.Mohammed, and A.M.Elgindy, Indian J.Chem.B, 1978, **16**, 505.
132. BRD P.2204989 (1973); Chem.Abs., 1973, **79**, 115429.
133. I.U.Numanov, R.Uzmanov, and M.Kurbanov, Dokl.Akad.Nauk Tadzh.SSR, 1979, **22**, 48.
134. R.Faure and G.Mattioda, Bull.Soc.chim.France, 1973, 3059.
135. A.A.Akhrem, A.V.Kamernitskii, I.G.Reshetova, and K.Yu.Chernyuk, Izv.Akad.Nauk SSSR, Ser. Khim., 1973, 1633.
136. US P.3733340 (1973); Chem.Abs., 1973, **79**, 32182.
137. A.Papadaki-Valiraki, Prakt.Acad.Athenon, 1977, **52**(A–D), 474; Chem.Abs., 1980, **92**, 181474.
138. H.J.Roth and K.Thassler, Arch.Pharm., 1971, **304**, 900.
139. K.Sato, S.Inoue, T.Kitagawa, and T.Takahashi, J.Org.Chem., 1973, **38**, 551.
140. K.Tonari, I.Ichimoto, et al., Nippon Nogu Kagaku Kaishi, 1970, **44**, 55.
141. N.S.Kozlov and V.I.Kovaleva, Izv.Akad.Nauk Beloruss.SSR, Ser.Khim., 1979, 118.
142. W.Felischacker and B.Koehl, Monatsch., 1978, **109**, 1099.
143. N.Holy and Y.Wang, J.Amer.Chem.Soc., 1977, **99**, 944.
144. N.Holy, R.Fowler, E.Burnett, and R.Lorenz, Tetrahedron, 1979, **35**, 613.
145. USSR P.537072 (1976); Byul.Izobret., 1976(44).
146. B.M.Gutsulyak and Z.L.Novitskii, Zhur.Obshch. Khim., 1978, **48**, 1872.
147. H.J.Roth and K.Thassler, Arch.Pharm., 1971, **304**, 824.
148. R.B.Miller and B.F.Smith, Synth.Comm., 1973, **3**, 129.
149. H.J.Roth and B.Mühlenbrach, Arch.Pharm., 1970, **303**, 156.
150. J.Ozols, S.Germane, V.A.Pestunovich, and A.Arens, Izv.Akad.Nauk Latv.SSR, Ser.Khim., 1972, 192.
151. E.Hannig, R.Heyde, and H.Matschiner, Pharmazie, 1973, **28**, 217.
152. E.Ravina, J.M.Montanes, M.P.Sieyro, and F.Tato, An.Quim., 1973, **69**, 915.
153. H.J.Roth and H.E.Hagen, Arch.pharm., 1971, **30**, 331.
154. H.J.Roth and G.Langer, Arch.pharm., 1968, **301**, 695.
155. H.J.Roth and K.Thassler, Arch.pharm., 1971, **304**, 816.
156. H.Krieger, A.Kojo, and A.Oikarinen, Finn.Chem. Letters, 1978, 185.
157. S.Danischefsky, M.Prisbylla, and B.Lipisko, Tetrahedron Letters, 1980, **21**, 805.
158. E.E.Smissman and P.C.Ruenitz, J.Org.Chem., 1976, **41**, 1593.
159. P.C.Ruenitz and E.E.Smissman, J.Heterocycl.Chem., 1976, **13**, 1111.
160. G.Trigo, G.E.M.Ruano, and C.Aguirre, An.Quim., 1979, **75**, 894.
161. BRD P.2428792 (1976); Chem.Abs., 1976, **84**, 150675.
162. V.P.Arya, Indian J.Chem.B, 1976, **14**, 982.
163. C.W.Thornber, Chem.Comm., 1973, 238.
164. P.L.Pauson, P.B.Kelly, and R.J.Porter, J.Chem. Soc.C, 1970, 1323.
165. French P.2143551 (1973); Chem.Abs., 1973, **79**, 53093.
166. H.J.Roth and F.Assadi, Arch.Pharm., 1970, **303**, 149.
167. I.N.Nazarov and E.T.Golovin, Zhur.Obshch.Khim., 1956, **26**, 483.
168. E.T.Golovin and A.P.Nikiforova, Khim.Geterotsikl. Soed., 1968, 268.
169. E.T.Golovin, B.M.Glukhov, L.S.Botsman, and T.V.Burdeleva, Khim.Geterotsikl.Soed., 1975, 903.
170. A.C.Cope and E.R.Trumbull, in "Organic Reactions" (Translated into Russian), Izd.Mir, Moscow, 1965, Vol.11, p.317.
171. S.A.Vartanyan et al., Izv.Akad.Nauk Arm.SSR, Ser.Khim.Nauk, 1963, **16**, 391.
172. E.T.Golovin, L.S.Botsman, and A.F.Sobol', Khim. Geterotsikl.Soed., 1975, 1487.
173. E.T.Golovin, B.M.Glukhov, and B.V.Unkovskii, Khim.Geterotsikl.Soed., 1976, 617.
174. E.T.Golovin, B.M.Glukhov, V.M.Mamontov, and B.V.Unkovskii, Zhur.Org.Khim., 1973, **9**, 614.
175. E.T.Golovin, B.M.Glukhov, and B.V.Unkovskii, Zhur.Org.Khim., 1973, **9**, 619.
176. E.T.Golovin, B.M.Glukhov, and B.V.Unkovskii, Zhur.Org.Khim., 1971, **7**, 2597.
177. E.T.Golovin et al., Zhur.Org.Khim., 1973, **9**, 840.
178. E.T.Golovin and B.M.Glukhov, Zhur.Org.Khim., 1971, **7**, 1727.
179. E.Sh.Kagan, V.I.Mikhailov, V.V.Pavlikov, and E.G.Rozentsev, Izv.Akad.Nauk SSSR, Ser.Khim., 1978, 2187.

180. V.D.Sholle, E.Sh.Kagan, V.I.Mikhailov, E.T.Rozantsev, P.T.Frangopol, M.Frangopol, V.I.Pop, and G.Benga, Centr.Inst.Phys., 1980, 2; Chem.Abs., 1980, **93**, 182216.
181. P.F.Wiley, J.Amer.Chem.Soc., 1952, **74**, 4326.
182. F.Eiden and C.Herdeis, Arch.Pharm., 1976, **309**, 764.
183. Y.Devi Uma et al., Curr.Sci., 1972, **41**, 773.
184. K.S.R.Krishna Mohan Rao et al., Proc.Indian Acad. Sci.A, 1976, **84**, 79.
185. H.Dorn and A.Zubek, J.prakt.Chem., 1971, **313**, 211.
186. T.J.Delia, J.P.Scovill, and W.D.Munslow, J.Medicin. Chem., 1976, **19**, 344.
187. Y.D.Kulkarni and V.K.Dwivedi, J.Indian Chem.Soc., 1976, **53**, 1044.
188. M.Schaefer, J.Weber, and P.Faller, Bull.Soc.chim. France, 1978, 241.
189. B.Bobarevic and M.Trkovnik, Glas.Hem.Technol. Bosne Hercegovine, 1970, **18**, 25.
190. J.L.Asherson and D.W.Young, J.Chem.Soc., Perkin Trans.I, 1980(2), 512.
191. V.J.Traynelis and J.C.Sih, J.Org.Chem., 1973, **38**, 2629.
192. A.Sato et al., Bull.Chem.Soc.Japan, 1973, **46**, 3530.
193. H.Böhme and F.Zigler, Arch.Pharm., 1974, **307**, 287.
194. G.Romussi and G.Giarallo, Farmaco.Ed.Sci., 1977, **32**, 635.
195. F.Eiden and C.Herdeis, Arch.Pharm., 1977, **310**, 573.
196. A.Ermili, M.Massei, G.Roma, and C.Cacciatore, Farmaco.Ed.Sci., 1977, **32**, 375.
197. A.Ermili, G.Roma, et al., Farmaco.Ed.Sci., 1974, **29**, 225.
198. A.Ermili, G.Roma, M.Mazzei, R.Ambrosini, and N.Passerini, Farmaco.Ed.Sci., 1974, **29**, 237.
199. A.Ermili, G.Roma, and A.Babli, Farmaco.Ed.Sci., 1974, **29**, 247.
200. A.Ermili, M.Mazzei, G.Roma, A.Cuttuca, and N.Passerini, Farmaco.Ed.Sci., 1975, **30**, 870.
201. A.Ermili, M.Mazzei, G.Roma, A.Ambrosini, and N.Passerini, Farmaco.Ed.Sci., 1975, **30**, 1001.
202. A.Ermili, A.Balbi, G.Roma, A.Ambrosini, and N.Passerini, Farmaco.Ed.Sci., 1976, **31**, 627.
203. G.Roma, A.Balbi, and A.Ermili, Farmaco.Ed.Sci., 1977, **32**, 393.
204. S.Herzi, H.Tanako, and H.Takao, Bull.Chem.Soc. Japan, 1977, **50**, 2823.
205. M.N.Tilichenko and G.V.Pavel', Zhur.Org.Khim., 1965, **1**, 1992.
206. G.V.Pavel' and M.N.Tilichenko, Zhur.Org.Khim., 1966, **2**, 2262.
207. G.V.Pavel' and M.N.Tilichenko, Zhur.Org.Khim., 1968, **4**, 1420.
208. G.V.Pavel' and M.N.Tilichenko, Khim.Geterotsikl. Soed., 1968, 484.
209. M.N.Tilichenko, G.V.Pavel', and A.D.Chumak, Zhur.Org.Khim., 1971, **7**, 704.
210. A.D.Chumak, G.V.Pavel', and M.N.Tilichenko, Khim.Geterotsikl.Soed., 1973, 738.
211. G.V.Pavel', M.N.Tilichenko, and A.D.Chumak, Article Deposited at the All-Union Institute of Scientific and Technical Information (VINITI), 4253:76 (1976).
212. M.N.Tilicenko, Revista de Chimie, 1970, **21**, 729.
213. J.V.Greenhill, P.H.B.Ingle, and M.Ramli, J.Chem. Soc., Perkin Trans.I, 1972, 1667.
214. B.M.Gutsulyak and M.V.Mel'nik, Zhur.Org.Khim., 1979, **15**, 558.
215. B.M.Gutsulyak et al., Zhur.Org.Khim., 1980, **16**, 1875.
216. B.M.Gutsulyak and P.D.Romanko, Article Deposited at the All-Union Institute of Scientific and Technical Information (VINITI), 3191-71 (1971).
217. H.Abu-Shady, U.A.R., J.Pharm.Sci., 1970, **11**, 295; Chem.Abs., 1971, **75**, 151708.
218. H.Abu-Shady, U.A.R., J.Pharm.Sci., 1971, **12**, 285; Chem.Abs., 1972, **77**, 152031.
219. U.Rehse, Arch.Pharm., 1974, **307**, 866.
220. M.Ohashi and T.Tokahashi, Bull.Chem.Soc.Japan, 1975, **48**, 1892.
221. E.H.Amer, F.Abdul Kadar, and A.El-Sayed, Z.Naturforschung Teil B, 1979, **34**, 867; Chem. Abs., 1980, **92**, 41903.
222. H.J.Roth and F.Assadi, Arch.Pharm., 1970, **303**, 29.
223. H.J.Roth and W.Kühn, Arch.Pharm., 1971, **304**, 413.
224. H.Böhme and B.Clement, Arch.Pharm., 1979, **312**, 531.
225. J.Schreiber, C.-G.Wermuth, and A.Meyer, Bull.Soc. chim.France, 1975(2), 625.
226. I.N.Azerbaev, T.T.Omarov, A.Sh.Gubasheva, K.A.Al'mukhanova, and S.A.Baisalbaeva, Vestnik Akad.Nauk Kazakh.SSR, 1975(2), 47.
227. J.W.Greenhill, J.Chem.Soc.C, 1971, 2699.
228. J.Chaaban, J.V.Greenhill, and P.Akhtar, J.Chem. Soc., Perkin Trans.I, 1979, 1593.
229. M.Hanaoka, N.Ogawa, K.Shimizu, and J.Arata, Chem.Pharm.Bull., 1975, **23**, 1573.

Mndzhoyan Institute of Fine Organic Chemistry,
Academy of Sciences of the Armenian SSR, Erevan